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The Dual Role of Neutrophils in Cancer: with a Focus on Targeted Cancer Therapy

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Abstract

Neutrophils have gained significant interest in recent years due to their ability to promote malignancy. A high neutrophil-to-lymphocyte ratio is seen as a prognostic marker for cancer patients. Neutrophils are now recognized as immunological cells of the innate immune system that have several functions and are actively involved in the pathological process of cancer, rather than being just spectators. Their wide range of variations and adaptability are becoming more and more acknowledged. This review provides a concise overview of prior research investigating the functions and processes of neutrophils in the onset, advancement, spread, and recurrence of cancer. We provide a general overview of many studies that examine the characteristics and roles of neutrophils associated with tumors. Additionally, we discuss the formation of neutrophil extracellular traps, which are web-like structures produced by neutrophils that contribute to the advancement of cancer. Furthermore, we explore the interactions between neutrophils and the tumor microenvironment. Furthermore, several focused research on therapeutic neutrophils have achieved notable advancements and shown promising approaches for cancer therapy.

Keywords: Genomic analysis, Autoimmune disorders, Personalized medicine, Neutrophil.

Introduction

Neutrophils are a crucial component of the body's defences that react to infections and tissue injuries. In humans, they make up 50-70% of circulating white blood cells, whereas in mice, they account for 10-25%. Neutrophils are derived from the bone marrow granulocyte monocyte progenitor (GMP) and are discharged into the bloodstream as fully developed cells with a segmented nucleus. Neutrophils are immune cells that have a limited lifespan. In humans, the half-life of circulating neutrophils is about 7 hours, whereas in mice it is roughly 8-10 hours (1). Furthermore, Pillay and colleagues discovered that the mean duration of circulatory neutrophil survival is 5.4 days, as determined using in vivo labeling with 2H2O. Allegedly, the basal production rate of neutrophils is estimated to be between 5×10^{10}–10×10^{10} cells per day. This rate is necessary to provide a sufficient quantity of neutrophils in the bloodstream. Variables like as inflammation and tumors might

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boost this generation rate (2). Importantly, persistent disruption of the body's internal clock may facilitate the spread of cancer cells and the formation of secondary tumors. The diurnal rhythm of neutrophils is closely associated with the C-X-C motif chemokine receptor 2 (CXCR2) and CXCR4. The transcriptional and migratory features of circulating neutrophils are influenced by CXCR2 in a diurnal manner, leading to the ageing of neutrophils. The function of CXCR4 is to facilitate the removal of neutrophils and provide protection to the cardiovascular system (3).

Neutrophils can enter tumors and contribute to the advancement of cancers via their adaptable characteristics and functional flexibility. Tumor-associated neutrophils (TANs) exhibiting a pro-tumor phenotype participate in every phase of tumor development, including tumor initiation, metastasis, and immunosuppression (4). High levels of neutrophil infiltration in solid tumors often indicate worse clinical outcomes for patients. For example, an elevated neutrophil-to-lymphocyte ratio (NLR) in the blood is associated with a worse chance of survival in several types of solid tumors, particularly in later stages of cancer. Nevertheless, accumulating data has also shown that TANs may hinder the progression of malignancies by directly eliminating tumor cells or stimulating innate or adaptive immune responses. Thus, TANs can exhibit both pro- and anti-tumor actions inside the tumor microenvironment (TME). Furthermore, gaining a more profound comprehension of the dynamic equilibrium of TANs will aid in the advancement of treatments that specifically target neutrophils in cancer (5).

In this analysis, we examine data from published research that pertain to the transformation of neutrophils in the TME, with a specific emphasis on the impact of neutrophils in either inhibiting or facilitating tumor advancement. Additionally, this study provides a concise overview of the developing therapeutic approaches that specifically target neutrophils for the treatment of cancer (2, 8).

Source and phenotype

the source, employment, and phenotypic alterations (transitioning between antitumour and pro tumour) of neutrophils in cancer tissues have been linked to particular medical results, and current investigations have successfully identified the precise function and pathophysiology of TANs (6). Neutrophils are constantly generated and stored in the bone marrow under typical physiological conditions. The haematopoietic cords, located in the bone marrow, act as the origin of neutrophils, with typical myeloid progenitor cells being the real origin of neutrophils inside the venous sinuses. Transcription factors include CCAAT-enhancer binding protein (CEBP/α) and AML-1 (acute myeloid leukemia 1), together with colony-stimulating factors, facilitating the production of neutrophils without any problems (6).

TANs may exhibit various phenotypes because of the presence of a wide range of transcription factors and specific proteins. Several studies have classified neutrophils into distinct subsets based on various criteria to study their differentiation. In this summary, we provide the most prevalent categorization outcomes based on morphological and functional distinctions: the N1, also known as antitumour neutrophils, and the N2, also known as protumour neutrophils (7). N1 and N2 are the two cell populations that have been widely researched in terms of their physical characteristics and biological roles. Interferon type 1 (IFN-1) is primarily responsible for inducing neutrophil polarization into the N1 phenotype, which enhances adhesion, transmigration, phagocytosis, oxidative bursts, dysregulation, and the formation of neutrophil extracellular traps (NETs). Alternatively, when exposed to transforming growth factor-β (TGF-β), neutrophil differentiation advances towards the N2 state, which regulates the immune system. The transition from N1 to N2 implies that IFN-1 and TGF-β may have opposing signaling pathways. Significantly, there are clear disparities between immature N2s and mature N2s, particularly when they are subjected to certain pathological circumstances (8).

N1 cells, known as antitumour neutrophils, exhibit cytotoxicity against cancer cells by the formation of reactive oxygen species (ROS). This ROS production activates TRMP2, an H_2O_2-dependent Ca^{2+} channel, resulting in the fatal influx of calcium ions in tumor cells. Recent research has shown further methods of inhibiting cancer cells, where Ribonucleic acids (RNS) released by N1 cells are taken in by tumor cells and modify the activity of genes associated with cancer. In contrast, N2 demonstrates the capacity to promote tumor growth by producing a wide range of enzymes, including myeloperoxidase, neutrophil elastase (NE), and matrix metalloproteinases. These enzymes can modify the dense ECM to facilitate the process of angiogenesis and the migration of cancer cells (9).

The role of neutrophils in the process of tumorigenesis

Onset of cancer

In cancer start, inflammation is a vital factor since it causes tissue damage, and neutrophils play a critical part in this mechanism. Neutrophils serve as a connection between inflammation and malignancy. Ovarian cancer that arises in different mouse models with KRAS mutations demonstrates increased expression of chemokines associated with neutrophils and an expansion of neutrophil populations. The observed characteristics may be caused by the direct

increase in the production of cytokines associated with neutrophils, such as GM-CSF and CXCL8 (10). In a zebrafish model of HRASG12V-driven melanoma, the presence of wounding-induced inflammation leads to an increase in cancer growth. This increase is specifically reliant on neutrophils and is accompanied by higher levels of prostaglandin E2 (11). The use of anti-Ly6G antibodies to eliminate all neutrophils has a detrimental effect on the development of cancer in both chemically induced and spontaneous cancer models. Neutrophils that have an increased level of CXCR2 are drawn to tissues that are prone to cancer via the action of the cytokine IL-8 and chemokine ligands CXCL1, CXCL2, and CXCL5. Papilloma or adenoma development is prevented by applying chemical carcinogens to mice that are defective in CXCR2, which results in decreased neutrophil transport. The movement of neutrophils from the bone marrow to the peripheral circulation is hindered by the presence of CXCR4, which causes the neutrophils to be held back by bone marrow stromal cells that produce CXCL12. Subsequently, bone marrow macrophages remove the residual neutrophils in a rhythmic fashion (11).

Neutrophils cause DNA damage

The aforementioned research has shown the essential role of neutrophils in the development of cancer. However, further investigation is needed to fully understand the specific processes via which neutrophils promote carcinogenesis. Neutrophils generate and discharge genotoxic DNA compounds that enhance DNA instability. Using an in vitro coculture paradigm that imitates intestinal inflammation in ulcerative colitis, it has been shown that neutrophils enhance the occurrence of replication mistakes in colon epithelial cells. Activated neutrophils in persons with chronic colon inflammation lead to the buildup of target cells in the G2/M phase, which indicates the presence of a DNA damage checkpoint (12). The process may be linked to neutrophil-derived elastase, the generation of ROS and reactive nitrogen species (RNS), as well as angiogenic factors like MMP-9. Additionally, the immunosuppressive capability of neutrophils may also play a role in this process. ROS that are generated by neutrophils during chronic inflammation, such as hypochlorous acid (HOCl) produced by myeloperoxidase (MPO), induce DNA damage and exhibit carcinogenic properties in lung cells when tested in vitro. HOCl is a primary oxidizing agent produced by neutrophils. The production of HOCl by MPO during lung inflammation is a significant cause of genotoxicity generated by neutrophils. Neutrophils contribute to DNA damage by generating ROS and triggering genetic alterations in premalignant epithelial cells. This process ultimately leads to the development of oncogenic transformation in lung cancer. In addition, at normal levels seen in the body, HOCl causes mutations in the hypoxanthine phosphoribosyl transferase (HPRT) gene, resulting in three main forms of DNA damage (13). Haqqani et al. examined a mouse model of subcutaneous cancer and demonstrated a substantial correlation between the number of mutations in the Hprt locus and the levels of inducible nitric oxide synthase (iNOS) and nitric oxide synthase (NOS) as well as the infiltration of neutrophils (14). Nevertheless, a novel mechanism that is independent of ROS has been recently discovered. Excited neutrophils that infiltrate the tissues of patients with inflammatory bowel disease and injury models release particles containing pro-inflammatory microRNAs, such as miR-23a and miR-155 (15). These microRNAs contribute to the occurrence of DNA double-strand breaks and genomic instability. miR-155 is implicated in both the induction of DNA damage and the regulation of DNA repair in acute colon injury caused by neutrophils. This process has a role in the beginning and development of colorectal cancer (15).

Neutrophils stimulate the formation of new blood vessels and inhibit the immune response

Coussens et al. reported that MMP-9, produced by neutrophils generated from bone marrow and other hematopoietic cells, has a role in the development of squamous cell carcinoma. Neutrophils create MMP-9, which also plays a role in the development of pancreatic islet carcinoma and lung cancer by promoting angiogenesis. NETs contribute to inflammation in individuals with nonalcoholic steatohepatitis, leading to the formation of hepatocellular carcinoma (16). However, this process may be prevented by treating it with deoxyribonuclease or by eliminating peptidyl arginine deaminase type IV, which reduces the creation of NETs. Moreover, there is a positive correlation between NETs and the higher count of regulatory T cells (Tregs) in cancer. This correlation is achieved by aiding in the metabolic reprogramming of naïve CD4+ T cells. Therapies that focus on the interplay between these two kinds of cells or hinder the function of Treg cells may enhance the immune system's ability to detect and prevent the growth of hepatocellular carcinoma (17).

The secretion of Bv8 by neutrophils has been identified as a characteristic that indicates the development of new blood vessels in tumors, known as tumor angiogenesis. Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is a cell adhesion molecule that is abundantly present on Gr1+CD11b+ myeloid cells. It has the ability to inhibit angiogenesis via the G-CSF-Bv8 signaling pathway (18). Moreover, the VEGFA molecule can control almost every element of tumor angiogenesis,

such as embryonic cell sprouting and assembly, lumen development, vascular expansion, and permeabilization. Scapini et al. discovered that VEGFA generated from neutrophils plays a crucial role in the process of angiogenesis triggered by CXCL1/MIP2. TAN2 is a significant contributor of MMP9 in the TME. Neutrophil gelatinase-associated lipocalin (NGAL), generated by TAN2 and neoplastic cells, might potentially boost the pro-angiogenesis impact of MMP9. Regularly, IFN-β hinders the synthesis of VEGFA and MMP9 by neutrophils, hence inhibiting their pro-angiogenesis capability in mouse cancer models. Neutrophils have been shown to have a vital role in promoting angiogenesis at the location of a tumor (19).

Neutrophil extracellular traps (NETs)

NETs generated by TANs contribute to tumor growth via their dual functionality. The anticancer activity of NETs mostly stems from their ability to directly kill cancer cells and activate the immune system. Nevertheless, NETs are well recognized for their pro-tumor characteristics (20). In a mouse model of infection, NETs were shown to accumulate in small blood vessels and catch circulating lung cancer cells by forming DNA webs. This process ultimately resulted in the formation of small metastases in the liver. NETosis, a process that increases the quantity of circulating DNA, has the potential to cause tumor-associated stroke. Neutrophils produce MMP-9 during degranulation, which may directly hinder cell death, stimulate cell proliferation, enhance tumor angiogenesis, and facilitate the distant spread of tumor cells by breaking down the extracellular matrix (21).

NE plays a crucial role in the bactericidal activity of NETs. The expression and activity of NE are increased in many types of malignancies, such as lung carcinoma and pancreatic ductal adenocarcinoma (PDAC). There have been reports indicating that the level of serum NE is directly associated with the disease status and progression in patients with lung cancer. Additionally, it is believed that this correlation may play a role in the development and spread of primary tumors. Neutrophils-derived MMP-9 and NE were shown to be involved in the breakdown of laminin by proteolysis. This process may activate integrin α3β1 signaling, which promotes the rapid growth of latent cancer cells. The use of an antibody against MMP-9 and NE can effectively inhibit the activation of dormant cancer cells (21, 22).

The possible underlying process may include the capacity of NETs to be captured or the commencement of chemotaxis and adhesion enhanced by a DNA receptor that directly interacts with NETs or integrins. Tumor cells need an ample supply of oxygen and nutrients, which are delivered by blood vessels due to their rapid growth and development. Angiogenesis, which refers to the formation of new blood vessels, is enhanced by the release of NETs triggered by the binding of angiopoietin 1/2 to Tie 2 receptors. NETs may directly promote the growth of cancer cells. For example, Houghton et al. proposed that NETs produced in Lewis lung carcinoma might directly enhance tumor development. They observed that tumor cells grew at a slower rate in animals lacking the PAD4 enzyme compared to normal mice (21).

The relationship between the NET and tumor resistance

Drug-resistant cancer is a globally significant condition that is considered incurable, posing a serious health hazard. Research on resistance has always captivated the attention of scholars. NETs worsen the prognosis following treatment since they have been previously explained to encapsulate tumor cells and increase resistance to chemotherapy, immunotherapy, and radiation. Tumor cells secrete IL-1β under certain chemical conditions, which subsequently stimulates the generation of NETs (22). A network is established when the two essential proteins, integrin-αvβ1 and matrix metalloproteinase 9, are both present. These proteins possess the capability to capture and stimulate TGF-β. The stimulation of TGF-β triggers the onset of epithelial-mesenchymal transition (EMT) in cancer cells, which is associated with the development of resistance to chemotherapy. The resilience shown by NETs may be associated with their structural attributes. More precisely, NETs that develop inside tumor tissues operate as defensive barriers, obstructing the interaction between tumor cells and therapeutic drugs. Furthermore, the chemical composition of NETs may have a pivotal impact on resistance. For example, IL-17, an interleukin present in NETs, may engage with cytotoxic CD8 T lymphocytes and hinder their infiltration into tumor tissues (23, 24).

Tumor metastasis

Neutrophils contribute to tumor metastasis by promoting the movement, infiltration, establishment, and breakdown of the ECM by cancer cells. The upregulation of the anti-apoptotic molecule Mac-1 (CD11b, αMβ2) on the surface of neutrophils in response to lipopolysaccharide (LPS) stimulation enhances liver metastasis by facilitating the adhesion of circulating tumor cells (CTCs) (25). The secretion of IL-8 by human melanoma cells may enhance the expression of β2 integrin on neutrophils. This process is facilitated by the contact between ICAM-1 on melanoma cells and β2 integrin on neutrophils, ultimately resulting in the spread of tumor cells to other parts of the body. Leukotrienes produced by neutrophils may facilitate the migration of cancer cells to remote locations. Moreover, specifically

blocking the activity of the enzyme arachidonate 5-lipoxygenase (Alox5) that produces leukotrienes might potentially restrict the spread of cancer to other parts of the body in animal models of breast cancer (25).

Neutrophils were discovered to function as transporters and suppliers of nutrients to facilitate the spread of malignancy. Szczerba et al. revealed that neutrophils could accompany circulating tumor cells (CTCs) in the circulation, hence promoting tumor advancement and hastening the spread of cancer to other parts of the body (26). Li and colleagues discovered that neutrophils may cause the buildup of neutral lipids when stimulated by lung-resident mesenchymal cells, resulting in the spread of breast tumor cells to the lungs (27). Neutrophils have a role in controlling the spread of tumors by interacting with other immune cells and mediators. IL-1β stimulates γδ T cells to produce IL-17, which causes the growth and differentiation of G-CSF-dependent neutrophils. This, in turn, inhibits the function of anti-tumor CD8+ T cells and promotes the spread of breast cancer. Neutrophils that express CD11b and Ly6G markers can inhibit the anti-tumor activity of NK cells, hence promoting the survival of cancer cells. Furthermore, this specific kind of neutrophils has the ability to release IL-1β and matrix metalloproteinases (MMPs) to enhance the movement of cancer cells from blood vessels into surrounding tissues (28).

Focus on targeted cancer therapy

Neutrophil function alterations have a crucial role in tumor development, metastasis, and angiogenesis. Numerous clinical trials have previously been undertaken to target specific treatment locations. The combination of specific suppression of neutrophil activities and a decrease in neutrophil quantities has resulted in limited options for safe and effective treatments. These targets do not necessarily have to be exclusive to the surface of neutrophils, and the therapeutic activities might be either direct or indirect. Nevertheless, advancements are being achieved in the field of neutrophil treatment (2, 8).

Focusing on the process of metabolism

Neutrophils are the most abundant form of white blood cells found in the bloodstream. Due to their high daily production and role in systemic immunity, it is difficult to develop medicines that target all neutrophils. Such therapies also pose a risk of increasing susceptibility to other illnesses, since they impair innate immunity (29). Focusing on the unique attributes of TANs might be a viable therapeutic approach. Interestingly, focusing on glutamine metabolism seems to be a promising approach for therapy, considering that both tumor cells and TANs have a crucial need for these amino acids. A recent study used mice models with 4T1 breast tumors implanted subcutaneously. These animals were treated with JHU083, a glutaminase inhibitor. The administration of this medication led to a reduction in G-CSF levels and the movement of MDSCs, while also inducing increased apoptosis in the tumor cells (29, 30).

Focusing on NET

As previously stated, NETs may facilitate the onset and spread of tumors. Platelets that are trapped by NETosis can block the entry of circulating tumor cells into the immune system, therefore preventing metastasis (8, 28). This is especially effective in instances when the immune system is not involved and there are no opposing effects from the shear forces of blood flow. This approach signifies a recently identified therapy objective. Recent study has shown that platelet-derived factors may limit the spread of cancer cells to other parts of the body. The complement system also contributes to the therapy of tumors. C5a, a crucial element that stimulates the movement of immune cells towards inflammation and the release of inflammatory substances, may activate PMN-MDSCs to support the development and spread of cancer cells via the creation of NETs. Inhibiting C5a and its receptor C5aR1 is an effective strategy for reducing the spread of tumors (31).

Neutrophil elastase (NE) is a distinct kind of serine protease that is usually found in the main granules of neutrophils. Before modern times, research has shown that the release of NE and the creation of NETs may work together to influence the growth and spread of tumors. The NE released by neutrophils is referred to as ELANE, and it selectively eliminates various kinds of tumor cells while preserving normal cells. Nevertheless, the abundance of protease inhibitors in the TME hampers the function of NE, resulting in the safeguarding of just tumor cells. Through extensive research, we have discovered that the porcine-derived ELANE homologue is very effective in overcoming this obstacle. Unlike other ELANE homologues, it is more resistant to serine protease inhibition due to its well-preserved catalytic activity (32, 33).

Drug delivery system targeting

Neutrophils, which are the most abundant white blood cells in the circulation, play important roles in acute inflammation and immunological responses against cancer. Neutrophil recruitment, adhesion, and tissue infiltration are crucial pathological alterations in cancer. Using these chemotactic properties and replicating the genetic material into a targeted medication carrier is a potential approach to cancer treatment. There are two main types of drug delivery systems: neutrophil carriers and nanovesicles made from cellular membranes (34).

Neutrophils with chimeric antigen receptors (CAR) have been created by ingeniously modifying pluripotent stem cells by the use of CRISPR/Cas9-mediated gene integration. This method allows for the creation of several, precise anti-glioblastoma (GBM) CAR constructs. The main goal of these modified neutrophils is to effectively cross the blood-brain barrier and deliver nanodrugs that respond to the tumor microenvironment, thereby precisely targeting glioblastoma with accuracy. Utilizing R-Sio2-TPZ nanoparticles to load CAR-T cells, which have shown high efficacy in eradicating GBM cells, has been scientifically validated as a safe and effective approach in cancer treatment (35).

Extracellular vesicles (EVs), produced by cells in the body, are a naturally occurring and effective medication delivery mechanism owing to their potency and ability to kill cells (36). These particles are produced from the membrane and function in the recognition and communication between cells. Neutrophils are attracted to cancerous tissues, and there is also a high presence of extracellular vesicles generated by neutrophils in these tissues. Next, we explore strategies for increasing the production of EVs and determining suitable therapeutic medicines for loading. Simpson observed that the use of nitrogen cavitation to disturb cultured cells may significantly enhance the generation of EVs (37). In a separate investigation carried out by Coffelt et al., scientists merged nanovesicles produced from neutrophils with nanoparticles carrying carfilzomib (CFZ), a proteasome inhibitor of the second generation. This compound is referred to as NM-NP-CFZ. Previous studies have shown that NM-N0-CFZ can decrease the presence of circulating tumor cells (CTCs), which are crucial for tumor metastasis. Additionally, it also hinders the development of an early metastatic environment (38).

Conclusions

This review has emphasized the existence and importance of neutrophils in cancer and examined the clinical evidence produced from studies investigating medicines that target neutrophils to treat cancer. Neutrophils can eradicate tumor cells via either indirect or direct cytotoxic mechanisms. Furthermore, the capacity of CD8+ T cells to kill tumor cells might be improved by the adaptive immune response that is generated by neutrophils. However, neutrophils found in malignancies often exhibit both phenotypic and functional flexibility. Recent research has shown the methods via which neutrophils contribute to the advancement of tumors at several stages, including carcinogenesis, tumor development, metastasis, angiogenesis, tumor-associated thrombosis, and immunosuppression. Current clinical and preclinical research have identified numerous significant target molecules that are associated with neutrophils. These molecules have been described and their potential as both cancer diagnostic biomarkers and therapeutic targets has been highlighted.

In the future, there will be continuous progress in the field of targeted neutrophil treatment via the fast improvement of biological technology. This will lead to discoveries and developments in the study of neutrophils. A deeper understanding of the mechanics behind recently discovered treatments may be supported by conducting more complicated studies that closely mimic the intricacies of human physiology. Further research should be conducted to optimize the targeting of medications since targeted therapies are more expensive than conventional chemotherapeutic agents and there is room for improvement in their use. The integration of targeted treatment with chemotherapy seems to have more therapeutic value, given the significantly reduced occurrence of adverse effects shown in the existing clinical trials. Studies on the processes and pathways related to neutrophils might also aid in the identification of novel biomarkers that can assess the effectiveness of current treatments for patients. Collectively, these results indicate that forthcoming cancer treatments may have the potential for specifically targeting neutrophils. However, at now, therapies aimed at neutrophil targeting are not the preferred choice due to the aforementioned problems.

Authors' Contribution

Farnaz Roshan Mehr and Fatemeh Gabeleh were involved in the conceptualization, design and writing of the manuscript draft. The authors read and confirmed the final manuscript.

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