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Future Direction of Neutrophil-based Cancer Immunotherapies

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Mini Review

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Abstract

Neutrophils are increasingly being investigated for their potential to be used as an immunotherapy for cancer. Research into this area has demonstrated that neutrophils can target and destroy cancer cells and stimulate an immune response to fight the cancer. The next step in this research is to understand how to optimize the use of neutrophils for cancer immunotherapy and to identify potential therapeutic targets. One concern is the possibility of excessive inflammation caused by the activated neutrophils, which could lead to tissue damage and adverse immune reactions in patients. Additionally, there may be a risk of off-target effects where neutrophils attack healthy cells instead of cancerous ones. Investigating these potential side effects and developing strategies to minimize them will be essential for ensuring the safety and efficacy of neutrophil-based therapies in clinical settings.

Keywords: Neutrophil; Inflammation; Cancer; Immunotherapy; Anti-PD1

Mini Review

More than 70% of all circulating leukocytes in humans' bodies are neutrophils, which are responsible for the first response of the body to injury, infection, and inflammation. Neutrophils trigger several effector functions in response to infection-associated signals, including the production of neutrophil extracellular traps (NETs), the production of reactive oxygen species (ROS), and the production of antibacterial peptides [1]. Perhaps because of the reported short lifespan of neutrophils, they were previously overlooked as functionally important. However, recent studies suggest they can survive in circulation for up to five days, bringing renewed attention to their role under varied biological conditions [2].

Over the last two decades, various immunotherapeutic agents have been approved as treatment for several human cancers, and the focus is on targeting important immunosuppressive molecules in both tumor and immune cells. Immune checkpoint blockade inhibition (ICI) therapy has been extensively tested and approved as first-line treatment for various cancers [3]. Although the development of ICIs has emerged as a revolutionary milestone in the regression of tumors, and enhancing immune system activity for promoting its antitumor activity, as well as overcoming immune suppression, multiple studies have shown that immunotherapy of cancers as a therapeutic modality has mostly failed in most patients with solid tumors [4]. It should be noted that certain combinatorial treatment approaches have improved the treatment of cancer patients with solid tumors. For example, anti-programmed death-1 (anti-PD1) monoclonal antibody in combination with chemotherapy has proven effective in non-small cell lung cancer patients (NSCLC). In another case, treatment with anti-PD1 monoclonal antibody, combined with the monoclonal antibody ipilimumab, which improves the response of the T cells by targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), successfully treated cancer in advanced melanoma patients [5]. However, due to a low response rate

or higher immune toxicities, most cancer patients still do not receive satisfactory benefits from immune checkpoint blockade therapy [6]. This negative reaction is associated with the multidimensional tumor microenvironment (TME), which seems to exert some resistance mechanisms, leading to a limited response to immunotherapeutic agents [7]. Neutrophils emerge as central effector cells of the innate immune system and are associated with poor results in many types of human cancers [8]. Accumulating evidence suggests neutrophils are key components of TME, drive tumor progression, limit the effectiveness of immunotherapy by establishing immunosuppressive properties, and reduce the effectiveness of immunotherapy by manipulating the adaptive immune system [9].

It has been shown that cytokines and chemokines play a crucial role in orchestrating neutrophil recruitment to tumor sites, ultimately influencing the function and behavior of these immune cells within the tumor microenvironment. Various cell types secrete these signaling molecules, including immune cells, stromal cells, and cancer cells themselves.

Cytokines, such as interleukins (ILs) and tumor necrosis factors (TNFs), modulate immune cell activation, proliferation, and differentiation. They can act on both neutrophils and other immune cells present at the tumor site to regulate their interactions. Chemokines, on the other hand, are a family of small proteins that primarily govern the directional migration of immune cells toward specific locations. By forming concentration gradients within the tumor microenvironment, chemokines guide neutrophils toward areas where they are needed for an effective anti-tumor response. Some key cytokines and chemokines involved in regulating neutrophil recruitment to tumor sites include [10]:

CXCL1/CXCL2: These chemokines bind to the CXCR2 receptor on neutrophils, promoting their migration towards tumors. Cancer cells often secrete high levels of CXCL1/CXCL2 as a means of attracting neutrophils to facilitate angiogenesis or suppress anti-tumor immunity.

IL-8 (CXCL8): IL-8 is another potent neutrophil chemoattractant that also signals through the CXCR2 receptor. In addition to promoting neutrophil migration, IL-8 can stimulate degranulation and release of reactive oxygen species (ROS) by these cells.

G-CSF: Granulocyte colony-stimulating factor (G-CSF) is a cytokine that stimulates the production of neutrophils in the bone marrow and enhances their survival. G-CSF can also promote neutrophil migration to tumor sites by upregulating the expression of chemokine receptors, such as CXCR2.

IL-17: This pro-inflammatory cytokine is produced mainly by T helper 17 (Th17) cells and has been implicated in enhancing neutrophil recruitment to tumors. IL-17 acts on stromal cells within the tumor microenvironment, inducing them to secrete chemokines like CXCL1, CXCL2, and IL-8 that attract neutrophils.

Recent studies have shown that the cancer-mediated secretion of CXCL5 promotes mature pro-tumorigenic neutrophil infiltration in non-small cell lung cancer and impairs the differentiation of antitumor CD8 + T cells [5]. Moreover, recent studies indicate that neutrophils can be classified into two main subtypes: N1 and N2. These subtypes have distinct roles in cancer immunotherapies, as they exhibit different behaviors and functions within the tumor microenvironment [11].

N1 Neutrophils are considered pro-inflammatory and possess anti-tumor properties. They release cytokines such as TNF-alpha, IL-12, and IFN-gamma, which promote an immune response against tumor cells. Additionally, N1 neutrophils can directly kill cancer cells through phagocytosis or by releasing reactive oxygen species (ROS) that cause cell damage. In cancer immunotherapies, N1 neutrophils are often targeted for their ability to enhance the effectiveness of treatments by stimulating the immune system to attack tumors [12].

N2 Neutrophils, on the other hand, are considered pro-tumorigenic and have been associated with tumor growth and progression. They secrete factors such as TGF-beta, IL-10, and VEGF that suppress immune responses or promote angiogenesis—a process where new blood vessels form to supply nutrients to tumors. Due to their immunosuppressive nature, N2 neutrophils can hinder the success of cancer immunotherapies by protecting tumor cells from immune-mediated destruction [13].

The seemingly contradictory roles of neutrophils as both pro-tumorigenic and anti-tumorigenic can be attributed to the dynamic nature of the tumor microenvironment (TME). This environment consists of various cellular components, signaling molecules, and extracellular matrix proteins that interact, influencing the behavior of neutrophils. For instance, when neutrophils are exposed to certain inflammatory signals or growth factors within the tumor microenvironment, neutrophils can be polarized toward the N1 phenotype. This process is characterized by the activation of transcription factors, such as NF-kB and STAT3, which promote a pro-inflammatory gene expression profile. As a result, N1 neutrophils release cytokines and chemokines that recruit and activate other immune cells to mount an effective anti-tumor response. On the other hand,

neutrophils can adopt an N2 phenotype in the presence of immunosuppressive cytokines or chemokines like TGF-beta or IL-10. The polarization towards this subtype involves different signaling pathways, such as PI3K/AKT and JAK/STAT6. N2 neutrophils contribute to an immunosuppressive tumor microenvironment by secreting factors that inhibit immune cell activation or promote angiogenesis. Recent studies have begun to shed light on the complex relationship between stress, psychological factors, and neutrophil function in cancer patients. These factors can influence the efficacy of immunotherapies and treatment outcomes [14].

Another important factor in the impact of neutrophils on cancer progression is Neutrophil Extracellular Trap (NET) Formation. NETs are web-like structures composed of decondensed chromatin and antimicrobial proteins released by neutrophils in response to various stimuli, including bacterial or fungal infections, inflammatory signals, and even cancer cells. The process of NET formation, known as NETosis, involves a series of steps that lead to the extrusion of these structures from neutrophils [15].

Activation: Neutrophils become activated upon encountering pathogens or pro-inflammatory signals within the tumor microenvironment.

De-condensation: The nuclear envelope of the activated neutrophil breaks down, leading to chromatin de-condensation.

Mixing: Granules containing antimicrobial proteins fuse with the decondensed chromatin, forming a mixture of DNA and proteins.

Extrusion: Finally, the cellular membrane ruptures, releasing the DNA-protein mixture into the extracellular space as NETs.

The role of NETs in cancer progression is complex and multifaceted. On the one hand, NETs can have anti-tumor effects by capturing circulating tumor cells and preventing their dissemination to distant sites—an essential step in metastasis. Additionally, certain components of NETs may directly kill cancer cells or stimulate an immune response against them. However, evidence suggests that NETs can also promote tumor growth and metastasis through several mechanisms [16]:

Enhancing inflammation: Persistent release of NETs can exacerbate inflammation within the tumor microenvironment by activating pro-inflammatory signaling pathways in both immune and non-immune cells.

Promoting angiogenesis: Components of NETs have been shown to stimulate endothelial cell migration and tube formation—a crucial step in blood vessel formation that provides tumors with nutrients for growth.

Facilitating invasion: By disrupting the integrity of extracellular matrix proteins, NETs may create a permissive environment for cancer cells to invade surrounding tissues and eventually spread to distant organs.

Given the dual role of NETs in cancer progression, targeting their formation or function could represent a promising therapeutic strategy. By selectively inhibiting the pro-tumorigenic aspects of NETs while preserving their anti-tumor properties, it may be possible to enhance the efficacy of existing cancer immunotherapies and improve patient outcomes [17].

The crosstalk between neutrophils and T cells or macrophages is another critical aspect of immune regulation within the TME. Neutrophils can influence macrophage polarization within the TME, promoting either a pro-inflammatory M1 phenotype or an immunosuppressive M2 phenotype. For instance, N1 neutrophils can release pro-inflammatory cytokines that drive M1 macrophage polarization, enhancing anti-tumor immunity. Conversely, N2 neutrophils may secrete factors that induce M2 macrophage polarization, contributing to an immunosuppressive environment that favors tumor growth. Moreover, macrophages can reciprocally modulate neutrophil function by releasing chemokines that regulate their recruitment or by producing cytokines that influence their activation state or polarization. These bidirectional interactions between neutrophils and macrophages help shape the immune landscape within the TME [18].

Neutrophils can directly impact T cell function through various mechanisms, including the secretion of inhibitory molecules, such as arginase-1 or reactive oxygen species (ROS), that impair T cell proliferation or cytotoxicity. In addition, neutrophil-derived exosomes may deliver molecular cargo that modulates gene expression in target T cells, altering their activation status or effector functions. Neutrophil extracellular traps (NETs) have also been implicated in suppressing T cell activity by inducing apoptosis or inhibiting their proliferation and activation. On the other hand, T cells can influence neutrophil behavior by releasing cytokines or chemokines that regulate their recruitment, survival, or activation state. For example, T helper 17 (Th17) cells have been shown to promote neutrophil recruitment and activation through the secretion of IL-17 and other inflammatory mediators. These findings suggest that targeting the interplay between neutrophils and other immune cells in the TME is a promising strategy for modulating cancer-associated inflammation and immune responses. For instance, therapies aimed at promoting M1

macrophage polarization or enhancing Th1/Th17-mediated neutrophil activation may help shift the balance towards a more anti-tumorigenic immune environment. On the contrary, blocking specific factors involved in neutrophil-mediated immunosuppression, such as arginase-1 or NETs, could potentially enhance T cell function and improve the efficacy of existing immunotherapies, such as immune checkpoint inhibitors. In conclusion, examining the complex interactions between neutrophils and other immune cells within the tumor microenvironment is essential for understanding their collective impact on cancer progression and response to treatment. Developing therapeutic strategies that target these intricate interplays is promising for optimizing cancer immunotherapies and improving patient outcomes [19].

Immune checkpoint inhibitors (ICIs) are a class of therapeutic agents that target immune checkpoints such as PD-1, PD-L1, and CTLA-4. These checkpoints regulate immune responses by preventing excessive activation of T cells, which could otherwise lead to autoimmune diseases. However, cancer cells often exploit these checkpoints to evade immune surveillance. ICIs work by blocking these inhibitory pathways and allowing T cells to recognize and attack tumor cells. The potential synergistic effects between neutrophils and ICIs have become an area of interest for researchers aiming to enhance the efficacy of cancer immunotherapies. Neutrophils possess various functions that may complement ICI therapy [20,21]:

Neutrophil Extracellular Traps (NETs): NETs are web-like structures composed of DNA and antimicrobial proteins released by neutrophils in response to infections or inflammation. While their primary function is to trap and kill pathogens, studies have shown that NETs can also promote anti-tumor immunity by enhancing T-cell infiltration into tumors.

Tumor-associated neutrophils (TANs): TANs are a subset of neutrophils found within the tumor microenvironment (TME). Depending on their phenotype, they can either promote or inhibit tumor growth. N1-type TANs exhibit anti-tumor activity by secreting pro-inflammatory cytokines and chemokines that recruit cytotoxic T cells into the TME.

Neutrophil-to-Lymphocyte Ratio (NLR): NLR is a prognostic biomarker that reflects the balance between innate and adaptive immune responses. A high NLR indicates a stronger neutrophil-mediated response and has been associated with better outcomes in patients treated with ICIs.

Neutrophil aging and senescence have emerged as important factors that can influence the efficacy of cancer immunotherapies. Understanding how these processes affect neutrophil function within the tumor microenvironment may provide critical insights for optimizing treatment outcomes. As neutrophils age, they undergo a series of functional changes that can impact their anti-tumor activity. For instance, these cells secrete higher levels of inflammatory cytokines, such as IL-6 or TNF-alpha, while simultaneously producing factors that inhibit T cell function, like arginase-1 or reactive oxygen species (ROS), and also exhibit increased chemotaxis, phagocytic capacity, and degranulation compared to their younger counterparts. While these alterations may enhance their ability to eliminate tumor cells, they can also contribute to tissue damage and inflammation within the tumor microenvironment. Moreover, aging neutrophils display altered expression of surface markers, such as CXCR4 or CD62L, which can influence their migration patterns and interactions with other immune cell populations. These changes may lead to imbalances in cellular composition within the tumor microenvironment, potentially affecting immune responses against cancer cells [22].

Modulating neutrophil aging or senescence may provide novel avenues for enhancing the efficacy of cancer immunotherapies. For example, pharmacological interventions to delay neutrophil aging or promote their clearance from the tumor microenvironment could help minimize their detrimental effects on immune responses. Alternatively, strategies designed to selectively target senescent neutrophils or block their immunosuppressive functions may help restore anti-tumor immunity and improve treatment outcomes. These approaches might include the use of senolytic drugs that selectively eliminate senescent cells or inhibitors of specific factors involved in T cell suppression [23].

Studies have begun to shed light on the complex relationship between stress, psychological factors, and neutrophil function in cancer patients. These factors can influence the efficacy of immunotherapies and treatment outcomes [24]. Chronic stress has been shown to compromise immune system function, including neutrophil activity. Under prolonged stress, the body releases cortisol and other stress hormones that can suppress neutrophil migration towards tumor sites, phagocytic capacity, and reactive oxygen species (ROS) production. This weakened neutrophil response may contribute to a more favorable environment for tumor growth and metastasis. Moreover, psychological factors such as depression, anxiety, and social isolation have also been linked to altered neutrophil function. These emotional states can exacerbate chronic stress responses and further impair the immune system's ability to combat cancerous cells. For instance, individuals with high levels of depression or anxiety may exhibit reduced neutrophil-to-lymphocyte ratios (NLR), which is associated with poorer prognosis in various cancers [25,26].

Exposure to environmental pollutants and toxins can significantly impact neutrophil behavior within the tumor microenvironment. These exogenous factors can modulate neutrophil functions, such as migration, phagocytosis, and release of cytokines and reactive oxygen species (ROS). For instance, air pollution has been shown to affect neutrophil activation, leading to an increase in pro-inflammatory cytokine production. This heightened inflammatory response may promote tumor growth and progression by facilitating angiogenesis and tissue remodeling. Additionally, exposure to heavy metals like cadmium or lead can alter neutrophil function by inducing oxidative stress and impairing their ability to perform effective phagocytosis. These findings highlight the importance of addressing both physical and mental health aspects when developing personalized immunotherapy strategies for cancer patients. Integrating psychosocial interventions alongside traditional treatments could potentially enhance neutrophil function and improve outcomes for patients undergoing immunotherapy. Moreover, certain environmental toxins, such as cigarette smoke or alcohol consumption, may induce chronic inflammation that can influence neutrophil recruitment and infiltration into the tumor microenvironment. This chronic inflammation can lead to a more immunosuppressive milieu that favors tumor evasion from immune surveillance [27,28].

The impact of nutritional factors and dietary interventions on neutrophil function has gained increasing attention as a potential modulator of immune responses in cancer immunotherapies. Certain nutrients have been shown to regulate neutrophil function, either directly affecting their activation, migration, or polarization or by modulating the production of cytokines and chemokines that shape their behavior. For example, omega-3 fatty acids have been reported to exert anti-inflammatory effects by reducing neutrophil recruitment and activation in response to inflammatory stimuli. Similarly, vitamin has been implicated in promoting the polarization of neutrophils towards an N1 phenotype with enhanced anti-tumor activity. Conversely, other nutrients, such as high levels of dietary fat or glucose, may contribute to a pro-inflammatory state that favors the recruitment and activation of immunosuppressive N2 neutrophils within the tumor microenvironment. This highlights the importance of maintaining a balanced diet for modulating immune responses during cancer immunotherapy [29]. Several dietary interventions have been proposed as potential strategies for influencing neutrophil function in cancer patients undergoing immunotherapies. These include [30]:

Caloric restriction: Reducing caloric intake has been shown to suppress inflammation and enhance anti-tumor immunity by limiting the availability of energy sources that fuel both tumor growth and immunosuppressive cell populations, such as N2 neutrophils.

Ketogenic diet: A high-fat, low-carbohydrate diet may help shift metabolic pathways towards ketone body utilization, which has been suggested to promote anti-inflammatory effects and reduce neutrophil-mediated immunosuppression within the tumor microenvironment.

Plant-based diet: Consuming a diet rich in fruits, vegetables, and whole grains may provide an array of phytonutrients with antioxidant and anti-inflammatory properties that could modulate neutrophil function and enhance immune responses during cancer immunotherapy.

Conclusion

Neutrophils are the most abundant white blood cells in the human body, playing a crucial role in the immune system. In cancer immunotherapy, neutrophils serve as essential players, participating in both anti-tumor and tumor-promoting activities. Upon activation by cytokines and chemokines, neutrophils are recruited to the tumor site. The tumor microenvironment (TME) influences their polarization into two distinct phenotypes: anti-tumor N1 and pro-tumor N2 neutrophils. The balance between these subpopulations significantly impacts cancer progression and treatment outcomes.

Given these findings, strategies to modulate neutrophil functions could potentially enhance the therapeutic effects of ICIs. For instance, stimulating the production of N1-type TANs or promoting NET formation may increase T cell infiltration into tumors, thereby improving ICI efficacy. In addition, further research is needed to elucidate the precise mechanisms by which nutritional factors and dietary interventions impact neutrophil function in the context of cancer immunotherapies. This includes identifying specific nutrients or dietary patterns that exert optimal effects on neutrophil-mediated immune responses, as well as determining the appropriate timing and duration of these interventions for maximizing treatment outcomes.

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