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Oncolytic Viruses: Mechanisms, Engineering Strategies, and Clinical Advances

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Abstract:

Today, personalized medicine advanced therapies play a pivotal role in the future of healthcare, an innovative breakthrough in personalized medicine that is shifting the paradigm in care delivery towards an exponentially more customized philosophy of healthcare delivery. These therapies harness the power of multidimensional patient data, such as clinical history, genomic sequences, proteomic and metabolomic profiles, epigenetic landscapes, and lifestyle to tailor interventions in a way that is optimal on an individual basis (maximizing efficacy and minimizing adverse effects). Technological advances that include second-generation sequencing techniques, high-throughput and omics, bioinformatics, and artificial intelligence have catalyzed the development of disease predispositions, molecular subtypes, and predictive biomarkers enabling custom patient stratification and treatment selections. In oncology, advanced therapies include targeted drugs selected by biomarkers, immune checkpoint inhibitors, CAR-T cell therapies, gene editing, and oncolytic viral platforms and are better therapies in specific subsets of patients. Even with all these implementations, hurdles abound, such as the need to standardize large amounts of data, ethical and privacy issues, exorbitant healthcare costs and fair access. Advanced therapies bridge the gap between multi-omics and more sophisticated methods of therapy, offering a promising platform behind which effective and patient-oriented approaches to treatment may become a reality against a wide variety of diseases, becoming a paradigm of new healthcare transformation worldwide.

Keywords: Genomics; Biomarkers; metabolomic signatures, Targeted therapy, Omics technologies.

Introduction

Viruses were considered to be typically morbid and mortal causative agents that could cause significant pathologies historically. The connotation of their image was associated with epidemics like influenza, polio and smallpox and the very idea that they can be used to create therapeutic benefit was counterintuitive (1). However, the entirely opposite notion involving the oncolytic viruses (OVs) redefines such an attitude as those noble agents that are only able to target malignant cells and destroy them leaving no trace on the healthy tissues. This dual ability lysis of tumor cells and stimulation of antitumor immunity lies in the basis of oncolytic virotherapy, the new therapeutic

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modality on the border of virology, immunology and oncology (2).

Early clinical observations tracing the roots of this field may be traced to occasional clinical observations in the first half of the twentieth century, when cancer regressions were reported in individuals with viral infections (measles, influenza, hepatitis) by chance. These tidbits led to experimental studies of naturally occurring lytic viruses, such as West Nile, rabies, yellow fever and hepatitis. Though crude in concept and not more than mechanistically revealed, these experiments planted the concept in the soil that, under certain conditions, viral replication could exert a de-growth of tumor effect (3).

The deficiencies of naturally occurring viruses, however, by the end of the twentieth century- poor selectivity towards tumor cells, safety issues, and inconsistent effectiveness limited the practical use of naturally occurring viruses. The introduction of molecular cloning, recombinant DNA technology and the development of advanced cell culture technology in the 1990s is a major shift (4). As the new millennium dawned, scientists started making genetic modifications to the wild-type viruses, to maximize therapeutic index. Other strategies were the removal of viral genes required to replicate in normal cells but non-essential in tumor cells thus creating increased tumor specificity; the addition of therapeutic transgenes such as cytokines, immune regulators, or prodrug converting enzymes; and the modification of regulatory cues to further control viral replication and immunogenicity (5).

This shift in approach, on the one hand resulting in the rational synthesis of OVs, made a big difference in the perception of OVs as viable anticancer compounds. Soon clinical translation appeared, and adenoviruses, herpes simplex viruses, vaccinia viruses, and reoviruses became major candidates. Notably these engineered viruses do not only exert direct oncolytic effects, but also discharge tumor antigens and danger signals, which essentially vaccinates the host against remaining malignancies (6). The position of oncolytic virotherapy, therefore, is a distinct niche between targeted tumor cytotoxicity and systemic immunization against tumor, and the prospect of synergy with other cancer treatments in the form of chemotherapy, radiotherapy, or immune checkpoint inhibitors (7).

Mechanisms of Action

This therapeutic activity is based on a carefully balanced interaction between viral replication, immunostimulatory effects and tumor cell sensitivity of oncolytic viruses (OVs). Oncolytic viruses wield specificity to exploit cancer cell-specific vulnerabilities, such as impaired tumor-suppressor pathways, impaired interferon-based antiviral antitumor response, and overexpressed cell surface receptors, which bias the virus to attack the cancer cells over sparing the normal cells. Response to treatment thus depends not only on the inherent characteristics of the virus, but also the molecular signature of the tumor to be treated (8).

The fact that OVs multiply selectively in the case of intratumoral replication systems represents a key advantage because it results in the development of the respective cytopathic effects which will lead into a series of forms of programmed cell death, some of which include apoptosis, necrosis, pyroptosis, autophagy, and ICD (9). In particular, release of tumor-associated antigens (TAAs), danger-associated molecular patterns (DAMPs) and cytokines by CLD, resulting in dendritic cell maturation and cross-priming of cytotoxic T lymphocytes is of importance. This way, direct oncolysis is coupled with induction of systemic antitumor immunity in the form of an in situ vaccine (10).

Along with a direct cytotoxic effect, OVs transform the TME to a significant extent. Local inflammation caused by viral infection, augmented antigen presentation, and attracting innate and adaptive immune effectors (like natural killer (NK) cells, macrophages, and T lymphocytes) are the results of this stimulation (11). These immunostimulatory activities also reverse immunosuppressive factors in the TME like Tregs, MDSCs and inhibitory cytokines. This wide-spectrum immune activation distinguishes OVs to any one-pathway targeting agent, such as immune checkpoint inhibitors, or small-molecule agents (12).

The single-cell level is modulated by proliferation rates, the metabolic activity, and the genetic alterations to influence the susceptibility of the tumor to OV-mediated cytotoxicity (13). Tumors with mutations in RAS, p53 or RB pathways tend to be less restrictive of viral replication. The anti-cancer efficacy is dynamic to maintain a balance between viral spread, immune responses, and tumor growth and needs to be extensive enough to generate oncolysis but insufficient to trigger an immune-mediated response (14).

The success of OVs is based on the combination of a direct antitumor effect through tumor cell killing together with a indirect immune effect. Such a dual mechanism can not only minimize local tumor load, but also induce systemic antitumor immunity sufficient to attack metastases and prevent re-growth (15). Through synergistic effects in the TME and activation of diverse immune repertoires, OVs are a multipronged approach that can be used complementarily with current cancer therapies, such as chemotherapy, radiotherapy, or immunotherapy (16).

Preclinical and Clinical Advances

Over the last 20 years, considerable preclinical

research has comprehensively assessed the potential of oncolytic viruses (OVs) in cancer therapy, including both viruses naturally occurring viruses, such as reovirus and vesicular stomatitis virus (VSV), as well as engineered viruses, including adenoviruses, vaccinia viruses and herpes simplex viruses (HSVs)(17). Preclinical models have demonstrated how OVs become tumor selective through a variety of mechanisms involving tumor inhibited pathways of tumor suppressors, altered interferon signaling and tumor enhanced surface receptors. Such studies have shown the ability of OVs to trigger many types of programmed cell death, including apoptosis, necrosis, pyroptosis, autophagy, and especially immunogenic cell death (ICD) at the same time they promote the migration and activation of innate and adaptive immune effector cells (18). In addition, therapeutic transgenes/modulators that can be transduced into engineered OVs can include cytokines, chemokines, or tumor antigens, to boost antitumor immune response and reshape suppressed tumor microenvironment (TME). In sum, these results established mechanistic support of developing OVs into a clinical trial (19).

A number of clinical milestones have established the feasibility, safety and therapeutic efficacy of OVs in humans. A genetically engineered adenovirus, H101, became the first OV to be approved by regulators in China in 2005 to treat nasopharyngeal carcinoma, and showed great efficacy in patients who could otherwise not respond to conventional treatment (20). The United States Food and Drug Administration (FDA) thereafter cleared an HSV-1-based oncolytic virus, talimogene laherparepvec (T-VEC), in advanced melanoma in 2015. T-VEC was described with direct oncolytic activity plus a capacity to produce a granulocyte-macrophage colony-stimulating factor (GM-CSF) that activates dendritic cell recruitment and a system-breadth antitumor immunity (21). Delytact is another genetically modified OV to be approved in 2021 in Japan, as malignant glioma, representing the increase in clinical use of OVs in hard-to-treat tumors. More broadly, what all four approved oncolytic virus therapies share is a variety of viral platforms that harness both cytolytic and immunomodulatory effects (22).

The clinical experience has observed that OVs can be optimally entailing the highest efficiencies when used in combination regimens as opposed to being issued as monotherapies. A mixture of viral replication, susceptibility of cancer cells and the immune system of the host has resulted in monotherapy as potentially inadequate in extending the response to tumors that are heterogeneous (23). The complementary mechanisms of action of different treatment modalities make combination with OVs of interest: OVs + immune checkpoint inhibitors (ICIs): combination with ICIs such as anti-PD-1, anti-PD-L1, or other T-cell-activating immunotherapies may augment T-cell-mediated antitumor immunity OVs + chemotherapy or radiotherapy: combination with chemotherapy or radiotherapy can boost viral penetration, tumor antigen release, immunogenic cell death OVs + targeted therapies: combination with targeted therapies Preclinical studies have repeatedly shown that such combinations are synergistic or additive to tumor growth, leading to a clinically significant increased regression, survival and systemic immunity when compared to monotherapies (24).

In addition, biomarkers and immune surveillance are also becoming an important component of the clinical trials to better design combination regimens. Studies of tumor-infiltrating immune cells, cytokines, and viral dynamics can inform on the mechanisms and predictive markers of response. Examples include those in which high levels of infiltration of cytotoxic T lymphocytes, NK cells, and dendritic cells in treated tumours are associated with better clinical outcomes, as a guide to the rational design of OV-containing regimens (25). Adaptive trial designs and phase I/II trials are evaluating combinations and regimens of doses to maximize direct oncolysis and systemic immune activation and minimize toxicity (26).

Overall, the translational history of oncolytic viruses constitutes a paradigm of mechanistic clarity, engineering know-how, and clinical synergising. These preclinical data have laid solid grounds to the tumor-selective immunostimulatory nature of these agents, and clinical milestones have revealed the safety and therapeutic potential across a variety of malignancies (27). The leading directions include combinations of therapies that are targeting tumor biology and host immune context supported by biomarker-based patient selection. By combining direct cytolytic killing and broad immune activation, OVs are a multi-faceted and increasingly validated type of anticancer agents, able to treat localized disease and metastatic disease (29).

Representative Oncolytic Viruses

Reovirus

Reovirus is a non-enveloped, two-stranded RNA virus that has tropism on the cancer cell level via junctional adhesion molecule-A (JAM-A) receptor, which is over expressed in several different malignancies, such as breast, ovarian, and colorectal cancers. In tumors with activated RAS signaling, its oncolytic specificity is further improved since activating RAS mutations inactivate the antiviral pathway protein kinase R (PKR), permitting productive viral replication (28). The type 3 Dearing strain, which is commercially available as Reolysin, has been studied substantially both preclinically

and clinically, showing a relatively favorable safety profile, the practicality of systemic administration (intravenous administration), and clinically achievable anti-tumor activity as a monotherapeutic agent and in combination with chemotherapeutic agents. Its application in solid tumors such as pancreatic, head and neck, and lung Cancers has been investigated in a clinical trial, indicating that it can complement the conventional treatment (29).

Single-Stranded RNA (ssRNA) Viruses

Coxsackievirus: The viruses of this enterovirus family also use the receptors, decay-accelerating factor (DAF) and intercellular adhesion molecule-1 (ICAM-1), to enter the tumor cells. Engineered Coxsackievirus A21 (CVA21) has been shown to have potential oncolytic effects in melanoma, multiple myeloma, and other solid malignancies, with clinical trials proving induction of tumor necrosis, immune Activity, and increased immune effector penetration of tumors (30).

Seneca Valley Virus (SVV-001): It is a naturally occurring picornavirus with a specificity to target neuroendocrine tumors such as small cell lung carcinoma and pediatric solid tumors. Although preclinical activity was oncolytic, there has been a mixed outcome in the clinic, which points to the need to select patients and the potential use of combined immune-modulatory agents (31).

0762 Poliovirus: The recombinant and attenuated poliovirus variants like HRV2-IRES chimera take advantage of the overexpressed CD155 receptor in glioblastoma cells. The engineering of viruses is being explored to probe whether they can enter the central nervous system, induce tumor lysis and thereby drive local antitumor immunity, without causing poliomyelitis. There have been early-stage trials with good safety and survival outcomes in recurring glioblastoma (32).

Paramyxoviridae Family

Measles Virus: These attenuated Edmonston measles viruses have been genetically altered so as to reduce pathogenicity, but not tumor tropism. It makes use of CD46, which is often overexpressed on cancerous cells or signalling lymphocytic activation receptors (SLAM) as entry receptors (33). Clinical applications have so far been in multiple myeloma, ovarian cancer, and glioblastoma with engineered strains expressing immunomodulatory transgenes (e.g., sodium iodide symporter, cytokines) that improve both direct-oncolysis and overall systemic immunity (34).

Newcastle Disease Virus (NDV): NDV is innately non-pathogenic in humans, and has intrinsic tumor selectivity as it preferentially infects cells with impaired interferon responses. STRs like MEDI5395 are already in clinical testing of solid malignancies and hematologic malignancies, and they are safe and efficiently induce strong immune activity, such as recruitment of NK cells and T cells to the tumor microenvironment (35).

Vesicular Stomatitis Virus (VSV): An enveloped, negative-stranded RNA virus, VSV enters cells by means of LDL receptors. VSV is a promising oncolytic virus since tumor cells with impaired innate immunity type I due to defects in type I interferon signaling are especially vulnerable to viral replication by VSV (36). To improve safety and anti-tumor effects, VSV-sodium-iodide-symporter- NIS, and interferon-B, that is, VSV-IFN beta-NIS, has been produced. Phase I/II studies are underway testing these strains against hematologic malignancies and solid tumors, and occasionally in combination with immune checkpoint inhibitors to synergistically enhance systemic antitumor responses in antitumor immunity (37).

Engineering Strategies

Enhancing Tumor Specificity

Tumor specificity is a central concept to the design of oncolytic viruses (OVs) as highly specific targeting minimizes bystander effects on noncancerous tissue, so viral replication and oncolysis can be focused without broad collateral toxicity (38). One of the most commonly used approaches includes receptor retargeting, whereby viral surface proteins are genetically engineered or adapted to target and bind since they are over-expressed on cancer cells. As an example, Ad5/F35 chimeras have been designed to target selectively CD46, which is often overexpressed in multiple tumors, including ovarian, prostate, and hematologic cancer (39). Similarly, the measles virus has been engineered to express an antigenic configuration that recognizes CD20, thus selectively targeting lymphoma cells but disruption of normal B lymphocytes. In addition to targeting via a single receptor, clever strategies have been developed to target multiple tumor-associated surface proteins using chimeric fibers, bispecific adaptors, and ligand-fused capsid proteins: these OVs can recognize novel targets simultaneously, e.g., epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and mesothelin (40). These adaptations increase the viral tropism, and thus provide efficient attachment, internalization and consequent replication of tumor cells. Other approaches in conjunction with receptor-retargeting are recombination with tumor-specific promoters or microRNA-regulated expression systems, additional modes to minimize viral migrating to normal cells (41). Together, these engineering endeavors enhance the predictability and security of OVs, making them as therapeutically potent as possible and as off-target toxic as minimal, as well as pave the way to

personalized oncolytic treatment that targets the specific molecular characteristics of individual tumors (42).

Improving Replication Selectivity

The selectivity of transduction and the specificity of killing of oncolytic viruses (OVs) is a key drug design feature of OVs, in that OVs need to be designed in a way that will allow the viral replication and killing process to be constrained within the tumor mass as opposed to all surrounding tissues, maximizing antitumor activity and minimizing adverse effects in normal tissue (43). A common strategy is to delete viral genes needed to replicate in the normal cell but not required in the cancer cell because it has acquired specific molecular defects. The best known example is the E1B 55kD deletion of adenoviruses, as used in H101 and ONYX-015, which only replicates in cells lacking p53 pathways, but not in normal cells (44). Besides gene deletions, tumor-specific promoters are used to regulate viral gene expression. Expression of such promoters as survivin, GP73, or E2F-1 is cancer cell-specific, which further contributes to safety and therapeutic specificity by ensuring that essential viral genes are transcribed only in a malignant setting (45). A third model is herpes simplex virus (HSV) based OVs, such as T-VEC, where replication of the virus in normal neurons is prevented by deletion of the neurovirulence gene, 34.5, and the local immune response and remote anti-tumor effects are potentiated by GM-CSF codominance (46). The increased selectivity of OVs can be achieved with dually controlled translation/transcriptional OVs (TTDR-OVs), which have tumor-specific transcriptional elements and either microRNA or another translational controlling element (47). These methods can limit viral action to the tumor site but also limit off-target effects, systemic toxicity, and permit systemic administration in a safer manner. More generally, enhancing replication selectivity is a synthesis of molecular virology, cancer biology, and genetic engineering, the basis of precision-targeted therapies that can exploit aberrations unique to malignant cells (48).

Safety Enhancements

Although tumor selectivity has been improved, the safety of oncolytic viruses (OVs) has been a key issue in the development and translational study of OVs. Several measures have been undertaken to mitigate any possible risk that may be brought about by viral therapy. The activity abatement strategy is a major intervention, whereby neurovirulence or other pathogenicity-related genes are removed or altered, compromising systemic safety and inhibiting infection of other healthy tissues (49). An example is herpes simplex virus (HSV)- based OVs, which can commonly be modified using a deletion of the 734.5 gene so as to reduce neurovirulence without affecting its specificity in tumor targeting (50).

The other important safety measure is the introduction of pharmacologic off-switches. Some of the engineered OVs can be sensitive to clinically accepted anti-viral drugs, and this option would give physicians a means to stop viral replication in case the side effects develop. To illustrate, VG161 harbors a thymidine kinase (TK) gene, and this allows the treatment to be controlled by the use of acyclovir, thus increasing the manageability of the treatment clinician-wise (51).

It is also important to control tropism to off-target organs. The adenovirus, like other OVs, tends to accumulate in organs such as the liver as a result of interaction with the blood factors. Viral capsid modifications, including elimination of factors X (FX) binding sites, have also been used to diminish hepatic sequestration and increase safety (52).

The other factor to consider is the genetic and environmental stability of OVs. Some viruses, including Newcastle disease virus (NDV) and vesicular stomatitis virus (VSV), can, in theory, revert to virulent forms in the presence of selective pressures (53). Clearly, to address this risk, strong genetic controls are incorporated into OV design and deployed, such as multi-gene deletions, synthetic regulators that contain or inactivate OVs or self-limiting systems of propagation (54).

Taken together, the safety improvements, such as attenuation, contact sensitivity, control of organ tropism, and genetic stability, are needed to allow the reliable clinical use of OVs, namely systemic administration with minimum off-target effects and maximum therapeutic benefit.

Integrated Considerations

Contemporary OV therapeutics is taking an increasingly combinatorial approach, involving combinations of objectives in a given therapeutic vehicle. A current development integrates receptor retargeting, transcriptional, and translational control, immunomodulatory transgene expression, and in-built safety switches to make a multi-layered platform (55). Combining viral-specific uptake within the tumor, specific infection of neoplastic cells, and activation of antitumor immune responses, this synergism repeatedly benefits the oncolytic potential of the virus and concurrent triggering of innate immune responses (56).

Receptor-specific structural changes result in specific binding and uptake of tumor cells, and transcriptional/translational control limits viral gene expression in non-tumor cells (57). Immunomodulatory payloads, e.g., cytokines, chemokines or checkpoint-blocking agents, in turn, add to the modification of the tumor

microenvironment (TME), facilitating infiltration and activation of cytotoxic T lymphocytes, natural killer cells, and dendritic cells. Safety features, such as gene deletions, drug sensitivity modules and environmental containment, are employed to protect against systemic toxicity and/or unintended viral release (58).

With the maturation of the field, rational OV design has been increasingly driven by information on tumor genomics, epigenetics and microenvironmental profiling to develop highly personalized precision virotherapies. By doing this, vectors are able to target both molecular weaknesses, immune profiling and the stromal nature of single tumors, further raising the chances of clinical response with minimal adverse effects (59).

This combined engineering approach therefore places oncolytic viruses in a highly flexible and versatile therapeutic platform, able to provide multimodal anticancer activity unique to the tumor biology of individual patients. With the combination of selectivity, immunogenicity, and safety in a single delivery vehicle, next-generation OVs are on the cusp of reshaping the use of virotherapy at the individualized level (59).

The Cold Weapons of Oncolytic Viruses

Engineering of modern oncolytic viruses (OV) is becoming more holistic in design, implementing several mechanisms on board an individual therapeutic vector to achieve the highest levels of effectiveness and mitigate safety. Modern designs are multiple receptor retargeting, transcriptional and translational control, immunomodulatory transgene expression and added safety switches to create a complex, multi-layered platform (60). This complex approach simultaneously augments tumor-specific lysis, blocks viral effects on nonmalignant host tissues, and activates anticancer immunity, profoundly increasing local oncolytic activities and mediating system-wide effects in addition (61).

The cell type-specific insertion of receptor-targeting mods ensures that the virus is only preferentially attached and internalized in tumor cells, whereas translation and transcription ensure only important viral genes are expressed under tumor conditions, reducing the risk of off-target replications in healthy tissues (62). The available knowledge is shown in the immunomodulatory payloads, e.g., cytokines, chemokines, or checkpoint-blocking antibodies, further redesigning the tumor microenvironment (TME), helping infiltration and activation of cytotoxic T lymphocytes, natural killer cells, and dendritic cells. Safety systems to prevent systemic toxicity and unintended viral proliferation are in place, such as system deletion of genes, drug-sensitivity modules, and environmental confinements (63).

As the field matures, rational OV design is facing an ever-greater influence of tumor genomics, epigenetics, and microenvironmental profiling, and as such, highly personalized precision virotherapies are being developed. With this kind of customization, vectors can target molecularly defined vulnerabilities, immune profiles, and stroma of individual cancers and have a higher chance of clinical response and a lower incidence of side effects (64).

Overall, the approach represents oncolytic viruses as a highly multipurpose and designable anticancer therapeutic that could address much more, and more effectively, than perhaps oncolytic viruses were initially intended to achieve. Seamless integration of selectivity, immunogenicity, and safety into one vector has allowed next-generation OVs the potential to revolutionize personalized oncology and to dramatically extend the clinical applicability of virotherapy (65).

Arming Oncolytic Viruses: Transgene Strategies to Enhance Antitumor Efficacy

The use of oncolytic viruses (OVs) to selectively infect and kill tumor cells has the potential to be augmented by genetic engineering of these viruses to incorporate transgenes to enhance their antitumor efficacy. Such cold weapons can help adjust the cancer microenvironment (TME), activate the body's immune system, or kill the cancer cells themselves (66). Among the strategies that have been the subject of most studies is the addition of immune-stimulatory genes, including granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-12 (IL-12), or interferon-beta (IFN-β). The expression of such cytokines draws in dendritic cells, increases antigen presentation, and activates cytotoxic T cells, in effect making the tumor an in situ vaccine (67).

Other transgenes produce pro-apoptotic proteins, e.g. TRAIL (tumor necrosis factor-related apoptosis-inducing ligand), which activate the programmed cell death pathways in malignant cells directly. Moreover, the presence of the genes, which alter the TME through degradation of extracellular matrix elements, decrease of the immunosuppressing cells, or preventing angiogenesis, contributes to promoting the spread of the virus and immune cell infiltration (68).

Newer approaches include bispecific T-cell engagers (BiTEs), or chimeric antigen receptor (CAR) ligands inserted into the viral genome, which can mediate T-cell bridging with tumor cells, bystander killing, and the enhancement of local cytotoxicity. Combination strategies might also include genes that predispose to additional treatment agents, e.g. increasing tumor cell sensitivity to chemotherapy, radiotherapy, or immunotherapy (69).

Modern OVs comprising a combination of selective tumor tropism, regulated viral replication,

and transgene-mediated immunomodulation are highly modifiable cancer therapeutic tools. This versatile engineering allows the design of a custom oncolytic targeted towards the cells of a particular tumor, depending on genetic background or immune microenvironment to maximize the desired therapeutic effect and minimize adverse effects (70).

DISCUSSION

The development of oncolytic viruses (OVs) is renewable to one of the most impressive examples of the convergence of virology, immunology and molecular engineering in revolutionizing cancer therapy. From their first identification as in vivo incidental findings of viral infections that resulted in tumor regression, OVs have become a rationally designed and clinically viable therapeutic platform (5).

Balancing Oncolysis and Immunity

The dual mechanism of OVs, where these vectors induce both lysis of tumor cells and elicit a systemic antitumor immunity is what makes them more different from the use of traditional anticancer agents. Direct oncolysis relieves tumor burden locally, and the release of tumor antigens and danger signals make the tumor an in situ vaccine (5). This duality has profound implications: OVs do not only act as cytotoxic agents, but they are also immune modulators that can reprogram the tumor microenvironment (TME)(72). Unlike immune checkpoint inhibitors, which target one pathway et seq., OVs can produce broad spectrum immune activation, which include dendritic cells, natural killer cells, cytotoxic TL and reversal of immunosuppressive networks (73).

Engineering Breakthroughs and Clinical Realities

Genetic engineering has played a major role in overcoming the shortcomings of the natural viral strains, especially their lack of tumor selectivity and safety issues. Strategies including receptor retargeting, tumor-specific promoters, gene deletions, and transgene insertions have helped dramatically improve not only the therapeutic index but also the safety of OVs.71 However, while those strategies have improved selectivity, they highlight the intricacy of balancing replication potency with the safety of the host cell population. Clinical translation has revealed that recrudescence of disease may occur following monotherapy with OVs, that OVs are often safe although preliminary responses are often limited in heterogeneous tumours indicating the need for rational combination regimens (71, 72).

Combinatorial Therapies: Toward Synergy

The most transformative direction that has emerged from clinical studies is that oncolytic viruses are more effective in combination therapies rather than acting as a monotherapy (32). Combining oncolytic viruses with either immune checkpoint inhibitors may promote longer-lived systemic immunity, but their combination with either chemotherapy or radiotherapy promotes leaky viral entry and triggers immunogenic cell death (72). Novel combinations with targeted medicines show promise, especially in tumours with defined molecular weaknesses. In the future, classification based on biomarkers will be essential in order to optimize these combinations, and get rid of trial and error approaches (73).

Challenges and Future Directions

Despite remarkable advances, several hurdles remain. One of the most pressing issues is the immune system itself: while OVs rely on immune activation for efficacy, premature antiviral clearance can limit viral spread and persistence. Engineering “stealth” viral particles, transient immune modulation, or repeated dosing strategies may help overcome this paradox (74). Another challenge lies in delivery: systemic administration is desirable for metastatic disease, but neutralizing antibodies and the restrictive blood–tumor barrier remain barriers to efficacy. Nanoparticle encapsulation, carrier-cell approaches, and localized delivery are being actively explored to address these limitations (75).

Equally important are regulatory and ethical considerations. The long-term safety of genetically engineered viruses, potential horizontal transmission, and risks of uncontrolled viral replication require stringent monitoring frameworks. Moreover, the high cost of development and manufacturing may limit accessibility, raising equity concerns in global oncology (76).

CONCLUSION

Oncolytic viruses (OVs) are a family of new antitumor agents with combined tumor cell destruction by direct lysis and the induction of a body-wide immune response. Their therapeutic success is linked to their tumor-specific viral replication, programmed cell death induction, such as immunogenic cell death, and/or effects on the tumor microenvironment. Reaction OVs hold promise as multifunctional platforms that can overcome resistance and engage systemic antitumor immunity by making tumors more specific, immune-stimulatory and safer through genetic engineering and transgene arming. The translational potential of their clinical advances, such as H101, T-VEC, and Delytact regulatory approval, is shown. With the fast-developing precision engineering and biomarker-guided interventions, OVs will take a central role in multimodal cancer treatment of the future.

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