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Review Article

The Role of Neutrophils in the Prevention and Treatment of Cancers

Nemat Khansari*
Tehran University of Medical Sciences, School of Medicine, Department of Immunology, Iran

***Corresponding author:** Nemat Khansari, Tehran University of Medical Sciences, School of Medicine, Department of Immunology, Iran

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Summary

Neutrophils are the most abundant type of white blood cells in the human body and play a crucial role in the immune system. They are primarily responsible for defending the body against invading pathogens like bacteria and fungi. Recent research has also revealed that neutrophils play a significant role in cancer biology. Neutrophils have been demonstrated to target and destroy cancer cells and stimulate an immune response to fight 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. This article will discuss the dual role of neutrophils in preventing and treating cancers.

Keywords: Neutrophils; Cancer; Immunotherapy; NET; ROS; TANs; TME; NLR

More than 70% of all circulating human leukocytes are neutrophils, responsible for the body's first response 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].

As the first line of defense against inflammation and infection, neutrophils are recruited from the vascular system to tissues via chemokines to play an anti-infection role [3]. However, the dysregulation of neutrophil chemotaxis and activation may lead to various diseases, including cancer [4]. The presence, recruitment, and activation of tumor-associated neutrophils (TANs) play a significant role in maintaining the Tumor Microenvironment (TME) and tumor progression. Singhal et al [5]. demonstrated the antitumor mechanisms of TANs. They showed that the TAN subsets CD11b+ CD15high CD10- CD16low progenitors have antitumor activity in the early stage of the tumor. Anti-tumor activity of infiltrating neutrophils is due to the expression of costimulatory receptors like 4-1BBL, OX40L, and CD86, which produce active T cells. In addition, neutrophils can directly kill cancer cells by secreting cytotoxic factors such as ROS, nitric oxide (NO), and neutrophil elastase [6]. TANs can also release various chemokines and cytokines to stimulate the proliferation and activation of T cells, natural killer (NK) cells, and dendritic cells (DC). Release of chemokines and cytokines by TANs, including CCL-3, CXCL-10, TNF and IL-12, recruits and activates cytotoxic CD8+ T cells [7]. Neutrophils can also engulf and destroy cancer cells through phagocytosis, a process by which they ingest and break down the cancer cells.

It should be noted that other studies demonstrated that TANs might promote tumor progression. NETs can promote tumor growth and metastasis through several mechanisms. They can stimulate angiogenesis by releasing matrix metalloproteinases and other pro-angiogenic factors. Moreover, NETs can facilitate cancer cell migration, invasion, and dissemination by remodeling the extracellular matrix. Additionally, NET-derived proteases have been shown to cleave immune checkpoint molecules on the surface of T cells, leading to immune suppression and reduced antitumor immunity. TANs also can induce mesenchymal stem cells (MSCs) by transforming into tumor-related fibroblast and secreting IL-17, IL-23, and TNF-proportional to activate the protein kinase B/p38 pathway leading to proliferation and metastases of tumor cells [8]. Another mechanism of TANs tumorigenesis is due to the reduction of antitumor activity response of CD8+ T-cells by secretion of arginase-1 and neutrophils-derived elastase (NE) to insulin receptor substrate-1, both of which induce cell proliferation [9].

Neutrophils can be classified into two distinct phenotypes based on their role in cancer:

1. N1 Neutrophils: These neutrophils exhibit antitumor properties and are associated with favorable clinical outcomes in cancer patients. N1 neutrophils can kill tumor cells and inhibit

their growth by releasing cytotoxic molecules [10]. Promoting the antitumor N1 phenotype can enhance the immune system's ability to attack cancer cells. This can be achieved by using immunomodulatory agents or cytokines that encourage the differentiation of neutrophils towards the N1 phenotype.

2. N2 Neutrophils: In contrast, N2 neutrophils promote tumor growth and metastasis by secreting pro-angiogenic and pro-inflammatory factors. These neutrophils have been linked to poor clinical outcomes in cancer patients [11]. Specific inhibitors or antibodies that target the signaling pathways responsible for the pro-tumor functions of N2 neutrophils can inhibit the pro-tumor N2 phenotype.

Given their dual role in cancer progression, targeting NET formation or degradation could offer potential therapeutic benefits:

1. **Inhibition of NET Formation:** Pharmacological agents or antibodies that inhibit the enzymatic processes responsible for NET formation could potentially reduce pro-tumor effects associated with excessive or dysregulated NET production.
2. **Enhancement of NET Degradation:** Promoting the clearance or degradation of tumor-associated NETs might mitigate their pro-tumor functions while preserving their antimicrobial properties. This can be achieved using DNase therapy or by modulating endogenous nucleases in the tumor microenvironment.
3. **Selective Targeting of Pro-tumor NET Components:** Another approach is to selectively target specific pro-tumor components of NETs, such as proteases or pro-angiogenic factors, without affecting the overall structure and function of NETs.

The Neutrophil-to-Lymphocyte Ratio (NLR) is a simple and easily accessible biomarker that has gained considerable attention recently for its potential prognostic value in cancer patients [12]. NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from a routine blood test. NLR prognosis markers are:

1. **Association with Clinical Outcomes:** Numerous studies have demonstrated that an elevated NLR is associated with poorer overall survival, disease-free survival, and progression-free survival across various cancers, including lung, breast, colorectal, and pancreatic cancer. A high NLR reflects an imbalance between pro-inflammatory neutrophils and anti-tumor lymphocytes, suggesting a more immunosuppressive tumor microenvironment that favors cancer progression.
2. **Predictive Value for Treatment Response:** NLR has also been investigated as a predictive marker for treatment response and its prognostic significance. Higher pre-treatment NLR values correlate with lower response rates to chemotherapy, targeted therapy, and immunotherapy in various malignancies. This indicates that patients with elevated NLR may require alternative or more aggressive therapeutic strategies to improve their clinical outcomes.
3. **Dynamic Monitoring of NLR during Treatment:** Monitoring changes in the NLR during cancer treatment can provide valuable insights into the patient's response to therapy and help guide clinical decision-making. For instance, a decrease in NLR following treatment initiation may suggest a favorable response to therapy and predict improved survival outcomes.
4. **Combination with Other Biomarkers:** Integrating NLR with other established prognostic markers or clinicopathological factors can enhance its predictive accuracy and provide more comprehensive risk stratification for cancer patients.

Neutrophil migration towards tumor sites is a highly regulated process involving numerous factors and signaling pathways. Understanding these mechanisms can help develop therapeutic strategies that modulate neutrophil recruitment to influence cancer progression. Factors involved in neutrophil migrations are:

1. **Chemokines and Cytokines:** Tumor cells and other cells within the tumor microenvironment secrete various chemokines and cytokines, such as CXCL1, CXCL2, IL-8, and G-CSF, which act as potent chemoattractants for neutrophils. These molecules guide neutrophils towards the tumor site via chemotaxis [13].
2. **Adhesion Molecules:** The interaction between adhesion molecules on neutrophils (e.g., integrins) and their ligands on endothelial cells (e.g., ICAM-1) is crucial for neutrophil extravasation from blood vessels into the tumor tissue. This process involves a cascade of events, including rolling, activation, firm adhesion, and transmigration across the endothelium (14).
3. **Hypoxia:** Hypoxic conditions within the tumor microenvironment can also stimulate neutrophil recruitment by inducing the expression of hypoxia-inducible factors (HIFs). HIFs promote the secretion of pro-inflammatory cytokines and chemokines that attract neutrophils to the tumor site [15].

Modulating neutrophil migration toward tumor sites offers potential therapeutic opportunities in cancer treatment:

1. **Inhibition of Chemokine/Cytokine Signaling:** Blocking the signaling pathways activated by chemokines or cytokines involved in neutrophil recruitment could reduce their accumulation at the tumor site. This can be achieved using small molecule inhibitors or neutralizing antibodies targeting specific chemoattractants or their neutrophil receptors.
2. **Targeting Adhesion Molecules:** Disrupting the interaction between adhesion molecules and their ligands can impair neutrophil extravasation into the tumor tissue. Therapeutic agents that block integrins or endothelial ligands may reduce neutrophil infiltration and potentially mitigate their pro-tumor effects.
3. **Modulating Hypoxia-Induced Neutrophil Recruitment:** Strategies to alleviate tumor hypoxia, such as improving tumor oxygenation or inhibiting HIF activity, could limit the recruitment of neutrophils to the tumor site and subsequently influence cancer progression.

Neutrophils are pivotal in shaping cancer-related inflammation and supporting and hindering tumor progression. Understanding this complex interplay is crucial for devising effective therapeutic strategies targeting inflammation-driven cancer growth. Mechanisms of neutrophil-driven inflammation in cancer are:

1. **Pro-inflammatory Cytokines and Chemokines:** Neutrophils secrete a variety of cytokines (e.g., TNF-α, IL-1β, IL-6) and chemokines (e.g., CXCL8) that contribute to creating an inflammatory microenvironment within the tumor. These factors can promote cancer cell proliferation, survival, angiogenesis, and invasion while suppressing anti-tumor immune responses [16].
2. **Reactive Oxygen Species:** Neutrophils generate ROS as part of their antimicrobial defense mechanisms; however, excessive or sustained ROS production can lead to oxidative stress and chronic inflammation within the tumor microenvironment. This oxidative damage can induce DNA mutations, activate oncogenic signaling pathways, and stimulate angiogenesis – all contributing to cancer progression [17].

3. Crosstalk with Other Immune Cells: Neutrophils interact with other immune cells in the tumor microenvironment (e.g., macrophages, T cells), influencing their polarization towards pro-inflammatory or anti-inflammatory phenotypes. For instance, neutrophil-derived factors can polarize macrophages towards the pro-tumorigenic M2 phenotype or suppress T cell activation, thereby promoting an immunosuppressive environment that favors cancer growth [18].

Given their multifaceted role in cancer-related inflammation, several therapeutic strategies will be available to modulate neutrophil-driven inflammation:

1. Inhibition of Pro-inflammatory Mediators: Targeting key cytokines and chemokines produced by neutrophils can help attenuate the inflammatory response within the tumor microenvironment. This can be achieved using small molecule inhibitors, neutralizing antibodies, or RNA interference techniques that block the production or function of these pro-inflammatory factors.

2. Antioxidant Therapies: Reducing oxidative stress generated by neutrophils may alleviate inflammation-driven cancer progression. Antioxidant agents, such as N-acetylcysteine or vitamin E, could help scavenge ROS and mitigate their detrimental effects on DNA integrity and cellular signaling pathways.

3. Reprogramming Neutrophil Function: Modulating neutrophil behavior to favor anti-tumor functions while suppressing pro-inflammatory activities could tip the balance towards a more favorable immune response in the tumor microenvironment. Immunomodulatory agents that promote neutrophil differentiation towards an anti-tumor phenotype or enhance their cytotoxic capacity against cancer cells can potentially achieve this goal.

Plasticity and heterogeneity of neutrophils in their functional states significantly shape the tumor microenvironment. Understanding this diversity is crucial for developing targeted therapies that effectively modulate neutrophil function in cancer. Neutrophils can adopt various functional phenotypes depending on the signals they receive within the tumor microenvironment. These include the pro-tumorigenic N2 phenotype, characterized by immunosuppressive and pro-angiogenic activities, and the anti-tumorigenic N1 phenotype, which exhibits enhanced cytotoxicity against cancer cells and supports antitumor immunity. Additionally, neutrophils may exist in an immature or mature state, with immature neutrophils typically displaying reduced antimicrobial activity and impaired ability to form neutrophil extracellular traps [19]. Several factors contribute to the diverse functional states of neutrophils in cancer, such as cytokines, chemokines, growth factors, and hypoxic conditions within the tumor microenvironment. For instance, pro-inflammatory cytokines like IFN-γ or TNF-α can promote N1 polarization, whereas transforming growth factor-beta (TGF-β) or IL-10 may drive N2 differentiation. Furthermore, interactions with other immune cells (e.g., T cells or macrophages) can shape neutrophil plasticity by providing stimulatory or inhibitory cues [20].

Exploiting the plasticity of neutrophils offers novel opportunities for cancer therapy:

1. Promoting Anti-Tumor Functions: Encouraging neutrophil polarization towards the N1 phenotype or enhancing their cytotoxic capacity against cancer cells could help boost antitumor immunity. This can be achieved using immunomodulatory agents or cytokines that stimulate N1 differentiation [21].

2. Inhibiting Pro-Tumor Functions: Targeting specific factors or signaling pathways that drive the pro-tumorigenic N2 phenotype could help suppress neutrophil-mediated tumor progression. For example, neutralizing antibodies against TGF-β or inhibitors of key signaling molecules involved in N2 polarization may prove beneficial.

3. Modulating Neutrophil Maturation: Adjusting the balance between immature and mature neutrophils could impact their functional capabilities within the tumor microenvironment. Interventions that promote neutrophil maturation, such as granulocyte colony-stimulating factor (G-CSF) treatment, enhance their antimicrobial and antitumor activities.

Neutrophils can influence the efficacy of immune checkpoint inhibitors (ICIs) in cancer treatment through various mechanisms. The potential impact of neutrophil activity on ICI therapy is [22]:

1. Modulation of Tumor Immunogenicity: Neutrophils can alter the immunogenicity of tumor cells by releasing factors that promote or suppress the expression of Major Histocompatibility Complex (MHC) molecules and other immune-related proteins. This can directly affect the ability of ICIs to facilitate T cell recognition and elimination of cancer cells.

2. Influence on Immune Checkpoint Expression: Neutrophil-derived cytokines and chemokines may modulate the expression levels of immune checkpoint molecules, such as programmed death-ligand 1 (PD-L1), on both cancer cells and immune cells within the tumor microenvironment. This could impact the responsiveness to ICIs targeting these molecules.

3. Immune Cell Recruitment and Activation: Neutrophils can regulate the infiltration and activation status of other immune cells, including T cells, macrophages, and dendritic cells, which play crucial roles in ICI-mediated antitumor responses. By secreting chemokines or cytokines that either promote or inhibit recruitment and activation of these immune cell populations, neutrophils may indirectly affect ICI efficacy.

4. Induction of Immunosuppressive Mechanisms: As discussed earlier, neutrophils contribute to an immunosuppressive environment within tumors by releasing factors that impair T cell function or promote polarization towards pro-tumorigenic phenotypes (e.g., M2 macrophages). This immunosuppression could potentially limit the effectiveness of ICIs by dampening antitumor immune responses.

5. Biomarker Potential: Neutrophil-related parameters, such as NLR or neutrophil infiltration levels within tumors, have been proposed to predict ICI treatment outcomes. High NLR or neutrophil infiltration has been associated with poor clinical responses to ICIs in several cancer types, suggesting that these factors may serve as indicators of ICI resistance.

Neutrophil-derived exosomes play a crucial role in intercellular communication within the tumor microenvironment, influencing various aspects of cancer progression and immune regulation. These small extracellular vesicles carry a diverse cargo of proteins, lipids, and nucleic acids that can modulate the behavior of recipient cells. The potential implications and therapeutic applications of neutrophil-derived exosomes in cancer are [23]:

1. Tumor Growth and Invasion: Neutrophil-derived exosomes can promote tumor growth and invasion by transferring growth factors or Matrix Metalloproteinases (MMPs) to cancer or stromal cells within the microenvironment. This enhances cell proliferation, extracellular matrix degradation, and tissue

remodeling processes that facilitate tumor expansion and metastasis.

2. Angiogenesis: The cargo of neutrophil-derived exosomes may contain pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) or angiopoietin-2 that stimulate endothelial cell activation and migration. Neutrophil-derived exosomes form new blood vessels that support tumor growth by transferring these factors to endothelial cells within the tumor microenvironment.

3. Immune Modulation: Neutrophil-derived exosomes can interact with various immune cell populations within the tumor microenvironment, impacting their functions and overall immune response against cancer. For instance:

a. T Cells: Exosomal cargo from neutrophils may include immunosuppressive molecules such as TGF-β or indoleamine 2,3-dioxygenase (IDO), which can impair T cell activation or induce regulatory T cell differentiation.

b. Macrophages: Neutrophil-derived exosomes may transfer cytokines or chemokines that influence macrophage polarization towards either pro-tumorigenic M2 or anti-tumorigenic M1 phenotypes, impacting the balance of immune responses within the tumor microenvironment.

c. Dendritic Cells: Transferring antigenic peptides or danger signals via neutrophil-derived exosomes can modulate dendritic cell maturation and antigen presentation capabilities, ultimately affecting T cell activation and antitumor immunity.

4. Therapeutic Applications: Exploiting the properties of neutrophil-derived exosomes offers novel opportunities for cancer therapy:

a. Drug Delivery: Neutrophil-derived exosomes can be natural drug carriers targeting specific tumor microenvironment cells. Loading these vesicles with anticancer agents or immunomodulatory molecules can enhance therapeutic efficacy while minimizing systemic toxicity.

b. Biomarker Discovery: The molecular cargo of neutrophil-derived exosomes may provide valuable insights into the biological state of tumors and immune responses. Analysis of exosomal contents could potentially reveal novel biomarkers for cancer diagnosis, prognosis, or treatment response prediction.

c. Exosome Engineering: Modifying the cargo or surface properties of neutrophil-derived exosomes could enable the generation of tailored vesicles that selectively target specific cell populations or pathways within the tumor microenvironment. These engineered exosomes could be utilized for targeted delivery of therapeutics or modulation of immune responses against cancer.

Cancer-related fatigue (CRF) is a common and debilitating symptom experienced by many cancer patients, negatively impacting their quality of life. Emerging evidence suggests that neutrophil activity and inflammation may contribute to the development of CRF. Links between these factors are [24,25]:

1. Inflammation and Fatigue: Chronic inflammation has been implicated in the pathogenesis of CRF through various mechanisms, including increased production of pro-inflammatory cytokines (e.g., IL-6, TNF-α), activation of the hypothalamic-pituitary-adrenal (HPA) axis, and alterations in neurotransmitter metabolism. Neutrophils, critical mediators of inflammation, may contribute to this process by secreting pro-inflammatory cytokines or generating reactive oxygen species (ROS) that exacerbate systemic inflammation.

2. Neutrophil Extracellular Traps and Fatigue: NET formation, a unique antimicrobial mechanism employed by neutrophils, has recently been associated with CRF. NETs can trigger an inflammatory response by activating immune cells or releasing damage-associated molecular patterns (DAMPs). This chronic activation could lead to persistent fatigue in cancer patients due to sustained inflammatory signaling.

3. Immunosuppression and Fatigue: The immunosuppressive environment created by neutrophils within the tumor microenvironment can also impact cancer-related fatigue. By inhibiting T cell activation or promoting M2 macrophage polarization, neutrophils may contribute to an overall state of immune dysregulation that exacerbates CRF through impaired immune surveillance or chronic low-grade inflammation.

4. Therapeutic Implications: Targeting neutrophil-driven inflammation could potentially alleviate CRF in cancer patients:

a. Anti-inflammatory interventions such as nonsteroidal anti-inflammatory drugs (NSAIDs), antioxidants, or inhibitors of pro-inflammatory cytokines may help reduce inflammation and improve fatigue symptoms.

b. Pharmacological agents modulating neutrophil function, such as CXCR2 antagonists or CD11b/CD18 inhibitors, could alleviate CRF by mitigating neutrophil-mediated inflammatory responses.

c. Integrative approaches, including exercise, stress management techniques, or nutritional supplementation, may also help counteract the effects of inflammation on fatigue by promoting a balanced immune response [26].

Dietary factors can significantly impact neutrophil function, shaping their role in cancer prevention and treatment. Specific nutrients and dietary patterns may modulate neutrophil activity in the context of cancer [27-29]:

1. Omega-3 Fatty Acids: Omega-3 polyunsaturated fatty acids (PUFAs), such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to exert anti-inflammatory effects on neutrophils by altering the production of pro-inflammatory mediators and promoting the resolution of inflammation. This may help reduce chronic inflammation associated with cancer development and progression.

2. Vitamin D: Vitamin D has been reported to enhance neutrophil antimicrobial functions, such as phagocytosis and ROS production while modulating their pro-inflammatory responses. Adequate vitamin D levels may support a balanced immune response that prevents excessive inflammation while maintaining effective anti-tumor immunity.

3. Antioxidants: Dietary antioxidants, such as vitamins C and E, selenium, or polyphenols found in fruits and vegetables, can protect against oxidative stress induced by neutrophil-derived ROS within the tumor microenvironment. These antioxidants may help prevent cancer initiation or progression by reducing oxidative damage to cells and tissues.

4. Amino Acids: Specific amino acids like arginine and glutamine regulate neutrophil functions like chemotaxis, phagocytosis, and cytokine production. Ensuring adequate intake of these amino acids through diet or supplementation could optimize neutrophil-mediated immune responses against cancer.

5. Caloric Restriction: Caloric restriction has been demonstrated to suppress systemic inflammation by influencing cytokine profiles and reducing neutrophil infiltration into tissues. This dietary intervention may help mitigate the pro-tumorigenic effects of chronic inflammation and promote cancer prevention.

6. Dietary Patterns: Certain dietary patterns, such as the Mediterranean diet, have been associated with reduced inflammation and lower cancer risk. These diets are typically rich in fruits, vegetables, whole grains, legumes, fish, and healthy fats

that may collectively modulate neutrophil function and promote a more balanced immune response.
Neutrophil aging and senescence can significantly impact cancer progression and the immune response against tumors.

The consequences of neutrophil aging and senescence on cancer development and potential therapeutic implications are [30-32]:
1. Aging Neutrophils and Cancer Progression: Aged neutrophils exhibit altered functional properties compared to their younger counterparts, including increased adhesion, degranulation, and production of pro-inflammatory cytokines. These changes may contribute to a heightened inflammatory state within the tumor microenvironment, promoting tumor growth and metastasis.
2. Senescent Neutrophils in Immune Regulation: Senescent neutrophils can acquire immunosuppressive properties that impair the function of other immune cells, such as T cells or natural killer cells. This may dampen anti-tumor immunity and facilitate cancer progression.
3. Neutrophil Clearance and Cancer: Efficient clearance of aged or senescent neutrophils by macrophages is crucial for maintaining tissue homeostasis and preventing excessive inflammation. Impaired neutrophil clearance may result in the accumulation of these cells within the tumor microenvironment, exacerbating pro-tumorigenic effects.
4. Therapeutic Implications: Targeting neutrophil aging or senescence could offer new opportunities for cancer therapy:
a. Enhancing Neutrophil Clearance: Therapeutic strategies that promote efficient removal of aged or senescent neutrophils from the tumor microenvironment may help mitigate their pro-tumorigenic effects. This could be achieved through pharmacological modulation of macrophage phagocytic activity or by stimulating efferocytosis pathways.
b. Inhibiting Pro-Inflammatory Signaling: Blocking key signaling molecules involved in age-related pro-inflammatory responses, such as NF-κB or JAK2/STAT3 pathway, could potentially suppress the detrimental effects of aged neutrophils on cancer progression.
c. Rejuvenation Strategies: Interventions aimed at rejuvenating aged or senescent neutrophils, such as targeting specific metabolic pathways or epigenetic modifications, might restore their anti-tumor functions and improve overall immune responses against cancer.
Neutrophils play a complex role in the context of hematological malignancies, such as leukemia, lymphoma, and myeloma.

Several neutrophil activities that may impact the development, progression, and immune response against these cancers are:
1. Neutrophils and Leukemic Cell Niche: Neutrophils can contribute to forming a supportive niche for leukemic cells within the bone marrow. By secreting factors that promote cell survival or modulate stromal cell behavior, neutrophils may facilitate the maintenance and expansion of leukemic stem cells [33,34].
2. Tumor-Promoting Effects in Lymphoma: Neutrophil-derived cytokines, such as IL-6 or IL-8, may promote lymphoma cell survival and proliferation by activating oncogenic signaling pathways. Additionally, neutrophils can contribute to lymphoma-associated angiogenesis by secretion of pro-angiogenic factors like VEGF [35].
3. Immune Evasion in Hematological Malignancies: Like solid tumors, neutrophils can exert immunosuppressive effects within the tumor microenvironment of hematological malignancies by inhibiting T cell activation or promoting regulatory T cell differentiation. These mechanisms may contribute to immune evasion and cancer progression [36].
4. Paradoxical Anti-Tumor Roles: In some cases, neutrophils have been reported to exert anti-tumor effects against hematological malignancies through direct cytotoxicity or antibody-dependent cellular cytotoxicity (ADCC). These findings underscore the context-dependent nature of neutrophil functions in cancer [37].

Recent clinical trials have explored the potential of neutrophil-targeted therapies in cancer treatment, demonstrating promising results and highlighting the need for further investigation. Some notable examples include:
1. CXCR2 Inhibition: CXCR2 is a chemokine receptor expressed on neutrophils that is critical in their recruitment to tumor sites. A phase I clinical trial (NCT02499328) evaluated the safety and efficacy of AZD5069, a selective CXCR2 antagonist, in combination with durvalumab, an immune checkpoint inhibitor, for treating advanced solid tumors. The study reported manageable toxicity and preliminary signs of anti-tumor activity, warranting further investigation of this combination therapy.
2. Anti-IL-8 Therapy: Interleukin-8 (IL-8) is a pro-inflammatory chemokine in neutrophil activation and migration. A phase Ib/II clinical trial (NCT03689699) is currently investigating the safety and efficacy of BMS-986253, a humanized monoclonal antibody targeting IL-8, in combination with nivolumab, an immune checkpoint inhibitor, for the treatment of advanced hepatocellular carcinoma. This study aims to determine whether neutralizing IL-8 can improve outcomes by reducing neutrophil-mediated immunosuppression [39].
3. CD11b/CD18 Blockade: CD11b/CD18 integrins are adhesion molecules expressed on neutrophils that facilitate their extravasation into tumor tissues. A phase I clinical trial (NCT03161431) assessed the safety and tolerability of BI 655139, a monoclonal antibody targeting CD11b/CD18 integrins, in patients with advanced solid tumors refractory to standard therapies. While the study did not report the significant anti-tumor activity as monotherapy, it suggested that combining BI 655139 with other immunotherapeutic agents could be a promising strategy to modulate neutrophil infiltration [40].

In a recent study, Wu et al. demonstrated that neutrophils, in addition to their anti-inflammatory and angiogenesis functions, can present antigens to T cells. This process is through evoking leucine metabolism and subsequent Histone H3K227ac modification. They conclude that this function of neutrophils could fine-tune the immune balance to enhance anti-PD-1 therapy in various cancers [41].

Conclusion

Understanding the factors involved in neutrophil migration toward tumor sites provides valuable insights for developing therapeutic strategies to modulate neutrophil recruitment. By targeting key molecules and signaling pathways implicated in this process, it is possible to influence the role of neutrophils within the tumor microenvironment and potentially improve cancer treatment outcomes. Neutrophils play a complex role in cancer-associated infections, acting as both protectors against pathogen invasion and potential contributors to infection exacerbation. A better understanding of these dual functions is essential for developing strategies to enhance the antimicrobial capacity of neutrophils while minimizing their detrimen-

tal effects in cancer patients. This could involve modulating neutrophil recruitment, improving their antimicrobial function, or targeting specific factors that drive excessive inflammation during infections. Elucidating the role of neutrophils in cancer-related inflammation is essential for developing therapeutic strategies that target this crucial aspect of cancer biology. Focusing on specific mediators and mechanisms driving inflammation within the tumor microenvironment makes it possible to harness the potential of neutrophils as allies in the fight against cancer while minimizing their pro-tumorigenic effects. There is a need for more research to uncover the molecular mechanisms of age-related changes in neutrophil functions. This will help to develop effective interventions to counteract their pro-tumorigenic effects.

Clinical trials suggest that neutrophil-targeted therapies could be helpful in cancer treatment, and it is necessary to investigate their use further in combination with other anticancer modalities. As our understanding of neutrophil biology and its role in tumor progression continues to evolve, new therapeutic strategies targeting these immune cells may emerge. This could offer new hope for patients with difficult-to-treat cancers.

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