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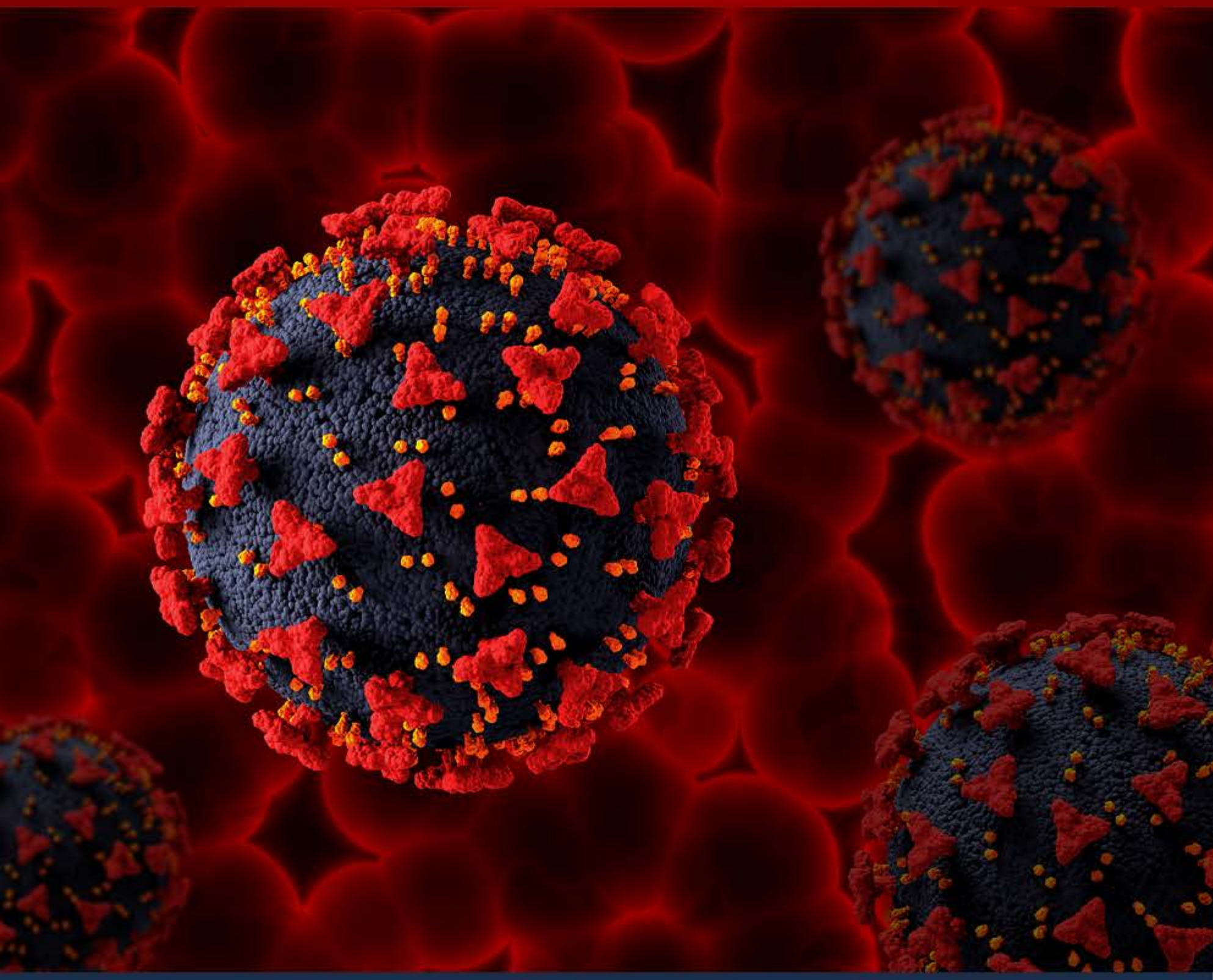

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The Functions of Artificial Intelligence in Addressing COVID-19

Naser Hosseinzadeh Asl Akhtehkhaneh[1*]

[1]Department of Medical Physics & Biomedical Engineering, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Corresponding Author's E-mail: nh.hoseinzadeh@gmail.com.

Abstract

The COVID-19 epidemic has engendered unparalleled problems globally. Artificial intelligence (AI) technologies has significant promise for addressing critical elements of pandemic management and response. This analysis examines the significant potential of AI technology in tackling the worldwide difficulties presented by the COVID-19 pandemic. This paper first examines the COVID-19 pandemic and its effects on public health, the economy, and society. Subsequently, we concentrate on pioneering uses of powerful AI technologies in critical domains such prediction, diagnosis, control, and medication development for the treatment of Covid-19.

Keywords: Artificial intelligence, COVID-19, Drug development, Machine Learning.

Introduction

The earliest report of the Coronavirus Infection (COVID-19) emerged in December 2019 in Wuhan, China, affecting over two hundred nations and regions worldwide, with 2,000,000 cases and 120,000 fatalities as of April 21, 2020. In response to this escalating catastrophe, organizations and specialists around are seeking approaches to address the challenges posed by this virus, mitigate its spread, and provide treatments for the pandemic (1). Significant apprehensions about the capacity of healthcare systems have emerged owing to the extraordinary demand for health services, particularly in underprivileged regions. In this context, methodologies that expedite diagnostic procedures, improve monitoring and tracking capabilities, forecast the evolutionary stages of contagion and its societal impacts, and simulate the outcomes of containment strategies, medical protocols, or novel molecules, can signify a transformative milestone in global efforts to address these critical events (2). The COVID-19 emergency has significantly accelerated the enhancement of current models and the creation of new prototypes to provide promising outcomes in areas such as infection tracking, diffusion prediction, and the assessment of restrictive measures' impacts (2).

Advancements in artificial intelligence (AI) are anticipated to serve as an effective approach to address these challenges: due to the extensive information provided by the emergence of ubiquitous IT and the consistently growing computational power, AI has demonstrated exceptional performance regarding the majority of the aforementioned issues (3). Its capacity to discern patterns and relationships among data has made this study domain especially appealing for jobs that involve the elucidation of intricate information and processes. Numerous successful applications of Deep Learning (DL) and Machine Learning (ML) techniques in image recognition and segmentation, time series forecasting, sentiment analysis, system control, and dynamics simulation

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are extensively documented in the literature, alongside effective robotic self-operating solutions that have demonstrated efficacy in minimizing social interactions. The positive findings illustrate the significant emphasis directed towards global research on AI as a tool to combat the COVID-19 pandemic (4). As per the Scopus database, almost 1000 peer-reviewed articles with the keywords "COVID-19" and "Artificial Intelligence" were published from the onset of the pandemic until March 1, 2021 (4).

Artificial intelligence may be used for predicting viral dissemination and creating early warning systems by pulling data from social media platforms, telephone communications, and news websites, therefore offering valuable insights into at-risk areas and anticipating morbidity and fatality rates (5). Bluedot detected a cluster of pneumonia patients and forecasted the outbreak and geographical distribution of COVID-19 using machine learning on available data. HealthMap aggregates publicly accessible data on COVID-19 to enable efficient monitoring of its dissemination. Recently, the significance of AI in the detection and prediction of COVID-19 outbreaks by the use of diverse and multimodal data was highlighted. Furthermore, artificial intelligence was used for the identification and quantification of COVID-19 instances using chest X-ray and CT scan pictures (6). Researchers have created a deep learning model named COVID-19 detection neural network (COVNet) to distinguish between COVID-19 and community-acquired pneumonia using visual 2D and 3D data derived from volumetric chest CT scans (7). The present study is on the application of AI advancements in combating the Coronavirus epidemic. It examines several technical developments used to mitigate and suppress the substantial impact of the eruption. This review seeks to evaluate the efficacy of the outlined techniques and propose their application methods. This study illustrates AI applications and offers an outline of how emerging technology may address the COVID-19 epidemic.

Overview of the COVID-19 pandemic

Pneumonia resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection originated in Wuhan, Hubei Province, China, in December 2019. On February 11, 2020, the World Health Organization (WHO) officially designated the sickness caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). COVID-19 encompasses a range of clinical symptoms, often include fever, dry cough, and exhaustion, frequently accompanied by pulmonary involvement (8). SARS-CoV-2 has great transmissibility, rendering the majority of the general population vulnerable to infection. Wild animal hosts and sick individuals are now the primary routes of disease transmission via respiratory droplets and direct contact. Following the outbreak, the Chinese government and scientific community swiftly identified the causal culprit, instantly disseminated the viral gene sequence, and implemented efforts to limit the pandemic (9). Despite the perception that the epidemic has concluded, the World Health Organization reports an average of 378,000 new cases everyday. A prompt collective reaction was established to inhibit the further dissemination of COVID-19. Numerous impacted nations enacted border closures and temporarily halted transit and tourism. The WHO and the Centers for Disease Control (CDC) issued worldwide standards for adherence by global and national enterprises, governments, and individuals to effectively control the epidemic (10). The CDC and WHO have delineated symptoms indicative of a potential COVID-19 infection, such as dry cough, fever, diarrhea, myalgia, and vomiting. Public awareness has been elevated globally to encourage prompt treatment in order to diminish morbidity rates. Governments have promoted and facilitated the study and development of COVID-19 vaccines. The containment of the epidemic necessitates heightened vigilance because to the rise of global COVID-19 infections (11). Reverse transcription-polymerase chain reaction (RT-PCR) is a method for identifying the COVID-19 virus. Timely and precise identification is essential for illness management; however, test results may be available within 2 to 48 hours. Numerous vaccines have been produced due to the emergence of coronavirus ribonucleic acid (RNA). These vaccines use many biological agents, including attenuated live viruses, proteins or subunits, messenger RNA (mRNA), and deoxyribonucleic acid (DNA) (12). Vaccines remain 95% effective, while they may impede the course of illness and assist individuals in developing immunity by stimulating the manufacture of optimal antibodies. Despite the availability of a vaccine, early diagnosis of coronavirus remains essential, since it enables the identification of persons who have been directly or indirectly exposed to the virus. Identifying these patients may avert the future spread of the pandemic, since COVID-19 infections present as lung illnesses. Consequently, computed tomography scans (CT) and chest X-rays are used to identify COVID-19 infection (13).

Introduction of AI

AI is a vital instrument in contemporary business, society, and healthcare, as it maintains a crucial equilibrium among patient care, administrative functions, and pharmacological entities. The notion of artificial intelligence originated in 1956 and pertains to "intelligent agents" or gadgets that assess their surroundings and enhance operations. Consequently, it is the intelligence shown by robots that replicate

and augment human intellect (14). AI involves the acquisition of data, its interpretation, and subsequent learning to get the intended result. In various healthcare models, AI is clearly regarded as performing at least as effectively as, if not superior to, humans in disease diagnostics, with AI systems surpassing radiologists in detecting malignant tumors and assisting researchers in the formation of cohorts for expensive clinical trials (15). AI employs supervised and unsupervised learning methodologies; the former involves training and testing to predict fresh data samples, while the latter entails learning from data samples without supervision. It comprises several components such as neural networks, deep learning, natural language processing, rule-based expert systems, and robotics, which are essential elements of artificial intelligence (16).

ML, a prevalent kind of AI, employs a statistical methodology for model fitting and training using data to facilitate learning. According to the 2018 Deloitte poll of 1,100 U.S. managers from enterprises using artificial intelligence, around 63% of the companies were implementing ML in their operations (17). Precision medicine is a prevalent use of machine learning in healthcare, focusing on predicting the success of treatment protocols based on patient characteristics and treatment factors (17). Most ML and precision medicine parameters depend on a training dataset, which requires prior knowledge of an outcome, such as illness start. This is termed guided learning. Neural network technology, a complicated aspect of ML, has been used in healthcare systems for decades, relying on neuronal signal processing to ascertain the likelihood of a patient developing a given ailment (18). DL and neural network models are essential components of ML, potentially including several latent variables, facilitated by graphics processing units and cloud architectures. DL plays a pivotal role in cancer radiology, radiomics, and the detection of substantial clinical data that surpasses human visual perception (19). The integration of DL with radiomics has significant applications in diagnostics, surpassing the previous generation of image analysis tools, such as computer-aided detection (CAD). A notable use of DL is to its capacity for voice recognition, particularly within natural language processing (NLP), which encompasses text translation, processing, generation, categorization, and comprehension of published research, clinical documentation, and other language-related tasks. Natural Language Processing (NLP) is a crucial component of artificial intelligence focused on the study of human language, a pursuit of AI researchers since the 1950s. NLP consists of two primary components: statistical and semantic, with the former relying on ML, DL, and NLP, necessitating a substantial corpus of languages for training (18, 20).

The study focuses on the use of AI characteristics in the treatment of infectious illnesses, particularly in relation to the ongoing COVID-19 epidemic. The use of AI technology in the diagnosis, prediction, classification, analysis, treatment, and detection of coronavirus infection is of paramount significance due to its rapid global dissemination. The AI programs employ Industry 4.0 technologies, information technology, the Internet of Things, ML algorithms, mobile applications, deep and convolutional neural networks, and digital healthcare systems to optimize time efficiency, address the shortage of healthcare personnel, accurately document cases of infection, recovery, and mortality, and facilitate public information dissemination aimed at expediting recovery and mitigating the COVID-19 pandemic. Concurrently, these programs assist researchers in vaccine development, disease diagnosis, symptom reduction, and comprehending the transmission cycle and genomic sequence of the virus.

Applications of AI in COVID-19 diagnosis and detection

Monitoring of outbreaks

Biosurveillance is the scientific discipline focused on the early identification and prevention of disease outbreaks within a community (21). Analytics, ML, and NLP are being utilized for biosurveillance. Analyzing social media, news articles, and other internet information may facilitate the early detection of localized disease epidemics prior to their escalation into pandemics (22). The Canadian firm Blue Dot efficiently utilized ML algorithms to identify early COVID-19 infections in Wuhan, China, before late December 2019 (23). The study of extensive medical records and satellite imagery, such as the clustering of vehicles near a hospital, are other methods used in the past for the detection of localized epidemics using big data analysis. Google Trends has already been used to identify the emergence of Zika virus infections in communities using dynamic forecasting algorithms (24).

Sentiment analysis is the use of NLP in social media to discern the positive and negative feelings of the populace. Unsupervised sentiment analysis has been suggested as a technique for the early identification of infectious illnesses within the population. Sentiment analysis may serve as a significant instrument for comprehending public responses, including overreactions, to illness outbreaks and may provide critical insights to the government for guiding public education initiatives. These sentinel biosurveillance approaches would facilitate the early detection of pandemics,

so affording the health system critical time for preparation and treatment (25).

Forecast of dissemination

Diverse statistical, mathematical, and dynamic forecasting methods have been utilized to effectively forecast the magnitude and dissemination of infectious illnesses within the population. In contrast to conventional epidemiological predictive models, big-data-driven models possess the advantages of adaptive learning, trend-based recalibration, flexibility, and the capacity for enhancement based on evolving insights into the disease process, as well as the assessment of intervention impacts, like social distancing, in mitigating its transmission (26, 27). The predominant approach used is the Susceptible-Exposed-Infectious-Recovered (SEIR) model, currently utilized to forecast the regions and magnitude of COVID-19 transmission. These tools may help ascertain other characteristics of the pandemic, including case under-reporting, intervention efficacy, and testing procedure accuracy (28). A modeling program sought to replicate the circumstances under which Ebola may proliferate inside Chinese society, assessing the efficacy of four tiers of state actions in these scenarios (29). Comparable models have endeavored to forecast the emergence and proliferation of the Zika virus in real-time throughout the Americas, achieving around 85% accuracy in quantitative assessments. An evaluation of several machine learning methods revealed that the backward propagation neural network (BPNN) had the greatest prediction accuracy in modeling Zika virus transmission (30).

Researchers from Johns Hopkins University created a COVID-19 prediction model derived on an earlier stochastic metapopulation epidemic framework. A comparison between the model's predictions and actual data revealed gaps in the comprehension of the virus's dynamics and the model's constraints (31). Nonetheless, the efficacy of a prediction model is contingent upon the quality of its underlying data, and during a worldwide pandemic, the sharing of data across communities is critically essential. This was a significant impediment in understanding and simulating the Ebola virus spread from 2013 to 2016. The World Health Organization (WHO) has advocated for a consensus on accelerated data sharing on the COVID-19 epidemic to enhance inter-community learning and analysis in this domain (32).

Prevention measures and vaccine formulation

Artificial Neural Networks (ANN) were used to forecast antigenic areas characterized by a high concentration of binders (antigenic hotspots) in the viral membrane protein of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) (33). This knowledge is essential for vaccine development. Employing ML for this objective facilitates the swift analysis of the whole viral proteome, so expediting and reducing the cost of vaccine development. Reverse vaccinology and ML were effectively used to discover six prospective vaccine target proteins within the SARS-CoV-2 proteome. ML has previously been employed to forecast the influenza virus strains likely to infect a population in the forthcoming year, thereby informing the composition of the seasonal influenza vaccine (34). Successful predictions regarding the future proliferation of minor subtrees of hemagglutinins (HA) within the viral antigenic repertoire were achieved by training on H3N2 and testing on H1N1, utilizing a reconstructed temporal phylogenetic tree. Additionally, machine learning can predict the hosts of newly identified viruses through the analysis of nucleoprotein and spike gene sequences, serving as a valuable supplementary tool for tracing viral origins, particularly when dealing with extensive datasets where comparative analysis is challenging or labor-intensive (35).

Proactive identification and monitoring of cases

Timely patient identification, isolation, and mitigating community exposure are essential components in the management of an epidemic like COVID-19. Mobile phone surveys may facilitate the early detection of illnesses, particularly inside isolated populations. These strategies have shown efficacy in Italy for detecting influenza patients using an online poll (36). Unlike conventional survey and analytic approaches, AI applications can gather and analyze extensive data, spot patterns, stratify patients by risk, and offer remedies for populations rather than individuals. Digital phenotyping is the innovative approach of gathering smartphone-based active (surveys) and passive (text, speech, location, screen use) data to generate an individual phenotype (37). This approach may be used to acquire several data points and facilitate the stratification of people according to their risk levels. The Government of India has introduced a mobile application named "Aarogya Setu" that monitors users' exposure to those possibly infected with COVID-19, using Bluetooth technology to detect nearby smartphone users. If a patient tests positive, the data from the mobile application may be used to identify every app user with whom the patient interacted in the last 30 days (38). Digital phenotyping approaches may be executed on basic cellphones and would be particularly advantageous in poor and middle-income nations as a cost-effective means of risk stratification, owing to the widespread availability of smartphones (39).

The close geographical and economic closeness to China should have led to elevated morbidity and death rates from COVID-19 in Taiwan. Nonetheless,

via the use of ML, they successfully reduced the number of infected patients to far lower levels than previously anticipated (40). They promptly recognized the problem, activated their national health insurance database, and used customs and immigration records to provide extensive data for analysis. ML applied to this extensive dataset enabled the stratification of the population into lower and greater risk categories based on many characteristics, including travel history. Individuals at elevated risk were confined to their residences and monitored via their mobile devices to verify compliance with quarantine protocols. The use of big data, along with proactive case identification initiatives, resulted in case numbers far lower than previously projected. DL algorithms have been used to discern patterns of infectious illness in imaging findings, including CT and MRI scans. CT scanning demonstrates strong associations with PCR-positive COVID patients, indicating that such methods are very effective in identifying COVID-19-related abnormalities in CT imaging (41).

Forecasting prognosis

Machine learning techniques have already been used to forecast prognosis in individuals afflicted with the MERS Co-V virus. The patient's age, illness severity at presentation to the healthcare institution, healthcare worker status, and existence of pre-existing comorbidities were found as the primary predictors of the patient's recovery (42). These results align with the presently reported trends in COVID-19. A smartphone application, Ebola CARE (Computational Assignment of Risk Estimates), was created using the data visualization tool Mirador to predict patient outcomes after Ebola infection. The instrument found 24 medical and laboratory indicators that may influence a patient's prognosis. There is an urgent need to modify these algorithms to aid clinicians in their decision-making process for COVID-19 management. Recovery prediction tools assist in resource allocation, triage, treatment decisions, and health system readiness (43, 44).

Development of therapeutic interventions

ML technologies have been used in drug research, drug testing, and drug repurposing. They facilitate the interpretation of extensive gene expression profile datasets to propose novel applications for existing pharmaceuticals (45). Deep generative models, referred to as AI imagination, may create innovative medicinal molecules with potential desired efficacy. These techniques facilitate the reduction of costs and time in drug development, assist in the creation of innovative therapeutic agents, and anticipate potential off-label use for certain therapeutic medicines. Bayesian ML methods have been used to create therapeutics targeting Ebola in in-vitro environments, with the results effectively translating to in-vivo contexts (46).

Future prospects and concluding remarks

This review summarizes the unique use of AI approaches in combating the COVID-19 outbreak. Improved ML and DL models show great potential for solving the critical difficulties raised by the global health crisis. AI-driven predictive analytics use medical, epidemiological, and omics information to produce precise estimates of disease dissemination patterns and individual predictions. Deep neural networks provide fast diagnosis using medical imagery. Intelligent systems that integrate risk assessment, decision support, and social sensing facilitate pandemic management and influence public health policy (47). Furthermore, AI-driven virtual screening may enhance therapeutic drug development and repurposing prospects. This analysis emphasizes that the use of AI in combating COVID-19 remains in its nascent phase. Significant advancements have been achieved in estimation, identification, and drug discovery. Nonetheless, prediction systems need further confirmation via empirical evidence. Diagnostic algorithms must go from binary classification to the measurement of infection severity. Although structural biology and bioinformatics models have identified various treatment options, extensive research investigations are required to test their security and efficacy (48).

Despite the great promise demonstrated by AI throughout the COVID-19 outbreak, various challenges remain in translating evidence of concept into concrete real-world consequences. A fundamental restriction is the lack of vast, high-quality, standardized datasets required for the construction of robust AI models, especially during the early phases of the pandemic when accurate testing was not available (49). Differences in demographics, procedures, and information forms may make it difficult to generalize models across different populations and settings. In addition, the relationship between existing clinical practices and legacy information technology systems creates barriers to adoption, which is worsened by a lack of AI knowledge among the initial stages healthcare personnel. Significant difficulties remain concerning scaling, economics, and inherent prejudices when AI is deployed on a big scale (50). The opacity of deep learning models impedes interpretability and accountability for AI-driven decisions. The pandemic response's necessity and unpredictably heighten these challenges, since relying on inaccurate projections or direction from undeveloped AI might endanger the lives of people and destroy confidence in society. To maximize the benefits of

AI in COVID-19 management, broad approaches including technical, medical moral, and societal aspects will be required (51).

Finally, ethical concerns about privacy, justice, and responsibility have to be solved, especially when AI is utilized for directing vital decisions like hospital triage. Transparency regarding data sources and model features is critical for building trust with the public and suppliers. To avoid disproportionate impacts on underrepresented communities, results must be thoroughly examined for biases and assessed on a regular basis. Finally, AI ought to enhance rather than substitute human abilities and expertise in handling pandemics (52). To summarize, transforming prospective AI applications into concrete real-world consequences necessitates considerable advancement in technological, medical, moral, and operational aspects. In spite of advances in algorithms and data, cooperation, facilities proof, and confidence are critical enablers for leveraging AI's ability to aid people around the world throughout the COVID-19 outbreak and beyond.

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Introduction of Oncolytic Viruses as Candidates for Targeted Cancer Therapy

Akram Sadat Ahmadi[1*], Zahra Zand[2]

[1]Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, 1417613151, Iran.
[2]Molecular Medicine Department, Biotechnology Research Centre of Pasteur Institute of Iran.

Corresponding Author's E-mail: Akramsadat.ahmadi@gmail.com.

Abstract

Given the progress in comprehending various forms of cancer and the subsequent pursuit of a remedy, along with improved survival rates for cancer patients, it is crucial to discover a therapeutic that may effectively counteract the aggressive mechanisms of this illness. Oncolytic viruses (OVs) have shown to be very advantageous in the treatment of cancer due to their ability to induce antitumor effects via several mechanisms. Viruses may be used to infect cancer cells, particularly in comparison to normal cells, to introduce tumor-associated antigens, trigger "danger signals" that create a less immune-tolerant tumor microenvironment, and function as delivery vehicles for the release of inflammatory and immunomodulatory cytokines. These modified OVs, which have been designed to have improved capacity to target tumors, increased oncolytic activity, or the potential to generate strong anti-tumor immune responses, are evaluated in animal models during preclinical testing and in clinical trials involving cancer patients. OVs have been recognized as one of the primary agents for cancer immunotherapy due to their ability to target tumors via many mechanisms. Nevertheless, given the restricted efficacy of innovative anti-cancer treatments including immunotherapies and cell-based therapies, it is imperative to evaluate the potential of combination therapy using OVs. This study aims to introduce oncolytic viruses and review their capacity to induce antitumor responses, their challenges and limitations.

Keywords: Cancer treatment, Oncolytic viruses, Tumor lysis, Therapy.

Introduction

For the past two decades, oncolytic virotherapy, a new cancer treatment method, has yielded encouraging outcomes. More than a century ago, it was discovered that cancer patients had cancer regression if they were infected with certain viruses. Revolutions in recombinant DNA technology have offered key tools for studying viral biology, enhancing biological treatment for cancer, and ushering in a new generation of cancer therapies. While chemotherapy and radiation therapies remain popular cancer treatments, their severe side effects are a big disadvantage (1). Biological therapy for cancer, despite its complexity and difficulty, is the preferred treatment choice because of its success, low negative reactions, and decreased discomfort for cancer patients. So far, research studies have found no fatalities or clinically significant side

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effects related to oncolytic virotherapy (OV). In cancer treatment, patient safety is critical, and treatment using oncolytic viruses appears to be the most promising in this regard. Most oncolytic viruses used in cancer therapy are attenuated strains, which may infect and multiply in people without causing major sickness. It is also critical that the viruses picked can employ the host immune system to identify and attack cancerous cells (2).

Oncolytic viruses (OVs) have gained popularity in recent years due to their capacity to specifically target and kill tumour cells while potentially stimulating antitumor immunity. There are several benefits to developing tumours that specifically target OVs while maintaining a tolerable safety profile and effectiveness against various malignancies. A candidate virus chosen to eliminate tumour cells must feature specific hallmarks: it must be proimmunogenic, not cause chronic infectious illness, be safe for diverse human populations, exert lytic activity in tumour cells, and have the power to integrate into the host genome (3). An oncolytic virus's proimmunogenicity is defined as the presence of antigenicity, which allows the immune system to recognise it, infectivity, replication, which causes a powerful immunological response, and genetic diversity, which can contribute to immune recognition and inflammation. Genetic engineering is critical in creating OVs with a tolerable safety profile and excellent effectiveness against a variety of malignancies. In this sense, OVs must be adjusted especially for the tumour type and mutations by changing noncoding mutations and adding or deleting certain activities, genes, and noncoding elements to impart extra positive qualities. There are three research directions for cancer therapy with OVs: Viral replication, tumour development, and immune activation. As a result, OVs primarily target tumour cells, host immunity, and the tumour microenvironment. Most viral vectors cause immunogenic cell death (ICD) by releasing tumor-associated antigens, which trigger antitumor immune responses. By stimulating antitumor immunity, OVs outperform ICIs and other precisely targeted medicines. OVs have a wide variety of anticancer, immune-boosting effects. Patients with acceptable molecular profiles must be identified before receiving OV treatment. Thus, the identification of prognostic biomarkers for OV therapy is critical. We will look at many features of OVs and their usage in oncolytic virotherapy. We think that oncolytic virotherapy provides a novel approach to cancer immunotherapy (4, 5).

Types of viruses used for oncolytic virotherapy

An optimal oncolytic virus candidate should have certain characteristics, including a strong fundamental grasp of their biology and genetics. The OV should be pro-immunogenic, have lytic action in infected malignant cells, not cause chronic or infectious illness, and be able to integrate into the human genome. Furthermore, the virus must be generally safe for a varied human population. It is also possible to genetically edit and arm with recombinant transgenes to increase its immunogenicity or induce specific anticancer processes. From the initial investigations, a variety of viruses with and without genetic changes have been investigated and joined clinical studies (6). They are composed of RNA as well as DNA viruses (Table 1). Oncolytic DNA viruses include adenoviruses, herpes simplex virus (HSV), parvoviruses, and poxviruses including vaccinia (VACV) and myxoma (MYXV). Oncolytic RNA viruses include Coxsackie virus, Maraba virus, measles virus (MV), Newcastle disease virus (NDV), poliovirus, reovirus, retroviruses, Seneca Valley virus (SVV), Semliki Forest virus (SFV), Vesicular Stomatitis virus (VSV), and Sindbis virus (SBV). Oncolytic DNA viruses offer the benefits of high genome stability and greater transgene insertion capabilities without impacting viral infection and proliferation. On the other hand, RNA viruses have limited genome-packing ability, yet some can be highly immunogenic. However, there are advantages and disadvantages to each OV virus that has been produced and tested thus far (7).

Once OVs attach to and invade tumor cells, they may use many destructive processes to eliminate the infected cancer cells. The effectiveness of these mechanisms may or may not be directly related to the level of viral replication occurring inside the target cells. The precise processes behind viral oncolysis remain partially known, exhibiting significant variation between different viruses and even substantial differences across various kinds of cancer cells being targeted (8). OVs are believed to exert antitumor effects through various mechanisms: (a) they replicate selectively within cancer cells, resulting in direct destruction of the cells (also known as oncolysis); (b) they induce cell death, either through apoptosis-like or necrosis-like processes, in both infected and uninfected cancer cells as well as the endothelial cells in the tumor-associated blood vessels, leading to decreased formation of new blood vessels (angiogenesis); and (c) they stimulate a systemic immune response against both the tumor and the virus, attracting activated immune cells into the tumor microenvironment (TME). Nevertheless, these pathways exhibit substantial variations between different viruses, as well as about the specific characteristics and types of cancer cells, and the overall interplay between the OVs, TME, and the host immune system (9). Many viruses inhibit the cell death pathways that are triggered by the host in response to viral infection.

Table 1. A list of oncolytic viruses and their characteristics.

	Name	Size of genome	Capsid symmetry	Envelope	Entry receptor	Host	Site of replication
DNA virus	Adenovirus	dsDNA 70–100	Icosahedral	Naked	CD46, CAR	Human, animals	Cytoplasm and nucleus
	Herpes Simplex Virus-1	dsDNA 200	Icosahedral	Enveloped	Nectin 1,2, HVEM	Human (HSV-1)	Cytoplasm and nucleus
	Vaccinia Virus	dsDNA 70–100	Complex	Complex coat	Without specific receptor	Humans and cattle	Cytoplasm
	Poxvirus: VACV, MYXV	dsDNA (160–190 kb)	-	Enveloped	Heparan, laminin, chondroitin, integrin β1	MYXV (rabbit)	Cytoplasm
RNA virus	Measles	ss(-)RNA 100–200	Icosahedral	Enveloped	CD46, SLAM	Human	Cytoplasm
	Vesicular Stomatitis Virus	ss(-)RNA 80	Helical	Enveloped	LDRL	Humans, mammals, and insects	Cytoplasm
	Newcastle virus	ss(-)RNA 100–500	Helical	Enveloped	Sialic acid	Birds	Cytoplasm
	Reovirus	dsRNA 60–80	Icosahedral	Naked	Without specific receptor	Human	Cytoplasm
	Zika virus	SS (+) RNA (10.8 kb)	Icosahedral	Enveloped	GAGS, Heparan sulfate, C-type lectin	Monkey	Cytoplasm

1.Antitumor effects induced by OVs

Viruses have been seen to produce proteins that may selectively affect several routes of cell death, acting as either inhibitors or inducers. Once infected by an OVs, the cancer cells often undergo cell death due to the activation of cell death pathways and/or the breakdown of cell integrity caused by the damage inflicted by the virus. In addition, several OVs have been modified to selectively trigger certain cancer cell death mechanisms, such as apoptosis, necrosis, autophagy, or pyroptosis, in order to enhance cell lysis (10). ICD refers to a specific type of cancer cell death that allows cancer cell antigens to be exposed to immune cells in the TME. In laboratory settings, ICD is typically measured by observing the external exposure of markers that are normally found inside cells or the release of internal mediators by the dying cells. OVs have the benefit of being able to activate many cell death pathways inside the tumor site. Out of them, it is considered that ICD plays a vital role in enhancing acquired anti-tumor immunity (11).

When the replication of OVs in cancer cells triggers ICD, it leads to the release of tumor-associated antigens (TAAs), damage-associated molecular patterns (DAMPs), OV-derived pathogen-associated molecular patterns (PAMPs), and increased production of various inflammatory cytokines. These factors collectively stimulate both the innate and adaptive immune responses. The presence of DAMPs, including extracellular ATP and high mobility group box 1 (HMGB1) proteins, as well as the exposure of certain cytoplasmic proteins on the cell surface, such as HSP70, HSP90, and calreticulin (CRT), are all characteristic signs of ICD. Following the release, DAMP molecules attach to their corresponding receptors CD91 (CRT), P2RX7 (ATP), and TLR4 (HMGB1) on dendritic cells (DCs). This interaction leads to the maturation of DCs, antigen processing, and the subsequent activation of T lymphocytes, resulting in improved antitumor responses. Extracellular adenosine triphosphate (ATP) and surface-exposed calreticulin (CRT) function as signals that attract and facilitate the engulfment of phagocytic immune cells. Cytoplasmic DNA in infected cells triggers the cGAS DNA sensor at the molecular level, leading to the activation of STING pathways. This activation results in the initiation of innate immunity through

the expression of type I IFN genes, the release of chemokines CXCL9 and CXCL10, and ultimately the recruitment of T cells (12). ICD, or immunogenic cell death, plays a crucial role in the establishment of anticancer immunity in metastatic locations in the context of oncolytic virotherapy. Recent research has shown that OVs, such as adenovirus, parvovirus, reovirus, coxsackievirus, vaccinia virus (VACV), Newcastle disease virus (NDV), and herpes simplex virus (HSV), all elicit different levels of immunogenic cell death (ICD). The activation of ICD by oncolytic viruses (OVs) is essential for transforming cancers that lack lymphoid cells or have minimal expression of immunological sensors (referred to as "cold" tumors) into tumors that are infiltrated by T cells and have an inflammatory immune microenvironment (referred to as "hot" tumors). In addition to ICD, autophagy may also trigger antitumor immune responses as a result of OV infection and replication inside cancer cells. For instance, the stimulation of autophagy increased the reproduction of oncolytic Adenoviruses and NDV. Autophagy also increased the effectiveness of tumor destruction by oncolysis, autophagic cell death, and immunogenic cell death (12).

OVs are capable of targeting specific genes

OVs employ gene targeting as a significant antitumor mechanism. For example, reoviruses capitalize on specific cellular characteristics that are frequently altered in cancer cells. The signaling of specific proteins, including TP53, PTEN, RB1, and RAS, is modulated in tumor cells, resulting in the activation of tumorigenesis, angiogenesis, invasion, and metastasis, as well as the inhibition of apoptosis (12). This is achieved by the activation of oncogenes and the inactivation of tumor suppressor genes. OVs modulate a variety of signaling pathways in tumor cells by targeting these signaling cascades. The action of reoviruses on tumor cell cultures has been investigated, and viral selective replication steps within the tumor cells have been identified. After reovirus infection, the Ras mutation can facilitate reovirus entry and oncogenic transformation, increase the production of OVs, induce apoptosis, and prevent interferon production, thereby facilitating the virus's dissemination as a result of a defective antiviral response. Reovirus enters cells by binding to particular receptors on the cell surface (13). The virus's capacity to enter and infect cancer cells may be enhanced by alterations in the expression or accessibility of these receptors. Oncolytic VVs and VSVs selectively infect tumor cells and induce endothelium death by exploiting the overexpression of ras/mitogen-activated protein kinase (MAPK). Some viruses, like reovirus, have an inherent inclination towards tumor cells, whereas other viruses, such as Ads, VSVs, and HSVs, need to be modified to specifically target tumor cells (14). Healthy cells that are infected with OVs prevent the spread of the virus via several mechanisms that are often lacking in tumor cells. The antiviral capability of a cell, which is connected with type I interferon, is linked to the preference of a vesicular stomatitis virus (VSV) for cancer cells. Typically, normal cells generate type I interferons (IFNs) to hinder viral replication. However, most tumor cells have impaired type I IFN production, making them susceptible to VSV infection (15).

Changing and interrupting the vascular environment at the tumour

Tumor angiogenesis is influenced by the expression of proteins regulated by oncogenes and by factors that cause cellular circumstances, such as low pH, hypoxia, nutritional shortage, or the production of reactive oxygen species (ROS). The antiangiogenic methods of OVs are as outlined below: (i) The tumor cells are directly infected and the newly formed blood vessels are destroyed; (ii) The immune response is activated by the OVs, causing cells to clump together and slowing down blood flow; (iii) The viral proteins produced by the OVs prevent the production of factors that promote the growth of blood vessels in the tumor. Direct antivascular characteristics are a common characteristic of several Ovs (16). OBP-301, an adenovirus engineered with human telomerase reverse transcriptase components that regulate E1 gene expression, was developed to generate IFN-gamma, a cytokine with antiangiogenic properties. This cytokine selectively destroys cancer cells in murine colon cancers in syngeneic animals. Viral Stomatitis Virions (VSVs) induce coagulation and provoke an inflammatory response inside the circulatory system (17). The infection with VV leads to the disruption of the EGFR/Ras signaling pathways, causing vascular leakage and collapse. The OV iNDV3a-LP improves the destruction of endothelial cells. Systems using Armed VV-, HSV-, MV-, and Ad-based approaches regulate the amounts of endostatin and angiostatin, leading to the collapse of blood vessels. Furthermore, the interaction between VEGF and antiangiogenic proteins may lead to the downregulation of VEGF. This downregulation then causes damage to newly formed blood vessels in the TME, eventually resulting in the destruction of cancer cells (oncolysis) (18, 19).

Methods of transporting OVs

Direct deliver

Intratumoral administration

The intratumoral method is often used to administer OVs in clinical studies. Multiple experiments have shown the efficacy of delivering drugs directly into tumors and have investigated its potential to

maintain sufficient levels of OVs by bypassing the bloodstream. The local method of administering the medication directly into the affected area helps to reduce the deactivation of the virus. The limited engagement of the innate immune system with the virus minimizes the chances of systemic toxicity and transmission of the targeted viral load during a distinct injection method (20). The drawbacks of this approach are the inability to reach a therapeutic level in the tumor because of a thick extracellular matrix (ECM) and the insufficient delivery of the treatment inside the tumor due to the formation of new blood vessels (neoangiogenesis). Systemic reactions may be triggered by the intratumoral administration of OVs. Tumor antigens are produced as a result of the interaction between OVs and tumor cells. Research on the use of T-VEC has shown a reduction in the dimensions of the examined melanoma growths, including those that were directly treated with the injection and those that were not (21).

Intravenous administration

Intravenous administration offers advantages for treating malignancies at the metastatic stage, particularly when there is a need to target several tumors of varying sizes and locations. It is also beneficial in situations when intratumoral administration is not possible due to the tumor's position. This delivery method may effectively enhance the dispersion of OVs throughout the tumor mass. However, the precise dosage of OVs that yields the best results is yet unknown (22). Certain OVs can elicit a heightened immunological response when given intravenously. The immune system employs many techniques to impede the effective dissemination of OVs to their intended target tissues. OVs can bind indiscriminately to serum proteins or circulating cells in the bloodstream, leading to their ultimate death. Since these processes are components of the innate immune system, they are also efficient in individuals who have not been exposed to a specific virus (21, 22). Additionally, a previous exposure may lead to substantial elimination of the virus due to the existence of a specific and robust immune response. Antibodies may be removed by either complement action or destruction by macrophages in various organs when they attach to virus particles. The liver, spleen, and lungs are the primary organs responsible for the neutralization of OVs. The tumor ECM and interstitial fluid pressure provide additional challenges to the successful intravenous delivery of OVs. The high interstitial fluid pressure restricts entry into the core of the tumor, where it is at its maximum due to the fluid flow around its edges. However, it also hinders the movement of big molecules (23, 24).

Transporting Ovs systemically via cargo

There have been several diverse investigations conducted on the subject of OV cargo delivery to tumors, which may be categorized into biological and nonbiological delivery methods. Biological carriers for oncolytic viruses (OVs) comprise cellular carriers, carriers mediated by cell membranes, and carriers mediated by serum albumin. Nonbiological vehicles for OVs contain mineralized nanostructures, magnetic nanostructures, and polymer-based nanocarriers (25).

Biological carriers of oncolytic viruses

Cellular Vectors

Mesenchymal stem cells (MSCs) have garnered growing interest in scientific research due to their unique biological characteristics, broad therapeutic potential, and influence on tissue engineering. MSCs demonstrate this ability by transforming into osteogenic, adipogenic, or chondrogenic tissues and possess an extensive network for secreting various mediators, cytokines, and signaling molecules. Furthermore, they possess notable characteristics of self-renewal and multipotency. This secretion modulates the inflammatory response and regulates essential infiltration processes necessary for tissue regeneration and repair (26). The regulation of MSCs is influenced by feedback mechanisms occurring inside the axis formed by the MSC molecule and the target cell. MSCs cannot exhibit costimulatory molecules, resulting in reduced immunological activity. This makes them suitable for use in cell-based immunotherapy for malignancies. MSCs may enhance the in vitro multiplication of oAds, promoting the transport and long-term survival of viruses by inhibiting immune responses specific to the virus in a rat model. In addition, as compared to viral injection alone in living organisms, CR-MSCs have the potential to reduce the production of IFN by activated T cells, resulting in a larger enhancement of both the dispersion and survival of oAds (27).

When mesenchymal stem cells (MSCs) infected with oAds were given to mice with hepatocellular carcinoma, the virus particles built up in the tumor and effectively stopped its growth. A further research study used human MSCs to carry a replicative Ad. This Ad had an E1A gene that was driven by the alpha-fetoprotein promoter. The study demonstrated significant inhibition of growth in both orthotopic and subcutaneous hepatic xenograft cancer mouse models. After being administered systemically, MSCs that were infected with an oncolytic adenovirus (oAd) showed therapeutic effects in mice with lung and breast cancers that were implanted in their natural locations. These effects resulted in an improvement in survival rates (28). Systemic administration of human MSCs modified with replicating viruses,

namely Ad5/3.CXCR4 and Ad5R6D. CXCR4 Ads, in experimental models of metastatic breast cancer, resulted in improved animal survival. Administration of MSCs that were infected with a HER2-retargeted oncolytic HSV resulted in the dissemination of the virus to breast and ovarian cancer cells in laboratory models. This was followed by a decrease in the spread of cancer cells to the lungs and brain. Investigation on SKOV3ip. An ovarian tumor xenograft study shown that intraperitoneal administration of MSCs laden with oncolytic MeVs in SKOV3ip resulted in positive outcomes. A single ovarian tumor xenograft can infiltrate tumor lesions and subsequently transmit viral infection in mice, resulting in an overall increase in the average lifetime. The use of CRAd5/F11 chimeric oAds specifically targeting MSCs resulted in a considerable suppression of colorectal cancer cell proliferation (29).

Extracellular vesicles (EVs)

Extracellular vesicles are membranous vesicles that are secreted by different cell types and play a role in intracellular communication by transporting lipids, proteins, RNA, DNA, and carbohydrates. These vesicles are categorized based on their size as exosomes, microvesicles, apoptotic bodies, and oncosomes (30). They are often used for transporting antineoplastic medications, such as oncolytic viruses (OVs). Garofalo et al. found that the combination of Ad5D24-CpG and PTX enclosed in extracellular vesicles (EVs) caused inflammation around the tumor, leading to improved effectiveness and toxicity against lung cancer cells both in laboratory settings and in living organisms. Exosomes originating from tumor cells often exhibit immunosuppressive properties. However, exosomes obtained from tumor cells infected with oncolytic viruses (OVs) may possess immunostimulatory properties. Labani-Motlagh et al. demonstrated that melanoma cells, when infected with oncolytic viruses (OVs) that were equipped with CD40 (CD40L) and 4-1BB (4-1BBL) ligands, resulted in increased activation of dendritic cells (DCs) and improved responses in the tumor microenvironment (TME) (31). Ovarian cancers may include exosomes, which can preferentially aggregate in tumors and exert anticancer effects either locally or in distant malignancies. The adenoviruses were specifically engineered to carry immunostimulatory transgenes and were intended to be loaded for therapeutic purposes. The tumor cells infected with LOAd carry the transgenes, which are enclosed inside the endosomal compartments and then released as exosomes. Furthermore, the levels of mRNA were notably elevated in exosomes obtained from cells infected with both LOAd700 and LOAd703 (32). It was noted that every infected cell can produce the transgenes, regardless of whether the virus exclusively replicates in tumor cells. The immature dendritic cells (DCs) were then infected with the LOAd viruses and then stimulated in a laboratory setting using exosomes. OVs arm the exosomes formed from arm tumors with immunostimulatory transgenes, which may contribute to the mechanism behind the ability of local therapy to induce systemic immunity. Furthermore, it was shown that the transportation of microRNA (miRNA) into exosomes is modified in cells that are infected (33).

Delivery of OVs throughout the body via inorganic vehicles

Several different kinds of nanoparticles (NPs), including liposomes, dendrimers, gold nanoparticles, silica nanoparticles, and iron oxide nanoparticles, may be connected to OVs. There are two approaches for the transportation of OVs employing NP carriers. The first approach involves the use of shielding and surface modification techniques, while the second approach focuses on the combined treatment of OV-NPs. There are two methods for transporting NPs to the tumor location, namely active and passive processes (34). The passive process involves the enhancement of tumor blood vessel permeability via the EPR effect, resulting in the concentration of NPs in the tumor area. Active delivery refers to the specific attachment of NPs to target cells, to raise the concentration of the therapeutic drug in cancerous tumors while minimizing adverse effects. Peptides, proteins, aptamers, and polysaccharides are examples of biological ligands that can bind specifically and with high affinity to molecules or receptors found in tumor cells (35).

Advancements in combination therapy and the drawbacks of single therapy

While several tumor-selective pathways have been shown for OVs in both preclinical and clinical settings, their effectiveness was restricted when used as standalone treatments. There are several possible explanations for the limited effectiveness of systemic OV monotherapy. Initially, the presence of antiviral antibodies, whether from therapy or preexisting, may impede the replication and destruction of tumors by OVs. Additionally, antiviral resistance mechanisms, including complement activation, antiviral cytokines, and macrophages, may facilitate the rapid elimination of Ovs (36). The presence of antiviral immunities may provide a significant obstacle for OVs. However, the impact of antiviral immunity is not well understood, and the use of intratumoral OV treatment may potentially overcome this challenge by exerting local and abscopal effects. Remarkably, preexisting immunity to NDV restricts its ability to reproduce in tumors. However, this does not hinder tumor elimination, abscopal antitumor

immune responses, or survival. These outcomes are enhanced in mice that have been inoculated with NDV and received repeated therapeutic doses (37). These findings provide a clinical justification for the use of repeated dose treatment. Furthermore, the presence of the extracellular matrix, fibrosis, necrosis, and interstitial hydrostatic pressure may create a formidable physical obstacle that prevents OVs from accessing cellular receptors located in tight junctions. This difficulty has garnered significant interest among researchers who are seeking ways to overcome it (38). Furthermore, the expression or manipulation of transgenes to achieve tumor selectivity might result in a decline in viral fitness, leading to a decrease in replication capability and oncolytic effectiveness. Furthermore, the activation of transgenes might trigger the elimination of OVs due to a significant immunological response, hence facilitating ongoing refinement and modification of transgenes. Due to the limited effectiveness of using a single drug, research has mostly concentrated on choosing both a virus and a combo partner (38).

Therefore, the use of combination treatment with OVs has become a compelling choice. Moreover, the processes of OVs are fundamentally unlike those of other anticancer therapies, and the toxicity profiles often do not coincide with those of other treatments (39). Additionally, OVs may be injected many times if necessary. OVs possess characteristics that make them a logical choice for stimulating individualized immune responses and integrating them with various other treatment approaches, such as chemotherapies, radiotherapy, targeted therapies, and immunotherapies like immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T-cell therapies, and adoptive T-cell therapies. When evaluating the advantages of combining the OV with another agent, it is important to consider various factors. These factors include comprehending the inherent lytic and immune-modulatory properties of the virus, as well as considering the site of action, duration of therapy required, and cost of goods. Multiple studies have examined the combined effects of OVs with chemotherapy or radiation to assess their synergistic impact (40).

A recent review provided a summary of the important molecules involved in signaling pathways that are relevant to the study, such as EGFR-KRAS (specifically KRASG12C), PI3K-AKT-mTOR, ERK-MEK, JAK-STAT, p53, PD-1-PD-L1, and epigenetic or immune pathways (including histone deacetylases, cGAS-STING). These pathways are currently being investigated and have the potential to be combined with OV (41). Conversely, the activation of a widespread immune response by OVs to convert non-responsive cancers into responsive tumors might enhance the effectiveness of immunotherapy methods like immune checkpoint inhibitors (ICIs). Genetically modifying OVs and combining them with CAR-T-cell treatment may effectively enhance the ability of CAR-T cells to identify and infiltrate tumors. These combinations have the potential to effectively address the weaknesses of each component, hence improving the overall output (42).

The most sophisticated combination treatment protocols now being used in medical practice use ICIs, and early evidence indicates promising results. The progress in the discovery of ICIs has revolutionized the landscape of contemporary cancer therapy. OV infection may result in the increased expression of immune cells and immunological checkpoint markers inside the TME (43). Liu et al. equipped OVV with IL-2 to efficiently alter the cancer-immune equilibrium, and when combined with an anti-PD-1/PD-L1 antibody, it successfully eradicated the majority of advanced tumors in mice (43). Bo et al. discovered that oncolytic HSV2 increases the expression of PD-L1 in the TME (44). Furthermore, it has been shown that OVs may increase the expression of immunological checkpoint molecules largely found on natural killer (NK) cells, in addition to those produced on T cells and tumor cells. According to Wang et al., they found that oncolytic HSV2 increases the expression of NKG2A in NK cells. They also discovered that using anti-NKG2A antibodies enhances the anticancer effects of UV light-inactivated oHSV2-stimulated NK92 cells, both in laboratory tests (in vitro) and in living organisms (in vivo) (45). Nakao et al. discovered that the intratumoral production of IL-7 and IL-12, facilitated by an oncolytic virus, enhances the body's response to immune checkpoint suppression, hence increasing systemic sensitivity. Increasing the expression of immune checkpoint molecules may provide potential targets for combining with immune checkpoint drugs in clinical trials (45). Extensive phase III studies have shown that oncolytic viruses have a significant role in both destroying cancer cells and inducing beneficial changes in the tumor immune microenvironment. "Priming" by viral infection may transform the "cold" TME into a "hot" one, characterized by the presence of many immune cells and cytokines. This sets the stage for the effective delivery of future ICI treatment. The quantity of clinical studies investigating the combination of OVs with ICIs is steadily increasing. Initial findings from these trials indicate encouraging therapeutic possibilities with favorable safety profiles (46).

T-VEC is at the forefront of this very promising combo immunotherapy. The phase Ib stage of the MASTERKEY-265 trial demonstrated encouraging tumor responses when T-VEC was combined with pembrolizumab. Additionally, a phase 1b clinical trial demonstrated a confirmed objective response rate of

62%, with a complete response rate of 33% when using the combination of T-VEC and pembrolizumab. This indicates that T-VEC has an effect on the infiltration of cytotoxic T-cells and improves the effectiveness of ICI therapy by modifying the TME (47). Sun et al. conducted a review of a case series and found that the combination of T-VEC with ICIs (including pembrolizumab, ipilimumab/nivolumab, or nivolumab) resulted in an overall response rate of 90% for the treatment of unresectable stage III-IV melanoma (48). This indicates that the combination therapy may have synergistic effects and be beneficial for patients. ONCOS-102, a kind of Ad5 virus that has been equipped with GM-CSF, has shown encouraging results in fighting tumors when used along with pembrolizumab in patients with advanced or inoperable melanoma (48).

Challenges associated with oncolytic virotherapy

Similar to other contemporary cancer treatments, oncolytic virotherapy also faces several problems and barriers on its path to becoming an effective anticancer therapy. The limitation of OV functions can be attributed to several key factors. Firstly, the presence of unknown host antiviral pathways restricts the activity and spread of OV in the tumor bed. Secondly, intrinsic physical barriers in the tumor bed hinder the access of OV. Lastly, adaptive immune responses indirectly limit the viral function (4). Moreover, there are supplementary considerations that must be taken into account:

1.Best choice of an OV candidate: So far, many DNA and RNA viruses have been investigated as possibilities for OVs. To be considered an ideal candidate, the selected virus must possess several key characteristics (45). These include the capacity to stably incorporate transgenes, minimal or no toxicity towards normal cells and tissues, low immunogenicity, the ability to be amplified on a large scale for clinical use, optimization of production, and appropriate therapeutic targets for the chosen Ovs (49).

2.Process of viral entrance, infection, and dissemination: OVs that rely on certain cell surface receptors for attachment and entry are often ineffective against cancers that have diminished or absent expression of such receptors. While engineering has successfully addressed this obstacle for some viruses, a small number of viruses (such as poxviruses) may bypass this problem by attaching to non-specific factors like widely distributed cell surface glycosaminoglycans (50). At the cellular level, there are intricate signaling channels that are connected, either directly or indirectly, to the antiviral pathways. These pathways often hinder the reproduction and transmission of viruses to new cells. AKT activation levels directly control the replication of MYXV in human cancer cells. Excessive ECM in the tumor bed hinders the propagation of viruses. For instance, the presence of fibrillar collagen in the ECM restricts the spread of oncolytic HSV inside tumors (50).

3.Delivery: Delivery of OV to both the main and metastatic locations is crucial for achieving the best treatment results. Regarding this matter, since only a small portion of human malignancies may be effectively treated by directly injecting the virus into the tumor, systemic delivery is the preferable method over intratumoral (IT) injection (45). Nevertheless, several obstacles impede the effective implementation of any OV. Neutralizing antiviral antibodies, complement activation, generation of antiviral cytokines, and the liver and spleen's natural clearance site for OVs all provide significant challenges for the systemic distribution of OVs. While IT delivery of viruses may overcome some obstacles, the dissemination of viruses can be restricted by tumor beds, and the tumor vasculature also poses limitations for IT and metastatic locations. An effective approach to address these problems is to use migrating leukocytes as carrier cells to transport the virus into tumor beds that permit cellular entry (51).

4.Antibodies that neutralize viruses and cytokines that combat viral infections: The primary challenge in delivering free virus systemically to the tumor site is the presence of preexisting neutralizing antiviral antibodies (48). In addition, the immune system of the host triggers antiviral immunity and restricts the oncolytic action of oncolytic viruses. The cellular receptor molecules responsible for detecting virus particles and virus-infected cells initiate type I IFN signaling pathways, which in turn activate antiviral defense pathways in uninfected cells. This process helps to restrict the infection and spread of the virus. Furthermore, the immune system's ability to eliminate infected cells, including cancer cells, not only stops the transmission of the virus but also plays a crucial role in triggering anti-tumor immune responses (52).

5.Immunosuppressive tumor microenvironment: Another obstacle to OV treatment is the common occurrence of a highly immunosuppressive TME. Within the area where the tumor is located, many types of cells such as cancer cells, stromal cells, inhibitory cytokines (such as TGF-beta), and immune cells that invade the tumor (such as regulatory T cells and myeloid-derived suppressor cells) all have a role in creating an immunosuppressive tumor microenvironment. While it is crucial for the tumor to avoid the host's natural and acquired immune system defenses, OVs must nonetheless operate inside this immunosuppressive TME (52). In addition, some OV infections may enhance the immunosuppressive environment of the tumor bed by stimulating the immune system. As an example, the Maraba virus increased the activity of the PD-1/

PD-L1 pathway on both tumor cells and immune cells that had infiltrated the tumor. Likewise, the oncolytic NDV virus induced the development of PD-L1 at the tumor site via the activation of type I IFN signaling. This led to the creation of an immunosuppressive tumor microenvironment, even in tumors located far away (52).

Conclusions

Oncolytic viruses have emerged as a strategy to overcome the tumor's ability to evade the immune system. The goal is to enhance the clinical state of patients by either stimulating the host immune system or directly destroying aberrant cells. Advancements in genetic engineering have enabled the enhancement of OVs, resulting in improved safety and effectiveness. These advancements allow for the precise targeting of the virus to the tumor and a reduction in the negative side effects associated with its usage. Moreover, it is feasible to detect substantial impacts of the therapeutic use of OVs, whether used alone or in combination therapy, on the treatment of malignancies. Hence, enhancing anticancer treatments and subsequently enhancing patient prognosis via the integration of molecular biology, structural biology, immunology, genomics, and bioinformatics establishes a strong basis for the future clinical effectiveness of OVs.

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Authors's Contribution

Akram Sadat Ahmadi and Zahra Zand were involved in the conceptualization, design and writing of the manuscript draft. All authors read and confirmed the final manuscript.

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New Treatments for Management of Diabetic Foot Ulcers

Shadi Zekri[1]

[1]Department of Biology, Faculty of Basic Sciences, Sciences and Research Unit, aiaslamic Azad University, Tehran, Iran.

Corresponding Author's E-mail: Shadi1800@gmail.com.

Abstract

Diabetic foot ulcers (DFUs) are one of the more common problems linked with diabetes. DFUs are persistent wounds which frequently result in non-traumatic lower limb amputations owing to ongoing infection and other ulcer-related complications. Furthermore, these difficulties place a major fiscal strain on the healthcare system since costly medical procedures are necessary. Furthermore, the therapeutic therapies that are now accessible have only been fairly successful, indicating a significant need to discover innovative ways for the better treatment of DFUs. Hydrogels are 3-D structures made from natural and/or synthetic polymers. Because of their unusual adaptability, tunability, and hydrophilic qualities, these materials have received substantial research for a variety of medicinal applications, including drug delivery and tissue manipulation. As a result, this review article examines the most recent improvements in hydrogel wound dressings for successful DFU therapy, offering an overview of current viewpoints and problems throughout this study area.

Keywords: Hydrogel, Diabetic foot ulcers, Wound dressing, Diabetes mellitus.

Introduction

Diabetes mellitus (DM) is a long-term global pandemic illness. Based on statistics released by the American Diabetes Association (ADA) and epidemiological studies, the worldwide financial impact of diabetes will exceed $2.1 trillion by 2030, corresponding to 2.2% of global GDP (1). Diabetes may lead to serious impairment such as blindness, diabetic retinopathy, kidney failure in its final stages, and lower limb amputations. The psychological and physical consequences on sufferers are severe and hard to treat (2). Diabetic foot ulcers (DFUs) are a serious DM-related disease that is usually associated with greater mortality and premature mortality. It impacts about forty to sixty million diabetes individuals globally and is distinguished by the development of persistent sores caused by a combination of metabolic abnormalities, nerve injury, insufficient blood supply, and biomechanical alterations in the lower limbs (3). DFUs may ultimately result in persistent damage, infection, and, in the most severe case, lower limb amputation, which is predicted to happen every thirty seconds worldwide (4). At present, treatment options for DFU include debridement, pressure release ("off-loading"), antimicrobial agents, and revascularisation. Nevertheless, in many situations, conventional treatments fail to provide complete wound healing, emphasizing the need for creative options that stimulate tissue repair while avoiding wound-related problems (5).

In this regard, wound dressing technology has received increasing interest as a possible path for developing clinically successful DFU therapy. The optimum dressing for treating persistent wounds,

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including DFUs, must meet many fundamental necessities: (1) provide moisture that promotes tissue healing; (2) inhibit bacterial infiltration within the lesion; (3) have suitable porosity for gas exchange; (4) encourage cell movement, growth, and new blood vessels formation; and (5) be sterile, biocompatible, and easily replaced (or biodegradable). Hydrogels, which are polymeric three-dimensional (3D) substances, have shown promise for effective DFU dressing manufacturing. First, hydrogels are very biocompatible (6, 7). This enables them to imitate the normal ECM microenvironment and offer an optimal setting for cell growth. Second, hydrogels are very water-retentive and permeable. Because of the existence of crosslinked networks, hydrogels may have a water content of as high as 96%, allowing for environmental hydrating and keeping the wound wet (8). Furthermore, the presence of a hollow network architecture creates an optimal environment for gas exchange and nutrition transfer. Third, because of their distinctive structural features, hydrogels do not produce further mechanical harm. As a result, the primary goal of this study was to analyze recent breakthroughs in the production of hydrogel-based wound-dressing platforms, with an emphasis on manufacturing techniques and effectiveness in relation to DFU therapy (6, 8).

Wound healing processes in normal condition

Wound healing is a normal physiological response to tissue damage. Wound rehabilitation, on the other hand, is a complicated procedure involving different kinds of cells, cytokines, mediators, and the vascular system (9). The process of early vasoconstriction of blood arteries and accumulation of platelets is intended to halt bleeding. This happens followed by the entry of various inflammatory cell types, beginning with neutrophils. These inflammatory cells, in turn, produce several cytokines and mediators which encourage blood vessel development, thrombosis, and reepithelialization (10). Fibroblasts, in turn, lay down extracellular elements that will function as scaffolds. The inflammatory stage is marked by hemostasis, chemotaxis, and enhanced permeability of the vessels, which prevent further harm, close the wound, remove cellular debris and microorganisms, and promote cellular movement. The inflammatory stage normally lasts a few days. Granulation tissue, reepithelialization, and neovascularization are all hallmarks of the proliferative stage. This period might extend for many weeks. In the third stage, the wound reaches its maximum strength during the stages of maturation and regeneration (11, 12).

A summary of wound regeneration at DFUs

The immune cells, both innate and adaptive, that make up the skin's immune microenvironment are found throughout each layer of the epidermis and dermis. They communicate with tissue cells like fibroblasts, keratinocytes, and vascular endothelial cells to support tissue repair and immunological equilibrium (13). Emerging data points to the critical functions of immune system cells and the immunological milieu in the healing procedure and restoration. Immunomodulation is involved in all four conventional wound healing phases: hemostasis, inflammation, proliferation, and remodeling (14). DFUs are often associated with immunological disorders, as shown by the failure of macrophage phenotypic transitions under pathogenic circumstances. DFUs are linked with chronic and severe inflammation, an aberrant immunological environment, numerous infections, poor blood vessel development, and delayed re-epithelialization (15). DFUs are unable to reach their proliferative phase owing to several biological reasons. Improving the shift of diabetic wounds from the inflammatory to the proliferative phase is a possible method for expediting wound recovery (16). In addition, MMPs impede the activity of growth factors, reducing angiogenesis and tissue oxygenation, leaving a wound hypoxic and persistently open. As a result, exposed lesions are more susceptible to pathogenic diseases, which increase due to the reduced phagocytosis activity caused by hyperglycemia (17). The interaction of all of these variables leads to even more serious health consequences for the patient. To address this problem, tissue engineering methods have permitted the construction of hydrogel-based platforms which act as frameworks that facilitate appropriate cell communication and occupy the injured area with bioactive substances which encourage re-epithelialization, reduce inflammation, accelerate rehabilitation, and enhance the development of scars (18).

Management of DFUs with hydrogel-based wound dressings

Although various kinds of dressings, such as hydrocolloids, foams, and alginates, are currently accessible for DFU administration, novel dressings that satisfy the stringent demands for proper wound debridement, appropriate systemic therapy with antibiotics, and regular replacement of dressings and wound examination are highly sought after (19). Hydrogels are very interesting options for the management of DFU because of their distinctive characteristics that promote wound regeneration. Multiple factors influence how hydrogels handle DFU. To begin, hydrogels' a great deal of water aids in the maintenance of a moist wound circumstances, which is required for effective wound recovery (20). The abundance of water in the hydrogel allows the

interchange of nutrients as well as oxygen among the wound bed and the tissues that surround it, resulting in a condition critical for cellular metabolism, tissue reconstruction, and the recovery process. Second, hydrogels are capable of absorbing and holding wound fluid, which helps to prevent inflammation and bacterial development (19). The absorption of fluid prevents the wound from developing a crust or scab, which may hinder recovery and raise the chance of infection. One of the primary benefits of hydrogels for DFU therapy is their capacity to discharge bioactive molecules including growth factors, which promote wound reconstruction, and cytokines and antimicrobial substances, which enable the movement of cells and avoid infection (21). Hydrogels, in especially, may be used as medication delivery vehicles, permitting the regulated and long-term discharge of bioactive substances at the site of injury. A new study found that a hyaluronic acid-based hydrogel filled with basic fibroblast growth factor (bFGF) hastened wound healing and improved revascularization in a DFU rat model. Furthermore, certain hydrogels contain inherent antibacterial properties that may help eliminate infections and enhance wound rehabilitation. In recent years, a chitosan-based hydrogel demonstrated remarkable antibacterial action on *Staphylococcus aureus* and *Escherichia coli* and hastened wound regeneration in a diabetic rat model (22, 23).

Natural hydrogels for diabetic wound management

Collagen based hydrogels

DM is a serious issue with DFU and the most prevalent DM consequence. A number of creative methods has been extensively created to address this crucial problem, including collagen, which is believed to be the most (24). Collagen (Col) polymer has been identified as the most attractive choice due to its capacity to swell in water, mechanical qualities, and gelling capability. Col may be obtained from a variety of sources, however animal collagen is now the most common source of col products, with the majority of them made from raw materials including cow products. Most col compounds are manufactured from bovine and porcine skin and many components (25). A hydrogel is made of water, which promotes diffusion of medication and preserves hemostasis. Collagen type I (Col-I) is believed to be necessary for attracting growth factors to the damaged area and initiating wound recovery and tissue repair. Nevertheless, in the chronic foot ulcer scenario, the epidermis is ruptured, causing the breakdown of the extracellular matrix and cellular structure damage, which results in Col-I insufficiency (26). Furthermore, it inhibits the normal growth and expansion of fibroblasts to the wound region, thereby slowing down the recovery process. Col is a biocompatible structural protein, with less immunogenicity, biodegradable, and biomimetic, which makes it an ideal source of biological materials for tissue engineering and regenerative medicine (24). The composition and functionality of the collagen fibres influence the cellular response that is commonly regulated by integrin. This phenomenon is achieved by a biological process that is known as fibrillogenesis. Fibrillogenesis is a process of col network formation and interaction within the cellular level to form a higher-order three-dimensional structure. Furthermore, its function in MMP inactivation assists in retaining favorable metabolic equilibrium and humidity levels in the damaged area (27, 28).

For example, Lei et al. investigated the efficacy of collagen hydrogels to stimulate revascularization and wound repair in diabetic rodent models. To do this, deep injuries were created and treated externally using a collagen hydrogel containing recombinant human epidermal growth factors. Following fourteen days of therapy, rats administered with the created hydrogel had considerably lower wound regions, suggesting quicker damage repair, when compared to the group that wasn't given hydrogel therapy (29). In terms of blood vessel development, the suggested hydrogel treatment promoted both endogenous collagen production and the creation of vascularized scar tissue. In addition, Munish and colleagues conducted a comparative case-control research and found that using a collagen-based covering greatly improved wound recovery (30). The treatment's efficacy was assessed in a trial of twenty-five individuals who had persistent DFU. The wound location was effectively assessed weekly during the initial week of therapy to the 12th week. During the first week of examination, two participants were entirely repaired, while 12 exhibited a considerable decrease in lesion diameter. In addition, the 12-week examination revealed that 21 patients recovered and four had ulcer decrease. Since collagen biological substances are slowly decomposed, it may operate as a temporary bio-template for cell adhesion, migration, and development, as well as fast wound development (31).

Chitosan-based hydrogels

Chitosan (Ch) is a flexible hydrophilic and cationic natural polymer that is neither poisonous, carcinogenic, or immune-stimulating. It consists of β-(1-4)-linked D-glucosamine and N-acetyl-D-glucosamine molecules. It is referred to as water-soluble chitin and is derived from chitin by alkaline deacetylation (32). Chitin is composed of unbranched chains of β-(1-4)-2-acetamido-2-acetamido-2-deoxy-D-glucose. Chitin occurs naturally in mushrooms, green algae, and various microbes, including yeast and fungus. In addition, it originates from

invertebrates including crab shells and insect cuticles (33). Ch's solubility, appearance, and rheological characteristics are all determined by its molecular mass and quantity of acetylation. Crossover, graft co-polymerization, carboxymethylation, etherification, and esterification should be emphasized as the key ways for functionalizing the Ch framework among particular chemical procedures in order to boost their possibilities (34). In general, Ch has shown promise in pharmaceutical fields, notably as carriers of drugs with specific wound treatment uses, such as DFUs. In this regard, Ch has just been demonstrated to be a desirable component for the production of hydrogels using additive manufacturing methods for creating porous three-dimensional scaffolds with precise forms and biological action for the effective regeneration of complicated structures (35).

Xue and colleagues developed Ch-Matrigel-polyacrylamide hydrogels to aid in the recovery of injuries and reconstruction of the skin. These hydrogels have excellent porosity shape, with pore diameters ranging from 20-30 μm, that can keep humidity. This is beneficial for cell movement, adherence, and survival. These hydrogels demonstrated excellent mechanical characteristics, including high fracture strain, compression, tensile strength, and durability (36). Masood et al. developed a Ch-polyethylene glycol (PEG) hydrogel containing silver nanoparticles for diabetic wound treatment. The average size of particles was 99.1 ± 2.3 nm. The hydrogel had an acceptable porosity of 72.2%, which helped to rapid wound repair by suggesting adequate oxygen transmission and exudate absorption. Plain hydrogels have much higher swelling capabilities than nanoparticle-loaded hydrogels. In vitro investigations showed that the polyvinyl alcohol/chitosan/FEN (PCF) hydrogel is highly biocompatible and has considerable antibacterial, pro-angiogenic, ROS-scavenging, and anti-inflammatory capabilities (37). Further animal investigations revealed that the PCF hydrogel may enhance blood vessel development and the accumulation of collagen. The PCF hydrogel significantly reduced the amount of TNF-α and IL-6, indicating its anti-inflammatory action. These striking results highlight the PCF hydrogel's prospective applicability in the management of ulcers caused by diabetes (38).

Artificial and semi-synthetic hydrogel for management of DFUs

Bio-functionality and physical characteristics are also important factors in developing a viable hydrogel covering for DFU therapy. While natural hydrogels have excellent bio-features, their mechanical qualities and manufacturing dependability must be enhanced. Artificial polymers, on the other hand, are more versatile owing to their distinctive features, which may be precisely altered using specialized physical/chemical alteration techniques (39). More crucially, artificial polymers be manufactured on a large scale. Synthetic polymer-based hydrogels often have more uniform and homogenous architectures than natural polymer-based hydrogels, as well as higher water absorption effectiveness due to their highly patterned hydrophilic and hydrophobic domains (39).

Polyethylene Glycol (PEG)

PEG-based hydrogels are currently used to create biological structures owing to their high biocompatibility and tolerance to protein attachment. The incorporation of functional compounds leads to PEG derivatives including polyethylene glycol diacrylate (PEGDA) and polyethylene glycol dimethacrylate (PEGDM), which may also be chemically crosslinked to generate durable matrices which permit tethering or embedding of biomolecules and encourage appropriate healing of tissues (40). Discovering creative techniques to decrease toxicity and improve the biological capacity of PEG-based treatments is so critical. One viable technique is to cross-link PEG with Ch to generate hydrogels that can be loaded with silver nanoparticles (Ag-NPs), which have excellent antibacterial, antioxidant, anti-inflammatory, and anti-platelet capabilities (41). These enriched Ch-PEG hydrogels exhibited significant porosity and swelling, as well as enhanced antioxidant and antibacterial properties against *P. aeruginosa*, *E. coli*, and *S. aureus*. Furthermore, infused hydrogels helped diabetic rabbits repair their wounds faster. Wu et al. also mixed four-armed aldehyde-terminated PEG (4-arm PEG-CHO) with quaternized Ch to generate a hydrogel for the loading of deferoxamine (42).

Polylactic Acid (PLA)

PLA is an aliphatic polyester that may be readily produced in an environmentally friendly manner by condensing lactic acid and then polymerizing cyclic lactides. PLA's biocompatibility, biodegradability, and generally excellent mechanical qualities make it a promising material for medical use (43). Furthermore, it has been linked to increased cell proliferation and growth factor signaling owing to its intrinsic properties that resemble natural collagen fibers in the extracellular matrix. PLA's limited hydrophilicity limits its therapeutic usage, which may be overcome by mixing it with other substances or loading it with biological substances (44). Yu et al., for example, created porous PLA nanofiber membranes and then coated them with sulfated chitosan (SCS) and polydopamine-gentamicin (PDA-GS). The combination of SCS was utilized to increase the hydrophilic properties of PLA tiny fibers and promote M2 macrophage polarization,

whereas PDA and GS were employed to enhance anti-inflammatory and antimicrobial properties (45). In addition, Di Cristo et al. created co-electrospun fibers from PLA and PVP that contained quercetin (QUE), an active compound with potent anti-inflammatory, antioxidant, antibacterial, and wound rehabilitation effects. The produced fibers showed strong hydrophilic properties and a rapid onset of QUE, which was followed by a steady and consistent release for up to 120 hours (46). Furthermore, these nanofibers demonstrated significant antibiofilm activity against S. aureus and anti-inflammatory potential in PMA-differentiated THP-1 macrophages, making them promising options for the successful therapy of diabetic foot infections (46).

Zwitterionic gels

Other artificial substances receiving attention in the area of diabetic wound recovery are hydrogels made from zwitterionic monomers, which have the same negative and positive charges on the same molecule (47). Because of its tightly repeated and strong charge framework, zwitterionic substances have been demonstrated to be excellent in resisting non-specific protein adsorption. As a result, this conduct may help to reduce the inflammation that occurs in injuries by reducing foreign body responses (48). For instance, a single investigation identified through H&E staining that a zwitterionic hydrogel (poly(carboxy betaine methacrylate) (PCBMA)) inserted in mice possessed substantially fewer inflammatory cells than a non-zwitterionic hydrogel (poly(2-hydroxyethyl methacrylate) (PHEMA)), suggesting that a weaker inflammatory reaction could be caused by the capacity of zwitterionic to resist protein adsorption (49). Furthermore, zwitterionic hydrogels may be manufactured with a broad variety of viscoelastic properties and pharmaceutical release capabilities, demonstrating their applicability for external wound healing uses (50).

Additional polymer dressings

Films

Films are smooth, elastic constructions made of clear polymers. Films are frequently employed in wound restoration due to the following benefits: the film surface has tiny holes which enable the transfer of gases blocking bacterial attack; their translucency allows modifications to the wound to be noticed without no removing the clothing; and they are soft and well-fitted to the skin (51). Furthermore, film has an autonomous debridement function, that permits it to dissolve layers and necrotic tissues while treating DUs. Absorption is an important feature of wound dressings. Because the majority of films lack hydrophilic molecules or extremely tiny holes, they offer inadequate water absorption and are hence only suitable for use on moderately oozing lesions (52). Nevertheless, diabetic wounds involve significant harm and exudate. To better address the demands of DU therapy, scientists created nanofiber films that can be readily manipulated and have adjustable pore diameters (46).

Sponges

Sponges are materials having interconnecting porous structures that have been freeze-dried. As previously stated, the size and variety of holes are directly proportional to the capacity to absorb discharge, and sponges' interconnected pores offer the structural foundation for their high water absorption. Furthermore, the great porosity of sponges allows for appropriate oxygen supply, nutrition delivery, and cell growth at the wound site (53). Furthermore, sponges are lightweight and feel gentle on the skin. Because of these benefits, sponges are commonly employed in the treatment of moderate to heavy oozing injuries, such as DUs. Ch is the most often utilized carbohydrate in sponge manufacture (54). Within the several forms of polymers, the distinct cationic linear arrangement of CS, is a deacetylated version of chitin. As previously stated, chitosan's antimicrobial capacity and low immunogenicity meet the fundamental needs of a dressing, whereas its additional biological properties, including biocompatibility, ability to degrade, antioxidant properties, and in situ gelation, which lays the groundwork for its multiple uses when used in a dressing. Nevertheless, sponges' drawbacks, such as weak adhesion, limited mechanical strength, and inadequate antibacterial characteristics, restrict their practical use (55).

Foam dressings

They typically comprise hydrophilic polyurethane foam and are intended to absorb wound fluid while maintaining a wet wound area. Foam dressings may incorporate extra absorbent substances like viscose and acrylate fibers, superabsorbent polyacrylate particles, or silicone coating for non-traumatic disposal (56).

Challenges and conclusions

Hydrogel dressings have shown potential in the management of DFU owing to its capacity to maintain a wet wound environment, stimulate wound regeneration, and alleviate pain. Nevertheless, using hydrogel dressings for DFU therapy has various problems. Diversity in the structure and features of hydrogel dressings is one of the most significant issues (57). Hydrogel dressings may be created from a wide range of polymers, that have unique features like water absorption, biodegradability, and mechanical strength. The kind of polymer used may have a major

influence on the dressing's ability to promote wound recovery. In addition, the characteristics of hydrogel dressings might differ based on the production procedure, resulting in variable effectiveness. A further issue is the requirement for regular dressing changes (40). Hydrogel treatments are intended to provide wet injury circumstances, however, too much moisture may cause ulceration of the skin around them and slow healing. To avoid the wound bed from being overhydrated, hydrogel dressings must be replaced regularly. Individuals may find repeated removal of dressings irritating and raise their risk of infection (58).

Finally, hydrogels have shown considerable promise as a treatment for DFU. They offer a humid environment that aids in healing wounds and may be programmed to release a variety of bioactive substances that encourage the growth of new tissues. In addition, the hydrogels may adapt to the wound bed, creating an additional defense against further damage and bacterial infections. In the meantime, it is important to remember that specific patient features, like wound dimensions and seriousness, must be considered while selecting suitable wound dressings. Yet, much remains to be discovered about the unique features of hydrogels which make them good wound care products, but current study suggests that they are a potential alternative for DFU therapy. With future advances in material science and ongoing research, hydrogels have a chance to greatly enhance the standard of life for patients suffering from DFU.

Authors's Contribution

Shadi Zekri was involved in the conceptualization, design and writing of the manuscript draft. The author read and confirmed the final manuscript.

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Overview of CAR-T Cell Therapy Application in Cancer

Mahtab Dolatabadi[1,*], Shabnam Radbakhsh[2]

[1]Kamali Hospital, Alborz University of Medical Science, Anesthesiology Department.
[2]Department of Medical Biotechnology, School of Medicine Mashhad University of Medical Sciences, Mashhad, Iran.

Corresponding Author's E-mail: Mahtab.Dolatabadi@gmail.com.

Abstract

Genetically engineered T cells expressing chimeric antigen receptors (CARs) have shown notable therapeutic efficacy in persons with certain subtypes of B cell leukemia or lymphoma. Moreover, there is compelling evidence of their efficacy in individuals diagnosed with multiple myeloma. Nevertheless, several barriers impede the efficacy and widespread acceptance of CAR T cell treatment in these individuals, as well as in persons with other forms of cancer, particularly solid tumors. Significant challenges related to CAR T cells consist of severe toxicities, restricted capacity to travel to, infiltrate, and activate inside tumors, insufficient long-term persistence in the body, antigen evasion and variety, and issues in the manufacturing process. In order to expand the application of CAR T cells to a wider range of cancer types, it is crucial to enhance the designs of CARs beyond conventional structures. Investigators are using several engineering strategies to address the current challenges and improve the safety, efficacy, and user-friendliness of this therapy method. This paper presents an introduction to the CART cell, including its system of action, problems and limits, and its engineering.

Keywords: Solid Tumor, Chimeric antigen receptor, Immunotherapy, Adoptive-cell therapy.

An overview of CAR T cell treatments

Cancer has emerged as a prominent global cause of mortality, responsible for 21% of all fatalities. Annually, there are more than 16 million newly diagnosed cancer cases globally, resulting in over 9 million fatalities. Cancer immunotherapy is an innovative approach that is transforming the treatment of cancer. It utilizes your immune system to fight against cancer and leverages the potential of antibody-based treatment to achieve the same outcome (1). Despite the development of many treatments such as surgery, radiation, chemotherapy, and specific therapies, the outlook for patients with advanced and recurring cancers is still unsatisfactory. Cancer immunotherapy has provided optimism for individuals with cancer. Cancer immunotherapy offers a new and efficient approach to treating malignant tumors by stimulating the body's immune system. The primary objective of cancer immunotherapy is to stimulate the immune system and eradicate malignant cells. Hence, it offers enduring responses and the potential to develop enduring protection against relapses. Nevertheless, tumor cells have the ability to evade the immune system's reaction via many ways. The outcome is that the immune response of the body is unable to accurately identify and eliminate cancerous cells. In order to address this issue, it is necessary to

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intentionally alter the immune system (2, 3).

Over the last ten years, chimeric antigen receptor (CAR) T-cell treatment has accomplished extraordinary triumphs. While CAR T cell therapies show promising potential, they also pose hurdles due to the CAR structure, the physiology of antigen targeting, the risk of on-target off-tumor reaction, safety concerns, and the occurrence of severe side effects. Their future application focuses on selecting prospective inhibitors that may prevent the promotion of T cells in controlling brain tumors, managing toxicity that occur on-target but off-tumor, improving the safety of CARs, and studying the capacity of malignant cells to be depleted in CAR T cell therapy research models. This review presents an analysis of the efficacy of newly created chemicals in managing T cell therapy and investigates the structure of CAR T cells in relation to tumor management. Due to technological advancements, it is expected that conquering immunity and enhancing the efficacy of CAR T cell treatment would be achievable (4).

The United States Food and Drug Administration has granted approval for three CAR T cell treatments to treat certain forms of acute lymphoblastic leukemia and non-Hodgkin lymphomas. This signifies significant advancements in transforming the idea into practical medical therapy. CAR T cell therapies utilize redirected T cells to effectively kill tumor cells and their targeting of distinct tumor antigens and wide acceptance greatly enhance their versatile applications (5). Meanwhile, the maturation of cell technology makes progress in genetic modification for therapeutic purposes and decreases the obstacle in CAR optimization to enhance safety, primarily with attention on the cytokine release storm and on-target off-tumor toxicity observed in clinical practice. Furthermore, beyond the existing tumor-associated antigens, novel candidate targets are being exploited and explored to enlarge the CAR T cell therapeutic reagent spectrum. These advancements greatly broaden CAR T cell therapy application for hematological and non-hematological disorders (6). Since the approval of ipilimumab for use in the treatment of melanoma, more than 1,000 immuno-oncology drugs are currently undergoing evaluation, with high expectations for further expansion of the treatment field. At the same time, it has also led to a lack of scientific understanding and public confusion. Caring for patients with cancer requires an understanding of cancer immunotherapy and its use while trying to dissipate health literacy and ultimately impart a new and better understanding of the world of oncology and scientific research (6).

T-cell therapy is used to enhance the immune system's defense in order to treat some forms of cancer. More than six decades of research has been dedicated to studying the use of CAR T-cells, particularly in treatments aimed against non-solid organ cancers. Clinical studies that confirm the therapeutic efficacy of mast cells primarily target lymphomas, since these types of cancer are more vulnerable to cell-mediated destruction, as shown in TIL treatment for melanoma. For personalized treatment, the individual's own T-cells are collected and a chimeric antigen receptor is genetically modified into a lentivirus. Patients get high-dose chemotherapy to eliminate the residual bone marrow, enabling the modified T-cells to successfully establish themselves (7). Nevertheless, the significant toxic consequences, such as cytokine release syndrome, pulmonary edema, neurotoxicity, resistance, or impaired engraftment, persistently limit its effectiveness in patient treatment. To fully harness the potential of cell-based therapeutic strategy, it is necessary to acquire a more profound and enhanced comprehension of the methodologies and instruments used in CAR T-cell treatment (5, 7). Chimeric antigen receptor T cell therapy is a kind of cancer treatment that utilizes the immune system. Oncology clinics use this technique to identify and eliminate cancer cells by guiding a patient's genetically modified T-cells to specifically attack and eradicate the cancerous cells. The technique is significant due to its capacity to prevent the return of cancer, especially in individuals with tumors that are resistant to traditional treatment methods. Nevertheless, CAR T-cell treatment encounters a multitude of obstacles and restrictions that diminish its effectiveness in the field of clinical cancer (6). These issues include a variety of problems, including a lack of specificity in targeting tumors and the occurrence of harmful consequences, even in cells that are specifically targeted. This publication provides a comprehensive analysis of the tools, tactics, and expertise involved in the implementation of CAR T-cell therapy. It aims to provide a clearer understanding of the inherent constraints and difficulties in using CAR technology for cancer immunotherapy (8).

Immune cells play crucial roles in the body's ability to detect, control, and adapt to changes in the tumor, contributing in many ways to both the establishment and the restriction of cancer. The clinical research using this approach has led to unprecedented cures in patients with refractory and relapsed malignancies who failed traditional treatments and even allogeneic HSCT (hematopoietic stem cell transplant) rescue. The exciting action of the therapy is mainly based on antigens-specific targeting, activation, and continuous amplification, with genetic infections to the patient's T cells in vitro (9).

In recent times, because to the rapid progress in CAR T cell treatment, there has been a resurgence of interest in cancer immunosurveillance as a prominent field of study. The efficacy of cancer immunotherapy has significantly improved in the past few years, with

cellular immunotherapy seeing a rise with the advent of CAR T cells. CAR T cells, also known as gene-modified T cells, are a novel and very promising form of cancer immunotherapy. These cells are made up of an extracellular ligand binding domain, a hinge region, and a transcellular signal transduction domain (10). Once communicated, either the recipients or the allogenic HSCT donor T cells may be selectively activated against particular cell surface antigens. Ultimately, the activated T cells undergo rapid and uncontrolled division due to positive feedback immunological responses, specifically targeting the cancerous cells. Modified CAR T cells have been used in the treatment of both recipients and allogenic HSCT donors. Additionally, there have been documented cases of repeated infusions of MSCs-CAR T cells after allogenic HSCT. Refractory and relapsed cancers are successfully removed in over 80% of the treated patients, similar to the results shown in the clinical tests conducted on patients. They received authorization from the U.S. Food and Drug Administration (FDA) and later from the European Medicines Agency (EMA) for cancer immunotherapy.

The two adoptive cell therapies are CAR-T cell therapies-Chimeric Antigen Receptor T Cells (sometimes called designer T cells). The first two products are also the first two gene therapy products to gain market approval. When a T cell receives appropriate signals through the T-cell receptor (mainly from the peptide-MHC complex) and co-stimulatory receptors (mainly CD28 or 4-1BB), it triggers T-cell activation. The main purpose of CARs is to combine the ability of antibodies (binding to specific target proteins) with the signaling properties of T-cells (13). These CARs have three main parts: a domain which works as the scFv from an antibody binding to the antigens, and an extra-cellular hinge and stalk region (which joins the domains and charge molecules to help signal transduction). Some authors have reviewed the methods used to derive monoclonal antibodies binding to different TAAs (13).

The efficacy of CAR-engineered T cells in inducing durable remissions for individuals with recurrent or refractory B lymphoid tumors is now well recognized. Our primary objective is to analyze the specific attributes of CAR-T cells that continue to exist in patients who remain in remission for at least 6 months after injection (14). Considering the established long lifespan and efficacy of traditional immune-mediated therapies, such as T cells developing specificity to antigens showed by cancer cells during allogeneic stem cell transplant (alloSCT), we had high hopes that highly lasting CAR-T cell responses could be produced by increasing the abundance of CAR-T cells by a factor of 1000 through the elimination of inhibitory signaling in T cells. In this study, we show that functional CAR-T cells remain present in patients for up to 10 years of clinical follow-up, and even after illness resolution, they may be reactivated by exposure to antigens. Additionally, we observed that cellular transplant can extend the persistence of CAR-T cells by an additional year (14). CAR-engineered T cells have the ability to induce prolonged periods of disease absence in individuals with relapsed or refractory B cell malignancies. In light of the growing recognition of relapses that happen many months following cellular infusions, our objective was to determine if CAR-T cells may remain in patients who are still in remission more than 6 months after the infusion. Our study shows that CAR-T cells, which have been linked to long-lasting responses, remain present in the body for a minimum of 6 years after being infused, with a maximum follow-up period of 10 years. The efficacy of CAR-T cells is reduced comparing to the first period after infusion, however it may be restored with further exposure to antigens. CAR-T cells that react to the antigen may remain in the bloodstream for over ten years after the illness has been resolved (4, 15).

Summary of CAR-T Cell Therapy

CAR-T cell therapy is now recognized as a very attractive and innovative therapeutic approach for blood cancers. The method has seen significant success in achieving sustained remission rates in individuals who have extremely chemorefractory illness. The exceptional reactions are believed to be primarily attributed to the distinctive biology of the modified cells, characterized by the presence of distinct antigen receptors and their capacity to systematically eliminate cancerous cells. While the initial response rates of CAR-T cells may seem encouraging, the long-term effectiveness of these biologicals is generally limited by their intrinsic durability (16). The primary function of CAR-T cells is their capacity to undergo excessive proliferation upon binding to antigens, often resulting in cytokine release syndrome. Subsequently, more than 99% of the remaining cells are eliminated through a controlled and sequential process of T cell differentiation. The continued existence of CAR-T cells is contingent upon and seems to be directly related to the amount of antigens present. Therefore, in cases where the quantities of antigens are low, it is uncommon to see long-lasting responses, which is why a significant number of individuals have a recurrence following their first remission produced by CAR-T cell therapy (17).

There is a growing body of research suggesting that TAA-positive escape variants provide a major obstacle to the long-term survival and effectiveness of CAR-T cells. Following the first notable achievements

in using CAR-T cells in treating leukemia patients, other clinical studies are presently underway globally. Each research team employs distinct iterations of CAR-T cell treatment and evaluates diverse iterations of CAR-T cells for various blood malignancies and solid tumors. According to their findings, a considerable proportion of patients who were previously diagnosed with cancer had remission after receiving a simple infusion of reprogrammed T cells. Initial evidence suggests that CAR-T cell treatments have the potential to make a patient almost completely free of cancer for a prolonged period of time, namely up to 18 years. Nevertheless, a significant number of first recipients of CAR-T therapy have just recently undergone the treatment. CAR-T therapy, being a novel and groundbreaking approach, has the potential to save the lives of many individuals suffering from cancer. Consequently, our comprehension of the long-term consequences of CAR-T treatment remains incomplete. At now, CAR-T is the only category of immunotherapies that has been effectively reprogrammed, and there is a growing number of ongoing clinical studies for CAR-T treatment. We are still in the early phases of fully harnessing the promise of CAR-T cells for cancer treatment (19).

CAR-T cell therapy, or chimeric antigen receptor T cell treatment, involves the modification of a patient's T cells, a specific kind of immune system cell, to specifically target and eliminate cancerous cells. The foundation for this emerging science was established some years ago, and only recently have we been able to advance and evaluate CAR-T cell therapy for those with cancer via clinical studies. CAR-T treatment involves the initial extraction of T cells from a blood sample in a cancer patient, followed by the introduction of a chimeric antigen receptor (CAR) into these T cells (20). After being reprogrammed, the T cells, which now possess the CAR protein, undergo rapid multiplication, resulting in a significant increase in the number of T cells capable of destroying cancer cells. Once these reprogrammed T cells are collected, they are reintroduced into the person's body. Although these reprogrammed T cells, which are designed to destroy cancer cells, are crucial in eliminating the tumor's malignant cells, their indefinite survival after the tumor has been eradicated is not attributed to the CAR component of the CAR-T cells (21).

CAR-T cells are T cells obtained from the individual's body via a blood collection technique known as leukapheresis. Subsequently, cells are sent to the manufacturing facility and genetically altered by introducing a gene that codes for a chimeric antigen receptor. A chimeric antigen receptor (CAR) is an engineered T cell receptor that combines the advantageous features of both antibodies and T cell receptors. Simultaneously, the duration of the CAR's lifetime is extensive. Once the CAR is inserted, the T cell has the capacity to selectively identify and attach to antigens. This leads to the stimulation of T cells, allowing the cell to multiply and produce significant quantities of cytokines. Additionally, the T cell develops cytotoxic function. Various CAR-T cells often recognize distinct antigens. These T cells are specifically engineered to identify and bind to tumor antigens, leading to the destruction of tumor tissue by the T cells. Hence, this technique signifies a paradigm-shifting advancement in the realm of cancer therapy. Simultaneously, the remarkable sensitivity and specificity of CAR-T cells render them highly responsive to the quantity of tumor antigens (22).

Types of Immunotherapy

CARs, also known as CAR-T cells, are highly potent immune cells that possess the ability to identify and target particular tumor antigens, therefore significantly bolstering the immune response. These super T cells exhibit both innate immune killing capabilities via NK ligand production and increase the immune system's response by binding to costimulatory signals (20, 21). Furthermore, the extracellular domain of fourth-generation CARs was modified to create sub-regions that functioned as a bispecific T-cell engager (BiTE). This modification not only increased the cytotoxic activity but also prevented any adverse impacts on the whole system. Following the first clinical report of CAR-T cell therapy in chronic lymphoblastic leukemia in 2011, the Food and Drug Administration (FDA) has granted approval for Kymriah in 2017 and Yescarta and Breyanzi (JCAR017) in 2018. These approvals allow for the use of CD19 CAR-T cell therapy in the clinical treatment of B-cell malignancy. Despite significant advancements in the treatment of blood cancers, the use of CAR-T cells for solid tumors still faces significant challenges in clinical practice (23).

Immunotherapy may be categorized into many groups, such as cytokines, adoptive cell transfer, and monoclonal antibodies. Adoptive cell transfer may be categorized into three subtypes: tumor-infiltrating lymphocytes, TCR-T cell treatment, and chimeric antigen receptor CAR-T therapy. These subtypes have shown encouraging clinical outcomes (24). The concepts of these forms of cell treatment rely on manipulating the in vitro culture by using non-specific (gamma chain cytokine and OKT3) or antigen-specific anti-CD3 monoclonal antibodies (mAbs) to activate T cells, prompting a cytotoxic response. Meanwhile, same T cells were grown along with γ-retrovirally or lentivirally transduced cells that had been modified to incorporate genes encoding TCR or CAR (24).

The research and development of CAR T treatment

has been at the forefront for over three decades. The first iteration of CAR T cells may alone identify tumor-associated antigens (TAAs) in a way that is not reliant on major histocompatibility complex (MHC), thereby failing to produce the intended anti-tumor impact. The second generation of CAR T cells has an enhanced architecture that incorporates individual or multiple insertions of costimulatory molecules such as CD28, 4-1BB, OX40, ICOS, CD27, and CD40, among others. The second generation of CAR T cells has been extensively and effectively used in several clinical research, thanks to their ongoing improvement in functionality. Tisagenlecleucel, Axicabtagene ciloleucel, and Lisocabtagene maraleucel are commercially available treatments that have been used to treat CD19+ B lymphoblastic leukemia and lymphoma (25). The third generation of CAR T-cells typically incorporates two costimulatory domains, with many of the second costimulatory molecules containing a beneficial cytokine or signal target. This enhances their toxicity reactions to the receptor and reduces the rate at which targeted cells can evade the immune response. The third generation of CAR T-cells has the most potential to be the most effective option for CAR T therapy. Moreover, the fourth-generation CAR T-cells are often known as armored CAR T-cells. These cells include transgenic products that encode small interfering RNA (siRNA), chimeric cytokine receptors (CCRs), or cytokines that improve the function of T cells and/or antigen-presenting cells (APC) (26). This enhancement primarily operates by increasing the specificity, synthesis of cytokine levels, and promoting the altered homing potential. It also supports various cytocidal activities of polyfunctional CAR T-cell populations that are highly AMP. Additionally, it extends the proliferation, persistence, and overall quality of CAR T-cells. Only a limited number of clinical experiments have used the fourth CAR T lineage in medicinal applications. Furthermore, it implies that this therapy has the potential to provide improved safety and decrease the immunosuppressive environment caused by the tumor (26).

Mechanism of Action of CAR T Cells

The best-documented evidence of a CAR derived from T cell receptor (TCR)-α and -β chains is the CD8 molecule, which recognizes the class I MHC/antigen peptide complex (pMHC). CARs are synthesized from single-chain variable fragments (scFvs), made up of paired variable regions of the heavy and light chains (VH and VL, respectively) of a monoclonal antibody (27) connected with a short linker peptide (21). The extracellular ectodomain is typically synthesized by combining VH and VL by a flexible peptide linker of 10-20 amino acids; the transmembrane domain links the extracellular portion to the endodomain and is both required for correct positioning within the membrane lipid bilayer and signal transduction. The endodomain is the key molecular component where the signaling cascades are triggered following the engagement of the CAR with its antigen. In most cases (but not all), it contains variants of well-known intracellular signaling domains, such as the CD3-ζ subunit of the T cell receptor and one or more additional co-stimulating molecules, such as 4-1BB or other elements from the tumor necrosis factor receptor (TNFR) superfamily, such as CD28 (28). Collectively, the composition of the various functional antigen recognition units indicates that CAR function ultimately draws upon the signaling machinery of the TCR, which is required to also produce polyclonal activation in unresponsive T cells, while at the same time not being able to exhaust the cells. In this sense, the CAR is representative of active receptor engineering. The challenges in translating a substantial amount of progress from decades spent studying TCR signaling cascades, science and human therapeutics, into CAR T cells are newly brought to the fore. With CARs in numerous pipelines to treat cancer, immune and inflammatory disorders, integrating novel insights into their activity versus endogenous TCR could offer more focused and selective therapeutic strategies (29).

Recent advancements in the field of T cell engineering have successfully transformed alternative T cell immunotherapy into a viable treatment option for patients. The integration of TCR and gene-editing technologies has facilitated the fast progression of CAR T cells from theoretical validation to practical use in a few of years. Undoubtedly, the discovery of very precise tumor antigens, together with the use of T-cells produced from the patient's own body, makes CAR-based treatment a perfect subject for personalized medicine. Patients in dire need are prepared to give their permission to such experimental therapy (1). Hence, the quantity of medicinal goods now being development and undergoing evaluation in clinical trials is rapidly increasing. This exemplifies the capacity of research in this domain to be used in practical settings. The first clinical results documented so far are very promising for certain hematological cancers. Nevertheless, obstacles and restrictions might be encountered in both the pre-clinical research and clinical implementation of CAR T cells (30).

Cancer treatment has been a major health challenge for countless millennia, with only minor degrees of progress being made for the vast majority of human existence. However, thanks to intense research and perseverance, great strides in therapeutic development have been made over the last few hundred years. These treatments have focused on

the disease with the entire objective identification and eradication of abnormal tumor cells, and they have roused interest from the public, healthcare professionals, and regulatory, and funding agencies ever since (31). Individual therapeutic modalities are superior to others for certain cases, with some modalities assuming first-line treatments while others are used as adjuvant therapies or utilized when disease recurs. With its demonstrated antitumor potential, T-cell therapy offers an important tool for countering cancer aggressiveness while offering the possibility of reducing many of the long-term, late events associated with conventional cancer treatments currently in use. T cells can be engineered to express chimeric antigen receptor-modified autologous T cells that are seamlessly integrated into the clinical oncological portfolio. They more effectively target and lyse the cells of most hematological malignancies which express the target antigens at levels that are considered to be safe (32).

Novel therapies for non-Hodgkin's B-cell lymphoma have the potential to greatly enhance long-term results for patients, even those with unfavorable prognoses. Chimeric antigen receptor T-cell (CAR-T cell) therapy is revolutionizing the treatment approach for afflicted patients. Due to its exceptional ability to enhance a patient's immune response against cancer and exhibit strong T-cell killing mechanisms in the body, CAR-T cell therapy has been shown to greatly improve survival rates in hematological malignancies that express CD19, especially when traditional treatments are ineffective. However, like any novel areas of medicine, CAR-T cell treatment has certain hurdles that are directly linked to its commercialization and the progress of clinical-grade practice (33).

Obstacles and Constraints in CAR T Cell Therapy

Antigen evasion

An important challenge in CAR-T cell therapy is the development of tumor resistance to CAR designs that specifically target a single antigen. Although individual antigen-targeting CAR-T cells can at first offer impressive outcomes, a significant proportion of individuals who receive these cells experience either a complete or partial inhibition of target antigen expression in their cancerous cells. The phenomenon being referred to is known as antigen escape. For example, a significant number of patients with recurrent and/or persistent acute lymphoblastic leukemia (ALL) have shown long-lasting favorable responses to CAR-T cell treatment that targets CD19, ranging from 70-90%. However, current follow-up information suggests that a common mechanism of resistance to treatment is starting to emerge. During the return of the illness after therapy, 30-70% of individuals report a reduction or absence of the CD19 antigen. Moreover, a reduction or lack of BCMA production has been observed in those with multiple myeloma who are receiving therapy with BCM-targeted CAR-T cells. Similar patterns of resistance to antigen escape have been discovered in solid malignancies (13, 34). A concrete example is a research study on CAR-T cell therapy that specifically investigated the role of IL13Ra2 in treating glioblastoma. The study showed that there was a decrease in the expression of IL13Ra2 in tumor recurrences. In order to reduce the frequency of recurrence in CAR-T cell treatment for both hematologic malignancies and solid tumors, many strategies are now relying on the specific targeting of distinct antigens. These use either dual CAR constructs or tandem CARs, which are single CAR constructions containing two single-chain variable fragments (scFvs) to concurrently target multiple tumor proteins. From a clinical perspective, it seems that both of these techniques have the potential to achieve durable rates of remission. Ongoing clinical trials are investigating the efficacy of combining CD19 with either CD20 or CD22 (35). Initial results from clinical trials using dual-targeted CAR-T cells (targeting CD19/CD22 or CD19/BCMA) demonstrate promising results. Specifically, first results from trials using CD19/CD22 CAR-T cell therapy indicate promising efficacy in adult individuals diagnosed with acute lymphoblastic leukemia (ALL) and diffuse large B cell lymphoma. Furthermore, preliminary results on the use of BCMA/CD19 targeted CARs for the treatment of multiple myeloma demonstrate their significant efficacy and favorable safety profile. Early-stage models of solid cancers, including glioblastoma and breast cancer, have been used to study the effects of sequential CARs targeting HER2 and IL13Ra2 in glioblastoma and HER2 and MUC1 in breast cancer (36). Simultaneous targeting in both cases resulted in superior anti-tumor reactions in comparison to therapy that addressed just one factor. The study on glioblastoma showed that CARs targeting HER2 and IL13Ra2 had improved effectiveness in fighting tumors and decreased the ability of antigens to evade therapy. These results were better than those of two other therapies that targeted two other factors simultaneously. This study highlights the importance of selecting specific antigens that not only improve the body's response to tumors but also minimize the development of antigen avoidance processes, therefore preventing the recurrence of the illness (37).

On-target, off-tumor impacts

A challenge in addressing solid tumor antigens is that they are often expressed in normal tissues at varying amounts. Therefore, the meticulous selection of antigens is crucial in the development of chimeric antigen receptors (CARs), as it ensures both the efficacy of the treatment and the reduction

of potential toxicity that may arise when CARs target healthy cells. An effective strategy to tackle the problem of antigens appearing in both solid cancers and healthy tissue is to selectively target distinct alterations that are only prevalent in tumors. The alterations consist of truncated O-glycans, namely Tn (GalNAca1-O-Ser/Thr) and sialyl-Tn (STn) (NeuAca2–6-GalNAca1-O-Ser/Thr), which are prominently present in solid tumors (38). Four notable targets for CAR-T cell therapy have been investigated, such as TAG7228, B7-H3, MUC1, and MUC16. Although the first CAR-T cells that aimed at TAG72 in colorectal cancer did not elicit any anti-tumor reaction, scientists are now investigating novel versions of second-generation TAG72-CAR-T cells and other modifications that specifically target tumors after protein production. In order to broaden the clinical application of CAR-T cell therapies in both hematological malignancies and solid malignancies, it is crucial to continue creating novel methods that can reduce antigen evasion and select antigens that can effectively trigger an immune response against tumors, while minimizing concerns regarding toxicity (39, 40).

CAR-T cell transportation and tumor invasion

The efficacy of CAR-T cell treatment for solid cancers is impeded by the challenge of CAR-T cells in accessing and infiltrating solid tumors, in contrast to blood malignancies. The limited mobility and penetration of CAR-T cells inside tumors may be attributed to the immunosuppressive conditions and physical obstacles, like the tumor stroma, present in the tumor microenvironment (38). One method to enhance these constraints is by use alternative distribution channels, like local management, instead of systemic delivery. This approach has two benefits: firstly, it obviates the need for CAR-T cells to migrate to the sites of illness, and secondly, it diminishes the likelihood of on-target off-tumor effects. By precisely targeting the CAR-T cells' activity towards tumor cells, the impact on normal tissue is reduced. Preclinical research has shown that administering CAR-T cells, which specifically target HER2 and IL13Ra2, by intraventricular administration is a more potent approach for treating brain metastases of breast cancer and glioblastoma (41). Although targeted injection might appear to be more successful in principle, this approach is only appropriate for treating specific tumor disorders or oligometastatic disease. A novel strategy has been developed to significantly improve the mobility of CAR-T cells. This involves adding chemokine receptors onto the CAR-T cells that specifically recognize and respond to chemokines released by tumors (43). Latest study indicates that altering integrin αvβ6-CAR-T cells to exhibit CXCR2 or enhancing the expression of CXCR1 or CXCR2 in CAR-T cells both enhance cellular mobility and significantly enhance their efficacy in combating malignancies. The effectiveness of CAR-T cell therapy is impeded by physical barriers, like the tumor stroma, which restrict the penetration of the tumor. The stroma mostly comprises extracellular matrix, whereby heparin sulfate proteoglycan (HSPG) serves as the principal part that CAR-T cells must degrade in order to infiltrate the tumor (43).

CAR-T cell-related toxicity

Although the application of CAR-T cells has a chance to revolutionize cancer treatment, its widespread adoption as the major therapeutic choice has been impeded by a range of adverse effects, notably death. The architecture of the CAR, the specific goal, and the type of tumor are important factors that are likely to affect the frequency and extent of cytokine release syndrome (CRS), hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), and immune effector cell-associated neurotoxicity syndrome (ICANS) (44). Thus far, the adverse effects linked to CAR-T cell therapy have been extensively examined by individuals who have undergone the first FDA-approved CAR-T cell therapy, which is those with CD19-directed CARs. Among the most influential clinical trials, individuals have had serious and sometimes fatal consequences. When it comes to those with ALL/LBL who are receiving CAR-T cell treatment, almost all patients report minor toxicity signs. However, a considerable number of individuals (ranging from 23% to 46%) show significant overproduction of cytokines and large growth of T cells in their bodies (45). The overabundance of cytokines being released into the circulation and the ensuing stimulation of immune cells in some people result in a few detrimental consequences: CRS is defined by an overproduction of cytokines and a substantial increase in T cell growth inside the body. HLH and MAS are two severe conditions characterized by excessive inflammation. These conditions are characterized by the presence of CRS, elevated levels of serum ferritin and hemophagocytosis, kidney failure, elevated liver enzymes, enlarged spleen, fluid accumulation in the lungs, impaired natural killer (46) cell activity, and ICANS. ICANS is characterized by a high level of cytokines in the CSF fluid and impairment of the blood-brain barrier (47, 48).

CRS occurs as a result of the stimulation of CAR-T cells, which triggers the creation of significant amounts of cytokines. Mild CRS is characterized by clinical signs such as fever, lethargy, diarrhea, headache, rashes, arthralgia, and myalgia. Individuals with serious illnesses may exhibit symptoms such as low

blood pressure, heart disease, circulation problems, respiratory difficulties, renal impairment, multiple organ dysfunction, and possibly fatal outcomes. A substantial proportion of leukemia patients who received CAR-T cell treatment encountered CRS, with rates varying from seventy-s to ninety-three In the same way, individuals diagnosed with lymphoma who underwent CAR-T cell treatment had CRS rates ranging from 37% to 93%. Out of the patients who had tisagenlecleucel treatment for relapsed/refractory B-ALL, 46% of them suffered CRS of any severity. The incidence of severe CRS in patients with diffuse large B-cell lymphoma was 13-18% for axicabtagene ciloleucel and tisagenlecleucel, accordingly (49, 50). From a pathophysiological standpoint, it is widely believed that CRS is mostly induced by IL-6. Consequently, the treatment for CRS entails administering tocilizumab and corticosteroids, that inhibit the IL-6 receptor. Although tocilizumab, an FDA-approved drug for treating severe CRS, is used, serious CRS and fatality rates remain high. HLH/MAS after CAR-T cell therapy may exhibit resistance to IL-6 inhibition and might require chemotherapy as an alternative therapy (51).

The precise incidence of HLH/MAS after CAR-T cell therapy remains unknown because to the challenge of differentiating it from serious CRS. Nevertheless, CAR-T cell therapy has been recorded to occur in around 1% of patients. The exact origin and factors contributing to neurotoxicity are not well understood. The clinical manifestations of ICANS may exhibit variability and include disorientation, cephalalgia, cognitive impairment, aphasia, localized neurological deficits, or encephalopathy. In extreme instances, it might result in life-threatening cerebral edema, transient coma, or convulsions. Neurotoxicity often arises during CAR-T cell treatment, impacting approximately 67 percent of leukemia patients and 62% of lymphoma individuals (52). Corticosteroids are primarily used to treat neurotoxicity, since IL-6 inhibitors are often inefficient in treating neurotoxicity associated with CAR-T cell therapy. At present, there are no officially sanctioned medicines available to prevent the hazards stated before. Hence, it is essential to optimize CAR engineering and use additional strategies to mitigate the toxicities associated with CAR treatment. In this discussion, we explore the insights gained from constructing Chimeric Antigen Receptor (CAR) therapies with the aim of reducing toxicity, as well as other strategies to enhance the management of adverse reactions in CAR-T cell therapy (52).

Design and development of CAR-T cells

Modification of TCR-related elements

The entire effector actions and longevity of regulatory T cells depend on the appropriate stimulation, which is achieved by well-balanced signaling via both the TCR-CD3 complex (signal 1) and the co-stimulatory substances (signal 2). Co-stimulation is often accomplished by the cooperation of CD28 receptors on T-cells with B7 molecules (CD80 and CD86) on antigen-presenting cells (APCs). This relationship is essential to avoid the suppression of activated T cells via the induction of anergy. However, antigen-presenting cells (APCs) in cancer patients, particularly in the TME, often persist in a rudimentary state characterized by the absence of CD80 and CD86 expression. Consequently, this results in the dysfunction of effector T cells (54). In order to tackle this issue, some TCR-T cells were modified to enhance co-stimulation via CD3ζ signaling utilizing various techniques. The development of Artificial T-cell-activating adapter molecules (ATAMs) aimed to enable the transmission of both CD3ζ signaling and co-stimulation signals. This was achieved by inserting either the CD28 or the 4-1BB intracellular domain (ICD) into the CD3ζ chain. The TCR:CD28ε complex had a higher binding strength to pMHC, leading to enhanced T-cell activity upon peptide stimulation in comparison to regular TCRs. The distinctive arrangement of TCR:CD28ε effectively avoids the erroneous combination of TCRs with native TCRs, hence ensuring the persistent existence of TCR:CD28ε and mitigating any potential unanticipated off-target toxicity. In addition, a mandated increase in the expression of co-stimulatory molecules improves the transmission of signals in T-cells. 4-1BB is a transiently expressed co-stimulatory molecule that is synthesized by T cells in response to TCR engagement. The ligand, 4-1BBL, is produced by antigen-presenting cells (APCs) and, in some cases, by cancerous cells. In relation to this issue, the incorporation of 4-1BB into TCR-T cells through genetic transfer and its excessive expression in melanoma patients who received vaccination with the associated antigen led to enhanced efficacy in combating tumors, as observed in a chick-embryo chorioallantoic membrane (CAM) model system (56). Tumor cells often evade immune system recognition by downregulating the production of peptide-major histocompatibility complex (pMHC), thereby diminishing the affinity between T cell receptors (TCR) and tumor cells. Ahmadi et al. performed an experiment to investigate the problem of reduced efficacy in TCR-T-cell therapy caused by the CD3 density. The researchers investigated the co-transduction of all four CD3 chains (CD3ε, δ, γ, and ζ) together with the TCR in T cells. The findings demonstrated a significant increase in TCR expression and tetramer interaction. The co-transfer of CD3 chains together with the TCR was associated with an improved affinity of T lymphocytes, enabling them to recognize low-density pMHC and exhibit greater efficacy against malignancies in live beings (57).

Alteration of CAR-related components

The addition of co-stimulatory domain from 4-1BB and/or CD28 to initial-generation CARs, which contain just one CD3ζ signaling domain, greatly enhances the efficacy of CAR-T-cell therapy. The limited efficacy of CAR-T-cell therapy in solid cancers underscores the need for precise modulation of signaling pathways for overcoming obstacles, as previously mentioned (refer to the "The co-stimulatory domain and CD3ζ signaling domain" section). The efficacy of CAR-T-cell treatment in various scenarios is mostly determined by the engraftment and durability of CAR-T-cells. According to Feucht et al., the second-generation CAR with the CD28 co-stimulatory domain has the ability to strongly activate T-cells but has limited lifespan. This CAR also causes distinct changes in the activation of T-cells (58). They successfully modified CD3ζ signaling by altering ITAMs in the CD3ζ chains. They specifically altered the ITAM arrangement in 1XX by interfering with the second and third distal ITAMs. This alteration enhanced the enduring efficacy of CAR-T cells by preserving a harmonious equilibrium among their capacity to replicate as memory cells and their proficiency in efficiently combating malignancies. Conversely, Guedan et al. demonstrated that a single modified amino acid in the CD28 co-stimulatory domain (specifically, changing asparagine to phenylalanine, CD28-YMFM) improves the enduring anti-tumor reaction by decreasing T-cell distinctions and exhaustion, while also promoting the formation of Th17-like T cells (59). CD28-YMFM was thought to interfere with the binding between the CD28 domain and the SH2 domain of Grb2. As a consequence, there was an elevation in the stimulation of AKT and a decline in the activation of VAV1 and PLCγ1, leading to a decrease in the entry of calcium into CAR-T cells upon antigen stimulation. These notable alterations in gene expression are linked to decreased T-cell differentiation and exhaustion. Considering the significance of T-cell exhaustion in cancer immunotherapy, namely in TCR/CAR-T-cell treatment, it is essential to prioritize the production of TCR/CAR-T cells that possess resistance to fatigue. Recent study has shown that replacing the CD3ζ chain with a CD3ε chain that includes both activating and inhibitory motifs as a signaling domain in CARs improves the ability of CAR-T cells to fight tumors (60). This implies that CD3ε has the capacity to function as an inherent signal modulator, enhancing the durability of CAR-T cells by averting depletion. Moreover, there have been reports indicating that the temporary cessation of CAR signaling may enhance the functionality of depleted CAR-T cells by altering their epigenetic characteristics. Dasatinib treatment leads to a decrease in CAR expression, causing the cells to undergo a metamorphosis resembling memory formation. This transformation is accompanied by alterations in their gene expression and epigenetic processes. This procedure eventually rejuvenates the capacity of depleted CAR-T cells to combat malignancies (61).

Clinical Trials

At present, multiple studies are examining the use of CAR T cell therapy in the management of solid cancers and other medical ailments. Studies indicate that T cells, which have been genetically engineered with mesothelin-specific CAR mRNA, may activate the immune system to target solid malignancies (6). Furthermore, the use of CAR methods for organ donation has included the utilization of two cutting-edge HLA-A2-specific CARs. One chimeric antigen receptor (CAR) has a CD28-CD3d signaling domain, whereas the other does not include an intracellular signaling domain (dCAR). Transferring Tregs that are particular to the donor (allospecific Tregs) is more efficacious in avoiding the rejection of transplanted tissue compared to transferring Tregs that are derived from several sources (polyclonal Tregs). The inclusion of the ICOS signaling domain in a chimeric antigen receptor (CAR) has been shown to be very successful in fighting against glioma that expresses the epidermal growth factor receptor variant III (EGFRvIII) (63). Preclinical studies demonstrate the efficacy of CAR T cell therapies in targeting the tumor antigen 5T4 for the treatment of ovarian cancer. Remarkably, an unexpected revelation was uncovered during the examination of CAR treatment for autoimmune disorders. A chimeric autoantibody receptor (CAAR) that includes the pemphigus vulgaris autoantigen, desmoglein (Dsg3), together with CD137-CD3d signaling domains, was able to precisely target and destroy cells that produce anti-Dsg3. This targeted approach showed precise toxicity against these cells (64). Ongoing research is focused on investigating CAR targets for certain malignant neoplasms.

Conclusion and Future Directions

CAR T cells are an innovative therapeutic strategy that represents a unique and separate way of treating diseases. The current CARs are constructed with a modular structure, enabling targeted enhancements to address the challenges posed by the tumor microenvironment (TME). Scientists can improve the safety and effectiveness of CAR T cells by using synthetic biology and gene-editing techniques. In addition, CAR T cells may function as living T cell 'micropharmacies' to selectively deliver immunomodulatory drugs to the tumor microenvironment (TME). Increasing the complexity

of CAR designs and changing the genes of T cells may significantly amplify the potential risks associated with CAR T cell therapy. For example, the process of viral transduction and the use of gene-editing machinery might potentially result in the unintended disruption of genes that are not the intended target. The transformation of T cells into malignant clones, resulting from the introduction of mutations that either activate oncogenes or disrupt tumor suppressor genes, is a well recognized inherent risk associated with gene therapy. Currently, there is no evidence of insertional mutagenesis leading to transformation in patients. Nevertheless, clinical data have shown the occurrence of viral insertion into genes in lentivirally transduced CAR T cells used for the treatment of a patient with CLL (67). Specifically, the CAR gene was inserted into the TET2 locus, leading to the development of a cluster of genetically identical T cells (67). Nevertheless, the population of T cells in this community gradually diminished in size without any external interference. This incident highlights the inherent risk involved in using engineered cells as a therapeutic approach for patients. As researchers get more familiar with adoptive cell transfer, they are growing more comfortable with the inherent danger. As a result, a study has been started (NCT03399448) to test the use of NY-ESO-1-directed transgenic TCR T cells that have undergone numerous CRISPR-Cas9 gene edits to remove the natural TCR and PD-1. The complex procedure of genetically modifying biological products exogenously also adds complexity to the manufacturing process.

Prior research on the existing CAR T cell production procedure has shown that the CAR design may inadvertently alter both tumor cells and lymphocytes found in the apheresis result. This might result in the concealment of antigens via the attachment of CARs generated by these cancer cells to tumor-associated antigens (TAA) on the same cells. Consequently, there may be an unregulated proliferation of these neoplastic cells and their dissemination throughout the organism (68). The CAR T cell technique is the first gene treatment to be granted clinical approval. Regular surveillance of gene editing-induced difficulties in clinical trials of CAR T cell products will contribute to a more comprehensive comprehension of the potential long-term hazards linked to the developing domain of gene editing in the medical profession. This monitoring may also aid in identifying remedies for certain issues. Introducing novel technological approaches may also increase the already high costs linked to the manufacturing of CAR T cells. One of the reasons that adds to the total cost of CAR T cell therapy is the high price and time-consuming process of manufacturing clinical-grade retroviruses. However, using non-viral vectors to decrease manufacturing costs has the potential to improve affordability (69). Ultimately, there are now ongoing efforts to improve the efficacy and scope of CAR T cell therapies, while simultaneously boosting their safety and optimizing their production processes. These novel engineering solutions, designed to optimize CAR T cell biology, will lead to the broader use of this technology in the therapy of cancer, hence enhancing the benefits of CAR T cells for patients.

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Authors' Contribution

Mahtab Dolatabadi and Shabnam Radbakhsh were involved in the conceptualization, design and writing of the manuscript draft. All authors read and confirmed the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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The Use of Bacteriophages in Cancer Therapy

Alireza Gharavi[1*]

[1]Department of Nanobiotechnolog Biomimetic, University of Tehran, Iran.

Corresponding Author's E-mail: gharavial@gmail.com.

Abstract

Cancer is a catastrophic illness with a significant worldwide fatality rate, anticipated to rise in the next years. Contemporary treatment modalities, including chemotherapy and radiation therapy, include constraints such as adverse effects, inconsistent efficacy, elevated expenses, and restricted accessibility. Bacteriophages have arisen as multifaceted instruments in bioengineering, with significant promise in tissue engineering, vaccine formulation, and immunotherapy. Bacteriophages are being used extensively in several fields of biotechnology and medicine, with cancer treatment being the most compelling application. A multitude of research is progressively confirming the efficacy and efficacy of phage-based carriers as broad delivery mechanisms for medicinal genes and medications in cancer therapy. Furthermore, the genetic makeup of phages may be utilised in the development of novel DNA vaccines and antigen presentation systems, since they offer a highly organised and repetitive presentation of antigens to immune cells. Bacteriophages have generated new possibilities for the accurate targeting of particular molecular markers in cancerous cells. Phages may function as anticancer agents and as vehicles for imaging agents and pharmaceuticals. This article presents bacteriophage and analyses the efficacy of bacteriophages and bacteriophage engineering in specific cancer treatment.

Keywords: Bacteriophage, Cancer treatment, Cancer vaccine, Phage display.

Introduction

In the last century, understanding of the biology of cancer has markedly progressed. This progress has been substantially propelled in the past few years by technological innovations and concepts across multiple fields, such as next-generation sequencing, "omic" sciences, high-resolution microscopy, molecular immunology, flow cytometry, individual cell analysis and sequencing, novel cell culture methodologies, and the creation of experimental animals, among others. Nevertheless, several problems remain unresolved and many difficulties continue to exist about this illness (1). Consequently, oncological research is deemed essential. Cancer now ranks among the leading causes of mortality globally. Data provided by the World Health Organisation (WHO) in 2020 indicates that cancer is the second leading cause of death globally, resulting in 10 million fatalities. Cancer is a predominant global issue (2). Cancer is a pathological condition that may manifest in several anatomical locations within the body of a person, such the lungs, breasts, male reproductive system, and colon, among others. Numerous factors correlate with an increased likelihood of cancer onset, including age, genetic susceptibility, lifestyle decisions such as tobacco and alcohol use, and exposure to environmental toxins. However, not all cases of the disease can be attributed to known risk factors, and some individuals may get malignancy without any apparent cause. The incidence of cancer is increasing; yet, the variability of lesions and their aetiologies complicates the

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development of personalised therapy for each patient. Surgery a resection treatment with chemotherapy, and radiation treatments have been the fundamental approaches of cancer treatment for years. While surgery is the preferred method for eradicating primary tumours, there are situations when not all cancerous cells are removed, resulting in tumour recurrence (2). Chemotherapy and radiation therapy can cause considerable cytotoxicity in normal cells, making them inappropriate therapeutic options for some types of cancer or individuals. Conventional treatments are incapable of specifically eliminating cancer cells while safeguarding healthy cells and tissues. Several factors must be assessed while developing cancer-targeting treatments, notably the detrimental microenvironment that facilitates the development of tumour cells. The study of cancer seeks to develop an effective therapeutic strategy using novel treatment and preventive methodologies. The tumour microenvironment is a vital component in the realm of immunology and this developing therapy paradigm. Moreover, the number of available medicines has increased owing to progress in gene editing and other biotechnological techniques (4).

Bacteriophages, or phages, are a diverse group of viruses with varying sizes and morphologies (icosahedral forms like λ, T4, T7, and filamentous types such as fd, f1, M13) that infect bacteria and lyse host cells to produce progeny phages for further infections, while typically not infecting eukaryotic cells (3, 4). Phages are the most abundant class of microorganisms in the biosphere and contaminate almost all identified pathogenic bacteria. Twort and d'Herelle separately discovered bacteriophages in 1915. Twort seemed to support the notion that it was not a distinct living form, but rather an enzyme released by bacteria. He forsook phage research and dedicated the remainder of his scientific career to the production of animal viruses. Nonetheless, d'Herelle first introduced the name bacteriophage and dedicated his life to the study of bacteriophages and their therapeutic applications in humans and animals (6). The utilisation of phages in anti-cancer or anti-tumor therapies represents a novel domain. The latest developments indicate that phage research has progressed to its second generation.

Phages used in cancer treatments and assessment as selective nanocarriers as and in gene therapy as carriers for therapeutic DNA or RNA. Phages are studied in immunological vaccine research due to their capacity to provoke both cell-mediated and antibody-mediated responses (7). Gene insertion may facilitate the production of specific peptides or protein fragments inside the phage capsid, therefore presenting them to immunological regions to provoke a vigorous immune response against diverse antigens from cancerous cells. Due of its small and uniform size, it is the most effective nanoparticle for drug delivery and multiple other uses, such phage presentation and focussing (6). Their omnipresence in nature allows their capsids to elicit an immune reaction or, through genetic or protein modification, enable any organism to produce specific proteins on its outermost layer to activate an immune system reaction. Another approach utilises phage display technology to generate recombinant humanised monoclonal antibodies that particularly target neoplastic cells and harmful microorganisms. Phages provide considerable promise for theragnostic applications, gene therapy, and immunotherapy in cancer therapy due to their nanoscale dimensions, flexible surface properties, precise target specificity, inherent safety, and non-pathogenic nature (8). This article highlights the promise of phage therapy as an innovative approach in cancer treatment. The book analyses the distinctive features of bacteriophages which offer feasible alternatives for targeted and customised cancer therapies.

Composition and biology of bacteriophages

Bacteriophages are essential bacterial parasites and represent the most prevalent group of biological creatures in the biosphere. In the lack of genes necessary for autonomously development, phages employ the biological machinery of host cells to produce their genetic material (6, 7). Bacteriophages demonstrate extraordinary variety and infected almost all referred to bacteria. These types of viruses substantially impact the evolution of prokaryotic species, modify bacterial interactions, and may disrupt the relationships between bacteria and multicellular organisms (9). The distinctive characteristics of bacteriophages make them a potential instrument in several domains of biotechnology. Furthermore, phages and bacterial anti-phage defence mechanisms have profoundly influenced the creation and advancement of genetic engineering. The distinctive architecture and genetic arrangement of bacteriophages greatly enhanced their attractiveness. Bacteriophage fragments have a distinct three-dimensional shape (9).

The primary structure of virions consists of a head and a tail. The head contains the virus's genome, which is enclosed by a capsid. The genetic information may include either one-stranded or two-stranded DNA or RNA. The baseplate, located at the tail's termination, is an essential element of the bacteriophage structure, into which elongated, thin filaments extend, facilitating the phage's attachment to bacteria. The baseplate contains receptor-binding proteins that recognise specific substances on the outermost layer of the bacterial membrane (10). The relationship between bacteriophages and cells of bacteria is specific; the target must possess the

requisite receptors on its membrane the outside, enabling phage attachment and internalisation. Certain bacteriophages are devoid of a tail. They possess receptor-binding proteins on the outside of their capsids. The interaction within a phage and a host bacteria occurs at many stages. Subsequent to the first interaction, enabled by the dispersion of phage fragments in the fluid and Brownian motion, electrostatic interactions promote reversible and unspecified adherence of the phage to the bacterium. The attachment becomes irreversible due to the binding of viral capsid elements to cell surface receptors, which may consist of amino acids, teichoic acids, glycoproteins, lipopolysaccharides, or pili segments, contingent upon the phage type (11, 12).

The baseplate coordinates the recognition of particular receptors on the cell surface and the adhesion of the phage fragment to the host bacterium. The effective binding to the microbial receptor causes a conformational change in the baseplate, resulting in tail shortening. The catalyst for the onset of these events is a modification in the position of the fibrils in relation to the baseplate. The reorientation of fibrils occurs only on the outermost layer of the host cell and is undetectable in the free state of viral pieces in solution (13). Additionally, no chemical energy is used to modify the filament direction and baseplate configuration.

Various proposed mechanisms clarify the particularities of phage attachment to the host cell. The strong binding of phage to a microorganism is enabled by the partial attachment of viral fibrils to particular receptors on the cell appear, while the alignment of the whole virion on the cell surface and later interactions of fibrils with cell receptors are affected by the movement of the surrounding medium. The restriction of phage fragment mobility causes a conformational change in unbound fibrils, increasing their attraction for the cell membrane. Another proposed mechanism is that the modification of the three-dimensional configuration of the baseplate and the reorientation of the viral strands towards the cell, leading to the strong adhesion of the phage to the bacterium, is mediated by divalent cations, especially Ca2+ (12, 13).

Numerous membrane polysaccharides and proteins of bacterial cells engage with divalent cations, significantly increasing their concentration at the interface between the phage and the host. It has been shown that, for some bacteriophages, the existence of calcium ions is crucial for the infection of host cells. The efficacy of bacteriophage engagement with prokaryotic cells is influenced by the presence of additional ions in the solution; heightened ionic strength augments the infectious capacity of phage fragments (14). It is essential to acknowledge that these methods are not incompatible and may concurrently coexist. Subsequent to the irreversible binding of the phage to the bacterium, the contraction of the viral protein coat occurs, during which the rigid tail tube penetrates the outermost membrane of the cell. Thereafter, the tube penetrates the periplasmic space and, with the assistance of enzymes at its end (mostly lysozyme), selectively dismantles the peptidoglycan of the cell membrane. The viral genetic code is then transferred into the bacterium's cytoplasm, however the phage's protein coat remains exterior.

Regardless of the method by which phage genetic material enters the host cell, there are a couple possible techniques for its future implementation. At the commencement of the lytic cycle, a thorough rearrangement of cellular metabolism occurs; the cell's energy is wholly diverted to the replication of viral genetic material, the transcription of viral genes, and the synthesis of viral proteins. The last stage of this cycle is the assembly of matured virions and their next dissolution by cell lysis. The lysogenic cycle is characterised by the reversible incorporation of the phage DNA into the bacterial genetic structure (16). In this circumstance, the viral genome replicates simultaneously with the host's DNA, while maintaining cellular integrity. The lysogenic cycle mostly endures until the activation of the prophage and the shift to the lytic pathway occur. A comprehensive analysis of bacteriophage structure, how they interact with bacteria hosts, and their lifespan facilitates the application of these viruses in multiple areas of modern practical and theoretical research (17).

Due to the rising antibiotic resistance of bacteria, phage therapy for infectious diseases is now seeing a revival. The effectiveness of bacteriophage use in food-related diagnostics has been demonstrated. Phages are used in the control of plant diseases, biomedical diagnostics, biological research, and genetic engineering. Bacteriophages are considered potential vectors for gene therapy for cancer (15, 16). They are regarded as having several advantages compared to non-viral and eukaryotic virus-based carriers. Phage-based vectors are superior to eukaryotic viruses because they lack inherent tropism for eukaryotic cells, hence improving the specificity of therapeutic cargo being delivered to cancerous cells. Contrary to previous beliefs that phages could not interact with organisms more complex than prokaryotes, recent evidence has progressively demonstrated that natural bacteriophages may directly interface with the cell membranes of higher organisms (18).

Oncology treatment: present obstacles and innovative approaches

Bacteriophage-mediated gene therapy for cancer

Phage-mediated cancer gene treatment is a method

that utilises the capacity of phages to specifically deliver genes that treat to cancerous cells. Phages have been extensively studied and are employed in various fields, especially medicine. Traditional gene therapy often utilises viral vectors derived from mammalian viruses to deliver therapeutic genes into target cells (17). However, the application of mammalian viruses has safety concerns and limitations due to their ability to integrate into the host genome, which may lead to unpredictable consequences. Phages provide a viable option owing to their pronounced selectivity for bacterial hosts and their incapacity to infect human cells. In the 1940s, Bloch presented the first evidence of phages' capacity to directly engage with mammalian cells. His findings suggest that phages may aggregate in malignant cells, impeding cancer growth (18). Kantoch subsequently demonstrated that phages could attach to and penetrate guinea pig leukocytes. A new investigation has reinforced the established associations among phages and mammalian immune system cells (19).

Despite being considered ineffective carriers for generating higher organism cells, bacteriophages unexpectedly offered a unique strategy for creating therapeutic gene methods of delivery. Bacteriophages are seen as a promising approach for cancer gene therapy owing to their absence of a preference for human cells, enhanced cloning efficiency, simplicity of alterations, and use of phage technology for display. The production of phage fragments within bacterial cells is defined by efficiency, speed, and cost-effectiveness (20).

Phages may be modified to transport therapeutic genes targeting various objectives in cancer treatment. For example, they may encode proteins that induce apoptosis in cancer cells, inhibit tumour development, or enhance the immune response to cancer cells. Phage-based gene therapy offers the potential for targeted and precise treatment by directly administering therapeutic genes to cancerous cells, thereby decreasing off-target effects. Moreover, phages have inherent advantages as vectors for gene transfer (21, 22). They are straightforward to manipulate in the laboratory, and their ability to infect a broad spectrum of bacteria enables the development of a varied library of phage variations with unique tumor-targeting properties. Moreover, phages may be administered via several methods, including intravenous injection, targeted injection, or consumption, providing diversity in therapeutic approaches. Despite the significant promise of phage-based malignancy gene therapy, issues must be resolved. Additional efforts are necessary to improve phage design, optimise targeting efficiency, and ensure the safety and effectiveness of this method. Ongoing clinical investigations are assessing the therapeutic potential of phage-based gene therapy for several types of cancer (23).

Phages have been recognised as promising carriers for gene therapy in oncology via many research and clinical trials. Despite the prior preference for eukaryotic viruses due to their enhanced efficacy in generating mammalian cells, their natural a preference for eukaryotic host cells presents challenges for therapeutic applications. Retroviral and lentiviral vectors possess drawbacks, such as potential oncogenicity, restricted replication of the target gene, and significant immunogenicity associated with adenovirus-based vectors. These issues have impeded the progress of gene therapy methodologies for cancer treatment. Recombinant adeno-associated virus (AAV) carriers have potential owing to their efficacy; yet, they are limited by reduced packaging capacity, the existence of neutralising antibodies, and a requirement to enhance transduction selectivity for systemic administration. In contrast, phages possess unique architectural and biological characteristics that provide innovative methods for targeted transfer of genes to cancerous cells. Scientists are exploring the possibility of phages as gene therapy carriers, therefore overcoming the drawbacks of other viral vectors. The effectiveness of the AAV/phage (AAVP) vector in suicide gene therapy for malignancy has been reliably corroborated in subsequent studies. AAVP-RGD4C-HSVtk, in combination with GCV, exhibited a substantial antitumor effect in preclinical trials utilising mouse models of Kaposi's sarcoma, bladder and prostate carcinoma, breast tumours, nude rats with human sarcoma xenografts, rat glioblastoma cells, mouse simulates of human glioblastoma, and human melanoma tumour cells (21, 24, 25).

Phage-based vaccines

Phages may be engineered to deliver specific antigens to the immunity system for vaccination purposes. Antigens are substances that elicit an immune reaction, leading to the production of antibodies and the formation of immune memory. Vaccines educate your immune system to recognize and combat certain diseases, particularly infections caused by bacteria and viruses, by introducing antigens. The use of phages as a vehicle for antigen transport in vaccinations provides multiple benefits: Phages has an innate ability to spread disease and target certain bacteria according to their intrinsic affinity. Phages may be modified to present antigens on their appears allowing them to selectively target certain bacteria and enhance the body's defense against particular germs; (ii) Phages possess significant immunogenicity owing to their inherent immunogenic characteristics. They may proficiently stimulate immune responses that are innate as well as adaptive when employed as a vaccine delivery strategy (30, 31). This may elicit a robust immune

response to the given antigens; (iii) Enhanced stability; phages demonstrate exceptional resistance to external conditions, including variations in temperature and pH levels. This stability makes them attractive candidates for vaccine development, since they can withstand the challenges of storage, transportation, and distribution. The manipulation of phages is very simple owing to their susceptibility to genetic alteration. Researchers may integrate genes encoding specific antigens into the phage genome, resulting in the display of these antigens on the phage membrane. This genetic engineering enables the precise development and customization of phage-based vaccines, as well as the potential for combinatorial immunizations, allowing phages to simultaneously deliver several antigens. This characteristic facilitates the creation of combination vaccines that target many illnesses or strains in a single formulation. This approach may optimize immunization schedules and improve overall vaccine acceptance (32).

The development of vaccines has extensively utilized multiple lytic and filamentous phages owing to their advantageous characteristics. Filamentous phages, especially those of the Inovirus family, such as M13, fd, and f1 phages, are favored due to their simple capsids, rod-like structure, and one-stranded (ss) DNA genome (33). These phages primarily infect microbes and has a historical history in phage visualization technology. The preference for phages in vaccine research is driven by the availability of established components and techniques for phage manipulation, particularly in the selection and production of antigens and antibodies. Recently, a wider array of phages, such as tailed phages including T4, T7, and λ, with icosahedral phages like Qβ and MS2, has been utilized in phage visualization vaccination methods for antigen presentation. Tailed phages, unlike filamentous phages, enable the production of larger peptides and proteins with more complex conformations. Filamentous phages predominantly exhibit short peptides (33).

Phage display technology offers a reliable approach for detecting surface markers on cancer cells and for creating effective anticancer peptides for therapeutic purposes. Phage display vaccines may generate tailored immunogenic viral fragments by attaching antigens to phage membrane proteins. A multitude of applicants have been evaluated as phage-based cancer vaccines in preclinical studies, incorporating epitopes from the VEGFR2, EGFR (34), HER2, MAGE (35), MUC1 (36), FGFR, Flt4, and mimotopes of TAA. Multiple anticancer phage vaccines have been utilized effectively in immunotherapy against cancer (37).

VEGFR2 is highly expressed in tumor endothelial cells and functions as a cancer-associated antigen. A VEGFR2-targeted vaccine was developed using phage display technology, which generated anti-VEGFR2 antibodies that inhibited tumor progression in mice via CD4+ T cells (38). The application of T4 phages as a vaccine carrier may assist in overcoming immunologic resistance to VEGFR2. The delivery of T4 transgenic phages producing the extracellular region of VEGFR2 reduces VEGF-mediated tumor angiogenesis by selectively binding to VEGF, hence blocking downstream signaling cascades and diminishing tumor development and microvascular frequency in vivo (39). Monoclonal antibodies, such as bevacizumab, and peptides discovered using phage display technology have been designed to obstruct VEGF-dependent tumor angiogenesis (40).

Investigation has examined the application of EGFR peptide ligands as efficacious therapeutics for targeting overexpressed EGFR receptors in various tumor cell types. The phage display approach has been used to identify high-affinity peptides and antibodies that attach to EGFR, so blocking its signaling pathway and consequently decreasing tumor cell growth and viability (41). Phage-derived ligands demonstrate potential in the development of tailored therapies for EGFR-positive cancers. Distinct study revealed that antagonistic anti-EGFR nanobodies, selected by phage display technology, effectively obstructed the interaction of endothelial growth factor (EGF) with EGFR, impaired EGF-mediated signaling, and delayed tumor development in vivo. Phage exhibition screening via panitumumab-isolated EGFR mimotopes (P19 and P26) and HSP70-P19/P26 fusion proteins reduced tumor progression in lung cancer models, indicating the possibility for anti-EGFR therapy (34, 42).

DNA vaccines of phages

DNA vaccines provide considerable benefits over proteins or peptides immunizations due to their accurate antigen packaging and lack of subsequent processing demands. However, comprehensive primate investigations revealed insufficient immunogenicity, leading to the inclusion of adjuvants in human trials. The carriers must also address the instability and dispersion challenges linked to naked DNA vaccines (43, 44). In contrast, novel nucleic acid-based vaccines have demonstrated promising results in clinical experiments, particularly after the COVID-19 pandemic. Phage fragments possess adjuvant properties and function as an efficient method for DNA transfer. Bacteriophage DNA vaccines use eukaryotic expression cassettes using target-specific bacteriophage amplifiers that contain antigen-encoding genes. Phage DNA vaccines offer an acceptable substitute to naked DNA immunizations, with various advantages, including the ability to include substantial DNA antigens of

up to 20 kb. Lambda phages have been extensively studied as carriers for delivering DNA vaccines that encode proteins such as green fluorescent protein (GFP) and hepatitis B surface antigen (HBsAg), via cytomegalovirus (CMV) promoter-regulated reporter genes (20, 45).

They serve as a cost-effective gene delivery mechanism while also offering distinct advantages in nucleic acid immunization and in directing antigen-presenting cells to enhance immunity. Research suggests that lambda-ZAP E7 bacteriophage-mediated DNA transfer may efficiently deliver and produce curative genes, resulting in substantial anti-tumor advantages in immunized mice (46). However, DNA vaccines targeting Δ16HER2, a protein linked to the severity of breast cancer and resistance to treatment, failed to elicit immune protection in mice due to tolerogenic mechanisms. This challenge was mitigated by engineering bacteriophages with immunogenic epitopes of Δ16HER2, that provoked an immune anti-Δ16HER2 response, hence breaking immunological tolerance. These findings support phage-based anti-HER2/Δ16HER2 immunization as an efficient and secure treatment for HER2-positive breast tumors (47). Unlike peptide vaccination, lambda phage-based genetic vaccination induced immune system reactions marked by heightened antibody levels, augmented generation of cytokines, and improved epitope binding facilitated by a Th1 reaction.

Filamentous phages are under examination as vaccine carriers, enabling immunization with several epitopes or antigens through a singular delivery method (48). Furthermore, phage DNA vaccines are safe, uncomplicated, and economical, lacking antibiotic-resistance genetic material, and may be administered in many doses. They demonstrate durability and improve protein folding, contain the adjuvant characteristics of phage parts, and contain lipopolysaccharides and lipids, making them more effective than traditional DNA vaccines. Current literature lacks investigation on RNA-based phage vaccines for immunotherapy for cancer. To impede viral replication and deliver antiviral agents for myocarditis, study used synthesized microRNAs linked to folate-conjugated bacterial phage packaging RNA (pRNA). Thus, phage DNA vaccines offer a feasible approach for developing secure and efficient immunizations against many diseases (49).

Combination treatments and targeted oncological therapy

Targeted drug administration is becoming recognized for improving chemotherapeutic efficacy and minimizing its negative effects. Phage libraries can identify peptides that bind to cancerous cells, enabling targeted drug delivery to tumor sites. Peptides generated via phage presentation are frequently employed for tumor targeting because of their small size and ease of integration with drugs and carriers. Innovative methods for improving chemotherapy are being examined, with promising outcomes. Phages have demonstrated the ability to improve chemotherapy effectiveness while reducing its negative impacts (50). Scientists utilized M13-based phage collections to identify specific peptides that may traverse cell membranes and transport active pharmaceuticals to cancerous cells. Two peptide motifs, LTVSPWY and WNLPWYYSVSPT, have been found to bind to breast cancer cells and promote the internalization of antisense oligonucleotides. The AGKGTPSLETTP motif from a 12-mer M13-displayed phage library demonstrated notable anticancer efficacy in mice with hepatocarcinoma (HCC) tumors when co-administered with doxorubicin (DOX) (51). A pentapeptide phage library identified the ASSHN motif, to inhibit tumor angiogenesis; when combined with DOX-loaded liposomes, it exhibited significant growth inhibition in comparison with untargeted liposomes (52).Bacteriophages have been explored as vehicles for medications and diagnostic dyes, with favorable outcomes. M13 fragments displaying epithelial growth factors may effectively contain plasmids that express siRNAs targeting focal adhesion kinases, especially aimed at lung cancer cells (53). An anti-prostate-specific membrane antigen (PSMA) antibody was coupled with the gp3 protein to create an anti-PSMA-M13-SWNT system that preferentially addresses prostate cancer cells and is suitable for in vivo fluorescence analysis (54). Bacteriophages are employed in photodynamic therapy for oncological treatment. Studies demonstrate that MS2 bacteriophages decorated with DNA aptamers and M13 bacteriophages targeting breast cancer cells may efficiently deliver photosensitizers, resulting in cellular death (55). Phage-based nanotechnology via light therapy may address cancer by producing singlet oxygen, and studies suggest that genetically modified phages targeting SKBR-3 cancer cells induce cell death upon laser activation (56). An M13 phage, adorned with silver nanoparticles and engineered to attach to Fusobacterium nucleatum (Fn), was developed to specifically target Fn in colorectal cancer, leading to improved longevity in an animal model of orthotopic colorectal cancer (CRC) (57).

Progression of phage application in clinical investigations

Phage-displayed antigens offer advantages over traditional immunizations in stimulating the proliferation of T cells and enhancing the optimal immune reaction. Traditional vaccinations via soluble foreign antigens or inactivated pathogens do

not effectively stimulate T cells via the MHC class I pathway, resulting in inadequate immune reactions (58). Fibrous phages efficiently activate the MHC class I and II processes, essential for anti-cancer and anti-viral therapies (59). Phages may activate antigen-presenting cells to secrete costimulatory molecules, so stimulating T cells and positioning themselves as potential enhancers of the immune system's function (60). Phage therapy is now being evaluated in global research studies as a potential remedy for antibiotic-resistant bacterial infections in people. The American Clinical Trials database includes multiple articles about the use of phages in medical studies, mostly focused on the treatment of infectious diseases. Nonetheless, a lot of study has focused on the lytic properties of phages to combat antibiotic-resistant bacterial infections. In recent years, scientists have investigated the application of phages as a potential cancer treatment. A European phase I/II clinical trial has been conducted with patients receiving a phage-based vaccine that links a particular B-cell receptor to the exterior of phage fragments. The vaccination was assessed in patients with terminal-stage multiple myeloma and was well tolerated, with minimal and transient side effects. The immunization decreased blood paraprotein and urine-excreted myeloma-specific light strand stages, suggesting a therapeutic response in most individuals (61).

Notwithstanding promising results in preclinical studies, multiple obstacles have to be resolved prior to the widespread use of phage therapy in human cancer treatments. A multitude of clinical trials is under underway to evaluate the safety and efficacy of phage therapy in patients. ABNCoV2, a vaccine using virus-like particles (VLPs) produced from bacteriophage AP205 and decorated with the receptor-binding region of SARS-CoV-2, was synthesized in S2 Drosophila cells and then administered to healthy volunteers for safety evaluation in the clinical research (NCT04839146). Despite promising preclinical results and the efficacy of phage-based vaccines for humans and animals, the FDA and EMA have not yet granted clearance for these vaccines. The FDA has approved the application of bacteriophages as antibacterial agents in food products to combat contamination, namely Listeria monocytogenes in ready-to-eat meat and poultry (71 FR 47729). Moreover, several patents related to phage administration for cancer treatment have been granted or are under approval. The inventions involve multiple facets of phage therapy, such methods for phage manufacture and administration, specific phage formulations designed to target tumor cells, and strategies to employ phages to enhance the antitumor effectiveness of the body's immune response.

Constraints and prospective developments

Phage-based cancer treatment holds considerable promise as a secure, efficient, and personalized therapeutic approach. However, multiple constraints and issues must be addressed to fully harness the power it has. A significant limitation is the potential for immunological responses directed against the phages, which may reduce their efficacy and limit their use in persons with pre-existing immune impairments. Additional research is crucial to clarify the mechanisms of phage-induced immune reactions and to develop strategies for their reduction, such the use of mutant phages with less immunogenicity (62). Another risk is the emergence of immunity to phages, that might reduce their long-term efficacy. Bacteria may evolve and develop mechanisms for resistance against phages, similar to their reaction to antibiotics. Addressing this issue requires continuous monitoring and adjustment of phage formulations to surpass bacterial resistance processes. Furthermore, improving the display of antigens on phage surfaces for phage-based immunizations presents an additional challenge. This involves determining the most effective approach for presenting cancer-specific antigens on phages to provoke a robust immune response against cancer cells (63).

Ensuring safety and efficacy is paramount for phage-based therapies. Comprehensive preclinical and clinical investigations are crucial for accurately evaluating the potential detrimental effects and therapeutic benefits of phage treatments. The extensive production of phages is a prospective advancement that merits attention. To guarantee the extensive accessibility of phage therapy, it is crucial to develop economical and scalable production methods to meet treatment requirements. Moreover, regulatory clearance is a substantial barrier that phage-based therapies must overcome (64). Cooperation among researchers, clinicians, and industry stakeholders is essential to enhance the regulatory process and substantiate the safety and efficacy of these novel pharmaceuticals. Despite these limitations and challenges, additional study and investment in phage-based cancer therapy are crucial for unlocking its full potential. Combining the benefits of conventional cancer medicines with the targeted and personalized advantages of phage therapy may provide better, less harmful, and cost-efficient cancer treatment options in future decades (64).

Discussion and conclusion

Cancer is a significant global health issue, resulting in millions of deaths each year. The limitations of current therapeutic modalities, such as side effects, costs, and variable effectiveness, highlight the urgent need for more targeted and alternative treatments to improve patient results and standard of life. Phages

have become appealing agents in cancer therapy due to their high specificity, enabling targeted delivery to tumor cells while safeguarding healthy cells (65). This precision facilitates the mitigation of detrimental side effects linked to traditional treatments such as radiation therapy and chemotherapy. Furthermore, phages may be genetically modified and tailored, enabling individualized treatments that address specific cancer alterations or genomic irregularities in individual patients, hence potentially enhancing therapeutic efficacy and reducing the likelihood of resistance. Furthermore, phages have potential as nanocarriers for the administration of medicinal agents and as vectors for gene therapy. Their use in vaccine development to stimulate defenses versus cancer cells is also encouraging. Current investigations into phage-based therapies may revolutionize cancer treatment and offer hope to patients worldwide (66).

Cancer treatment has advanced significantly, including several conventional modalities like radiation therapy, chemotherapy, surgery, immunotherapy, specific therapy, and more. Each has persistent limitations, such as negative impacts, resistance, and cost. Phage therapy has attracted attention as a feasible alternative due to its specificity, flexibility, and genetic modifications, enabling targeted delivery to cells with cancer while sparing healthy ones. Its safety profile, ability to reduce toxicity, and potential to penetrate the tumor microenvironment make it a promising contender for future cancer therapies. Tailoring treatment to specific cancer types or mutations enhances efficacy, and its immune-modulating characteristics may further bolster the body's ability to fight cancer (67).

Phages are employed in nanotechnology for identifying and treating illnesses, healing of tissue, identification of bacterial and fungal infections, vaccine formulation, and gene therapy. Phages may be employed in personalized medicine for specific purposes. Phage-based vaccinations provide benefits over traditional immunizations in stimulating T cells and generating an optimal immunological reaction; nonetheless, their immunogenicity need enhancement prior to application. Phage display technology may be utilized in immunology of tumors for preventative and/or therapeutic vaccination or as a small-molecule drug. Phages may be engineered to function as more effective and precise vehicles for delivering drugs to cancerous cells, making them an attractive option for cancer treatment and testing, supplanting vectors derived from eukaryotic viruses. Phage treatment has shown efficacy in preclinical trials when combined with other drugs, enzymes, or particles. Scientists must address many challenges, include clarifying the mechanisms of phage interaction with the immune system and other cellular components, as well as confronting issues like phage resistance, allergic reactions, and other adverse consequences.

Bacteriophage-mediated cancer therapy has repeatedly shown its promise in several preclinical investigations to far. An rise in studies using phage-based vectors for the precise delivery of therapeutic transgenes into target tumor cells is envisaged in the near future. The altered phage particles offer a safer and more accurate systemic method for delivering therapeutic agents to cancer cells compared to carriers developed from eukaryotic viruses. The quest to improve the effectiveness of cancer gene therapy with bacteriophages has resulted in the development of innovative vector systems and transformational particles that demonstrate significantly greater amounts of targeted genetic expression in eukaryotic cells. Such vehicles may improve experimental methods for treating cancer by delivering therapeutic genetic information. The amalgamation of advanced vectors with CRISPR/Cas9 genetic modification technology constitutes a feasible approach for cancer therapy using genes. Enhanced improvement of this technology might lead to the creation of controlled nanoparticles demonstrating exceptionally specific nuclease activity aimed at eliminating mutant oncogenes.

Authors's Contribution

Alireza Gharavi was involved in the conceptualization, design and writing of the manuscript draft. The author read and confirmed the final manuscript.

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Approaches to Traditional Vaccines and the Development of New Person-Centered Vaccines

Ramesh Ranjbar [1*], Romina Hosseinzadeh[2]

[1]Department of Genetics, Faculty of Basic Sciences, Shahrekord Islamic Azad University, Shahrekord, Iran.
[2]Department of Biology, Faculty of Basic Sciences, East Tehran Branch, Islamic Azad University, Tehran, Iran.

Corresponding Author's E-mail: Ranjbar.Ramesh@gmail.com.

Abstract

A vaccine is a biological product that specifically leads to acquired immunity against a pathogenic pathogen and prevents the disease in the face of the main pathogen in a person. Therefore, vaccines are an important tool for maintaining health in the global community. Traditional vaccines have been used against a wide range of pathogenic pathogens, both viral and bacterial, and have been successful. However, these vaccines do not work and are ineffective against pathogens that change rapidly in terms of genetic material and surface epitopes.

During the last decade, vaccines based on nucleic acids, viral vectors and biomaterials have shown promising results. This study has discussed an overview of traditional vaccines, mRNA-based vaccines, viral vector-based vaccines, and biomaterials.

Keywords: Traditional vaccines, mRNA vaccines, Viral vector vaccines, Biomaterials, Immune system

Introduction

The World Health Organization estimates that vaccines prevent 2 to 3 million deaths annually by preventing disease. In addition to these immunizations, eradicating human smallpox was possible and is close to eradicating polio. In addition, vaccines have a significant economic impact because they prevent hospitalization of patients and other care costs (1-3).

Traditional vaccines have been effective against many diseases. Still, there are infectious diseases for which no effective vaccine has been definitively developed, such as human immunodeficiency virus (HIV), tuberculosis (TB), and respiratory syncytial virus. (RSV), cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein Barr (EBV) (4). In addition, other infectious agents such as the Ebola virus, Zika virus, and acute respiratory syndrome virus have become major threats to global health (3).

Vaccine development began in 1791 by Edward Jenner, who noticed that people who received cowpox had a much milder illness than the original disease (5).

Since then, safer and engineered vaccines have been developed, for example, inactivated/live-attenuated pathogen vaccines (6), subunit vaccines (7), immune epitopes (8), and various classes of adjuvants have significantly increased long-term immunogenicity(9). Newer vaccines produce higher antibody titers and also have fewer side effects (10). After three hundred years since the first vaccination, there are still many

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challenges in the development of new vaccines, including low stability, inefficient delivery, and lack of translation in human cells (11, 12).

Fighting the spread of such diseases requires making vaccines with a new method, which is usually not possible with traditional vaccines. These challenges have led to the development of research related to new vaccine manufacturing technologies. Table 1 lists some of the challenges in vaccine development.

The human body has different defense barriers that protects the human body against pathogenic agents. The human immune system consists of two parts: the innate immune system and the acquired immune system. The first barrier of the innate immune system is the skin, mucus and stomach acid, which prevents the entry of pathogenic pathogens (13). After the first barrier of the innate immune system, there are macrophage cells, dendritic cells, monocytes, complement proteins, natural killer cells, mast cells, neutrophils, basophils and eosinophils (14).

The next barrier of the acquired immune system includes B and T lymphocytes. If the innate immune system fails to control the infection, the acquired immune system comes into action. The innate immune system acts non-specifically against all pathogens, but the acquired immune system specifically recognizes and targets the type of pathogen. Also, due to having memory B and T cells, it can create permanent immunity to that pathogen. Therefore, in vaccine production, the goal is to stimulate the acquired immune system to prevent the re-infection of the disease by creating memory cells and appropriate and quick responses و to the pathogen (14).

In general, vaccines work by exposing a person to the whole or part of the pathogen, and as a result, it leads to the activation of the person's immune system.

Traditional vaccines

There are different types of vaccines. Traditional vaccines are live attenuated, killed pathogens, as well as subunit and conjugate vaccines (Fig 1) (15). Live attenuated vaccines consist of a weakened form of a pathogen and can induce a strong immune response. Clinically approved live attenuated vaccines include those against smallpox, measles, mumps, rubella, and yellow fever (16). Although the injection of live weakened pathogens leads to a strong immune response, it can be a risk factor for people with a weak immune system or with underlying diseases. Therefore, an alternative approach such as a completely inactivated pathogen is needed to reduce the risk of disease. Inactivated vaccines are such as hepatitis B virus, poliovirus and rabies vaccines, the development of live attenuated and inactivated vaccines requires the growth of pathogens on a large scale, which is associated with biosafety risk (3).

Finally, subunit vaccines are composed of a pathogen fragment. Subunit vaccines are better in terms of immunogenicity and eliminate the need for pathogen culture. But they often need a booster to create effective immunity (17). The limitations of traditional vaccines have led to the discovery and development of new technologies in the production of vaccines, which include carrier vaccines, nucleic acid-based vaccines, and materials science approaches to vaccination (Fig1).

Virus-like Particle Vaccines (VLP vaccine)

One of the unique features of viruses is that viral structural proteins and envelope proteins can self-assemble to form virus-like particles (VLPs) without the viral genetic material. Therefore, this feature can be used to make viral particles without pathogenicity. VIIPs have many applications in medical sciences such as therapy, drug delivery, some diagnostic tests and the development of vaccines (18).

Unlike conventional vaccines, VIPs have many features that make them attractive platforms for vaccine design. They are 20-200 nm in size and also have special geometric structures with multivalent epitopes (19-22) and have the ability to activate helper T cells.

In addition, VLPs are considered harmless because they do not contain the genetic material of the virus and therefore cannot replicate. However, VLPs, like any other vaccine, can cause side effects such as

Table 1. Challenges in vaccine development.

host variability	Pathogen Variability	Environmental factors
Individual variability	Pathogen diversity	Pollution
Non-responder populations	Hypervariable viruses	Co-infection
Age, Race, Sex, Ethnicity	Antigenic drift	Poor nutrition
	Interactions of Host-pathogen	Obesity
	Immune response evasion	Prior immunity

pain and swelling at the injection site. VLP-based vaccines have been developed using viruses that infect humans. These vaccines are approved against three human viral infections, hepatitis B virus, human papilloma virus and hepatitis E (18).

mRNA vaccine

The concept of vaccines based on DNA and RNA nucleic acids was proposed in the past decades with the hope of being able to develop a flexible, easy-to-produce and safe vaccine. Until the late 2000s, DNA-based vaccines were emphasized due to the stability of RNAs (23). Also, efficient in vivo delivery as well as stimulation of excessive inflammatory responses were obstacles to nucleic acid-based vaccines (24) Fig1. The production of transcribed mRNA in vitro is a relatively simple process (25-27), but the production of therapeutic, non-infectious and high-quality mRNA that can be well translated and cause serious inflammatory responses has been one of the main limitations in this field. In the early 2010s, the problems facing mRNA by optimizing the coding sequence, and purification of mRNA in the laboratory environment by HPLC to remove possible contaminants in the synthesized mRNA led to the reduction of toxicity and improvement of mRNA performance (28). However, there was still a problem with mRNA stability and efficient cytoplasmic delivery (29, 30). Various approaches have been developed to transfer mRNA into the cell, such as the use of gene guns and electroporation (31). These approaches are complex and expensive, and on the other hand, it is difficult to use them in humans, so the most ideal method is to use a substance that prevents mRNA degradation. In the past few years, many materials have been developed for the efficient delivery of nucleic acids, which have brought significant results (32).

mRNA vaccines work by delivering a fragment of mRNA that corresponds to a protein from a virus or other pathogen. People who receive the mRNA vaccine are not directly exposed to the virus, so they cannot be infected by the vaccine. Using this mRNA, cells can produce viral proteins, and as a natural immune response, the immune system identifies pathogen proteins and secretes antibodies against them (33).

The mRNA in these vaccines is not uniform and is rapidly degraded shortly after injection and after the target protein is made, reducing the risk of toxicity and long-term complications. mRNA vaccines enable the precise design of antigenic proteins and on the other hand, by delivering multiple mRNAs to a cell, it enables the production of multi-protein complexes or protein antigens from different pathogens, and thus a single vaccine It can act against several pathogens (34, 35).

Mechanisms that may affect the response of these types of vaccines by B and T lymphocytes include the half-life of antigen availability, the extent of antigen presentation by MHC Class I/II, the participation of other components of the innate immune system, and the cytokine-induced environment. by the mRNA molecule itself as well as its delivery substance (23).

Viral vector vaccines

Adenovirus vectors were initially used as a promising strategy for gene therapy for gene transfer and gene therapy and basic studies to analyze gene function (36). Because these vectors have high transfer efficiency, and relatively large capacity (37), and on the other hand, they are able to infect a wide range of cells, including liver cells, myoblasts, epithelial and endothelial cells, and also induce a moderate level of innate immunity, have high thermal stability (37) Fig1. Therefore, adenovirus vectors are a suitable option for making vaccines. These types of vaccines can be effective in preventing infectious diseases such as the Ebola virus and HIV.

Adenoviruses are non-enveloped viruses that contain linear double-stranded DNA enclosed in a protein capsid.

This group of viruses cause 70 types of diseases in humans and is classified into 7 types (A-G) (38). Infection in humans causes symptoms of cold, sore throat, diarrhoea and vomiting.

Viral vector vaccines use a harmless virus to transfer a piece of genetic sequence to our cells, allowing them to produce pathogenic proteins. The harmless virus acts as a vector to transfer the genetic sequence. Our cells then make the viral protein that was transferred to our cells by the vector and present it to the immune system (39).

However, viral transmission itself plays an important role by enhancing the immune response. Which leads to a more severe reaction to the presentation of the pathogen's genetic sequence to the cell.

Biomaterials vaccine

However, three centuries after the first vaccination, many challenges remain in the development of new vaccines, including low stability, inefficient delivery, and inability to translate into human cells (40). In the last three decades, biomaterials such as synthetic and natural polymers, lipids, microneedles, scaffolds and other particle carriers have been developed to improve the efficacy, long-term safety and stability of vaccines (41, 42) (Fig1).

Biomaterials offer a unique strategy for safe cargo delivery, protection, modification and management for targeted delivery, minimizing the number of injections and reducing systemic toxicity (43-45).

Biomaterials offer many advantages, including

Table 2. Viral vector vaccines are presently authorized for human consumption (59).

Vector class	Vector	Vaccine	Target pathogen	Encoded antigen
Adenoviruses	d5	Ad5-nCoV (Convidecia)	SARS-CoV-2	Spike protein
Rhabdoviruses	VSV	VSV-EBOV (rVSV-ZEBOV, Ervebo)	Ebola virus	Zaire strain (Kikwit 1995) of glycoprotein
Heterologous regimens	Ad5/Ad26	Gam-COVID-Vac (Sputnik V)	SARS-CoV-2	Both spike proteins
Flaviviruses	YF 17D	ChimeriVax-JE (Imojev)	Japanese encephalitis	Viral envelope (prM and E) of JE strain SA14–14–2

biocompatibility, tunable immunogenicity, low inflammatory responses, and relatively high stability over different classes of vaccine delivery. Several types of biomaterials have been developed in micron and nano sizes, there are a large number of biomaterials, few of which offer sustained release properties (40).

Synthetic biodegradable polymers, including polylactic acid (PLA), polylactic-glycolic acid (PLGA), polyurethane (PU), and poly ε-caprolactone (PCL), are the most widely used biodegradable polymers in medicine (46-48).

Meanwhile, PLGA copolymers have been recognized as safe by the FDA and are suitable as a carrier for the sustained release of antigens and vaccine adjuvants due to their safety profile (49, 50).

Another type of biomaterials is polysaccharides, which are composed of carbohydrate polymers and are made of monosaccharide subunits. Polysaccharides form a very wide category of compounds found in plants, bacteria, fungi and even mammals (40). There are different types of polysaccharides, such as alginate (51, 52), cellulose (53), chitosan (54), hyaluronic acid (55), and starch (56), which have been evaluated in vaccines.

Approaches that combine immunogens with biomaterials have emerged as a promising approach for various types of vaccines (57, 58).

Discussion

In the past decade, significant progress has been made in the field of making new vaccines, including mRNA-based vaccines. These vaccines, by optimizing the design of mRNA and its manufacturing processes, have led to the creation of vaccines that are effective in humans. They can be expressed well and have a higher immunogenicity. Another important feature of mRNA vaccines is targeting multiple pathogens simultaneously. They have also been found in some studies to be able to produce strong and long-lasting responses (57, 58).

Viral vector-based vaccines are also a promising field for developing new vaccines. The design of vaccines based on adenoviruses is based on most of the uncommon and non-pathogenic viruses. The structural components of viruses can be modified and optimized to increase tropism to body cells and tissues to optimally bind to body cells and tissues and express antigens efficiently. Adenovirus-based vaccines can be rapidly developed and produced on a commercial scale. Adenovirus vaccines mentioned suitable features such as stability, no need for cold chain transfer and targeted selection. Also, their use against various pathogens and the flexibility of these vaccines have made them suitable candidates for vaccine production (59, 60).

The use of biomaterials due to their wide spectrum and capabilities such as increased control in the release of pathogens, targeted delivery, minimizing the number of injections and reducing systemic toxicity has turned them into a promising approach for the production of new vaccines. Also, biomaterials are biocompatible and produce low inflammatory responses and stable immunogenicity. In general, for any pathogenic pathogen, especially diseases such as HIV, TB, RSV, CMV, and Ebola virus that cannot be prevented with traditional vaccines, it is necessary to develop vaccines with a new method. However it still requires specialized research in the field of each emerging disease (60-63).

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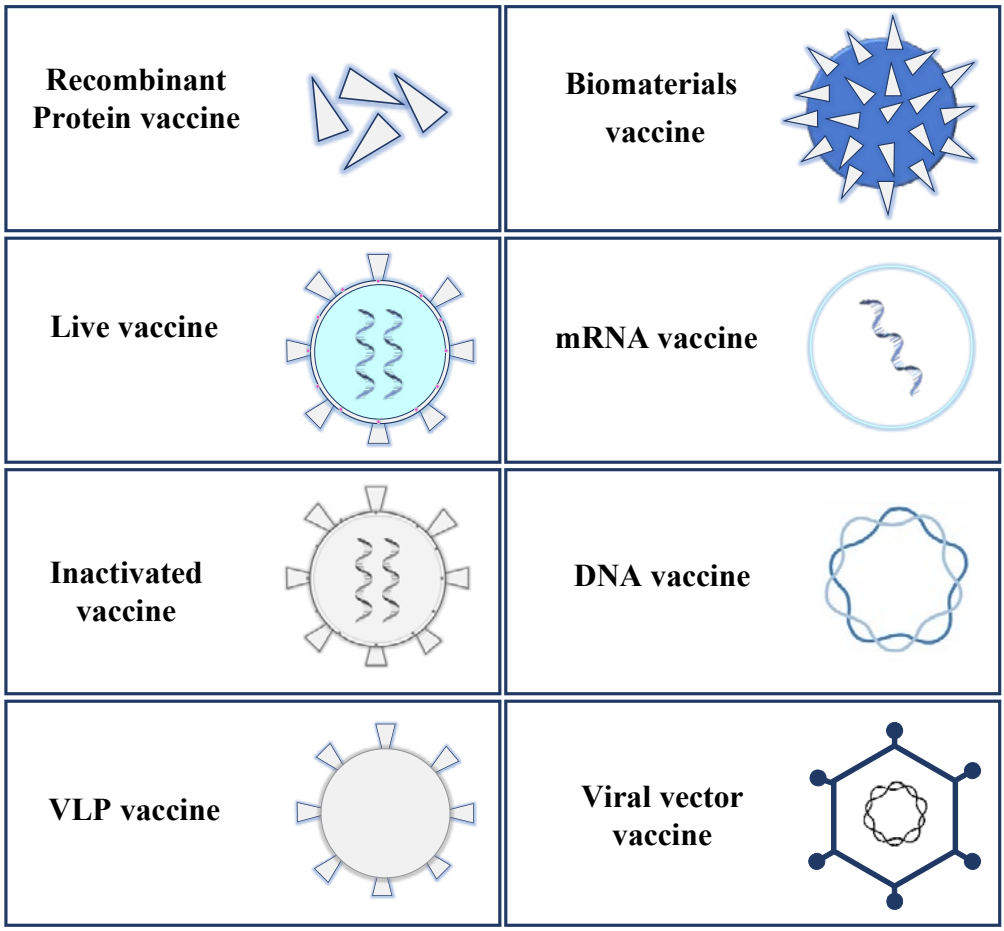

Fig1. All types of vaccines show this figure.

funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent to publication

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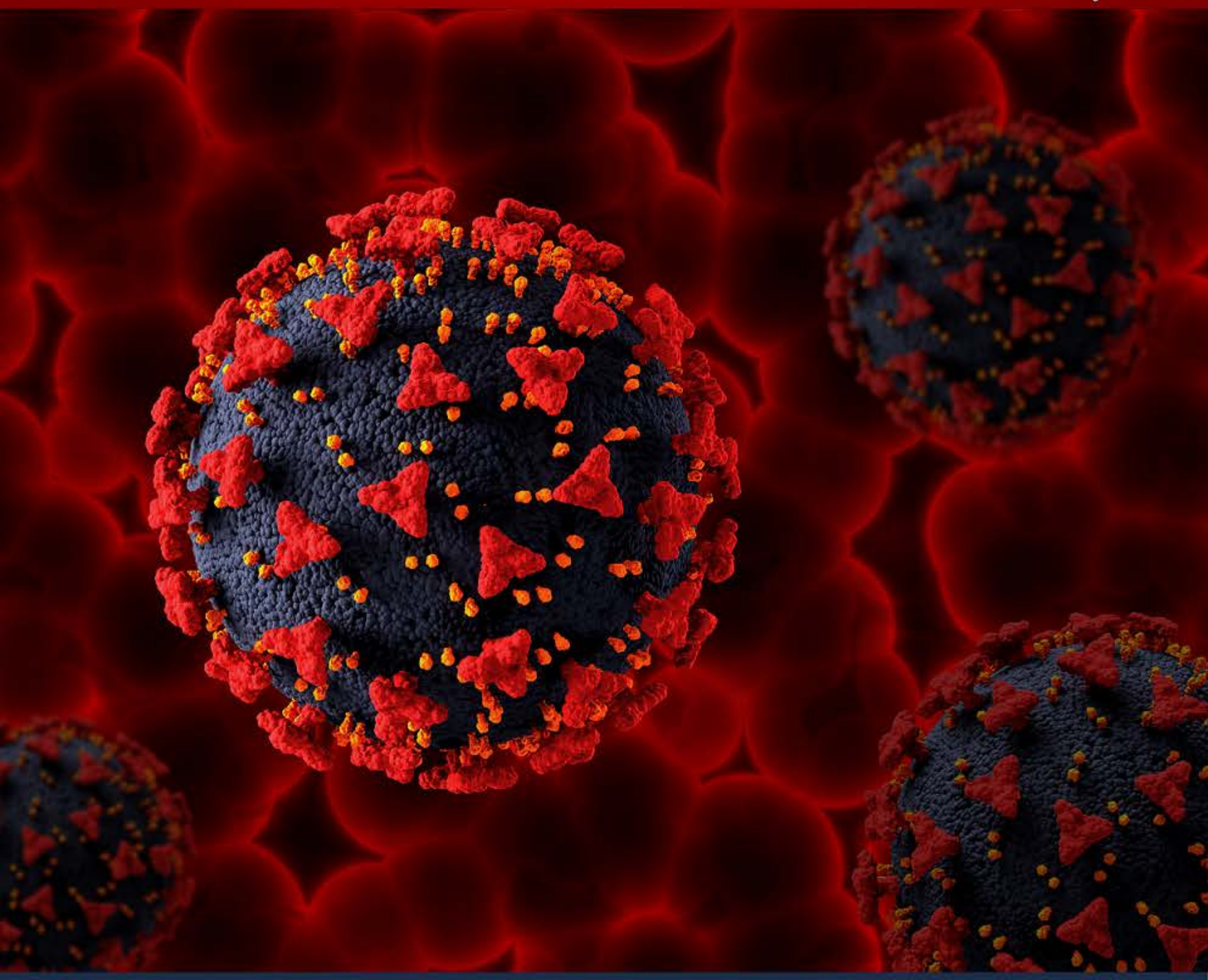

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