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N1 and N2 Neutrophil Polarization in Breast Cancer: Predictive Value for Treatment Outcomes

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Abstract

Neutrophils, the most abundant white blood cells in the immune system, play a crucial role in breast cancer progression through their ability to polarize into two distinct phenotypes: N1 and N2. N1 neutrophils are considered antitumor effector cells that promote immune responses and inhibit tumour growth, while N2 neutrophils support tumour progression by promoting inflammation, immune suppression, and metastasis. The balance between these two phenotypes within the tumour microenvironment (TME) can significantly influence breast cancer development and response to treatment. The polarization of neutrophils in the TME is influenced by various factors, including cytokines, growth factors, and interactions with other immune cells. N1 neutrophils exhibit pro-inflammatory and cytotoxic properties that help limit tumour growth, while N2 neutrophils contribute to an immunosuppressive microenvironment that facilitates cancer progression and therapy resistance. Studies suggest that an increased presence of N1 neutrophils correlates with improved prognosis and response to therapies, whereas a predominance of N2 neutrophils is often associated with poor treatment outcomes and increased metastatic potential. This review examines the mechanisms underlying neutrophil polarization and the implications of these phenotypes on treatment responses in breast cancer.

Keywords: N1 neutrophils, N2 neutrophils, neutrophil polarization, breast cancer, treatment outcomes

Introduction

Neutrophils, the most abundant type of white blood cell in the human body, are traditionally known for their role in innate immunity, acting as the first line of defence against infections. Over the past few decades, however, their function in cancer biology, particularly in breast cancer, has been increasingly recognized[1,2]. Neutrophils infiltrate the tumour microenvironment (TME) in response to signalling molecules produced by the tumour and surrounding stromal cells. These immune cells play a dual role in cancer progression, influencing tumour growth, immune evasion, and metastasis[3]. Notably, neutrophils can exhibit distinct phenotypic polarization, primarily into two subtypes: N1 (pro-inflammatory) and N2 (immunosuppressive). The balance between these two phenotypes in the TME is pivotal in determining the tumour'sbehaviour and its response to therapies[2,3]. N1 neutrophils, also known as antitumor neutrophils, are characterized by their ability to produce pro-inflammatory cytokines and reactive oxygen species (ROS), which are capable of killing tumor cells directly[3]. These neutrophils exhibit a cytotoxic profile and are associated with enhanced immune responses, including activation of T cells and natural killer (NK) cells. They are often found in regions of the TME where active immune responses are taking place and are considered beneficial for controlling tumor growth[4]. On the other hand, N2 neutrophils, which are more immunosuppressive, contribute to the creation of an environment conducive to tumor progression. These cells promote angiogenesis, tissue remodeling, and the suppression of T-cell activity, facilitating tumor escape from immune surveillance[4,5].

The polarization of neutrophils into N1 or N2 phenotypes is regulated by a variety of factors within the TME, including cytokines, growth factors, and interactions with other immune and stromal cells. Tumor-derived factors such as interleukins, colony-stimulating factors, and tumor necrosis factor-alpha (TNF-α) can skew neutrophil differentiation toward the N2 phenotype, which is associated with tumor progression and poor prognosis[6,7]. Conversely, signals such as interferon-gamma (IFN-γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are known to promote N1 polarization, fostering an immune response that targets tumor cells. In breast cancer, the TME is particularly dynamic, with neutrophils playing an integral role in modulating both the tumor and the surrounding immune cells[6,10]. The presence and function of neutrophils within this environment are

shaped by various molecules secreted by the tumor, stromal cells, and immune components. A high density of neutrophils, especially N1 neutrophils, in breast cancer has been associated with improved prognosis and a better response to conventional treatments like chemotherapy. In contrast, an accumulation of N2 neutrophils in the TME often correlates with tumor metastasis, resistance to treatment, and overall poor survival outcomes. This shift in neutrophil polarization is of great interest as a potential therapeutic target for improving treatment efficacy[8,9].

The role of neutrophil polarization in treatment outcomes is an area of active investigation. Neutrophils' ability to influence the effectiveness of therapies, such as chemotherapy, immunotherapy, and radiation, has been increasingly acknowledged[10]. For instance, an N1-dominated TME is thought to enhance the efficacy of immune checkpoint inhibitors by promoting a more immunogenic environment, whereas an N2-dominated TME may hinder the effectiveness of such treatments. Additionally, strategies that aim to reprogram N2 neutrophils into the N1 phenotype or enhance the function of N1 neutrophils are under investigation as potential methods for improving treatment responses in breast cancer[11]. Despite the promising therapeutic implications of manipulating neutrophil polarization, several challenges remain. One of the major obstacles is the complexity of the TME, which consists of numerous immune cells, cytokines, and other factors that can influence neutrophil behavior. The plasticity of neutrophil polarization is another challenge, as these cells can shift between phenotypes in response to changes in the microenvironment[12-14]. Furthermore, the potential for off-target effects and toxicity in therapies that aim to modulate neutrophil function remains a concern, particularly when considering the delicate balance between promoting antitumor immunity and avoiding exacerbation of inflammation or autoimmunity. Recent advances in immunotherapy have fueled the exploration of neutrophil polarization as a therapeutic strategy. Several approaches are being tested, including cytokine therapy to promote N1 polarization, immune checkpoint inhibitors to enhance antitumor immunity, and small molecules that target key signaling pathways involved in neutrophil differentiation[13]. The ultimate goal is to develop strategies that can shift the balance of neutrophil phenotypes in favor of antitumor immunity, thereby enhancing the overall effectiveness of cancer therapies. However, further research is needed to identify the most effective and safe strategies to modulate neutrophil polarization in clinical settings.

Aim

The aim of this review is to explore the role of N1 and N2 neutrophil polarization in breast cancer, focusing on their impact on tumor progression, metastasis, and response to treatment.

Rationale

Neutrophils, the most abundant type of white blood cell, have long been recognized for their role in host defense against infections. However, their involvement in cancer biology, particularly in the tumor microenvironment, has garnered increasing attention in recent years. Neutrophils exhibit plasticity and can undergo polarization into two distinct phenotypes: N1 neutrophils, which have antitumor properties, and N2 neutrophils, which promote tumor growth and metastasis. The dynamic interplay between these polarized neutrophils within the tumor microenvironment significantly impacts the progression of breast cancer, influencing both the immune response and the efficacy of therapeutic interventions. While N1 neutrophils exhibit the potential to inhibit tumor growth by promoting immune surveillance, N2 neutrophils have been implicated in facilitating tumor progression, immune evasion, and chemoresistance. The ability to manipulate neutrophil polarization from an immunosuppressive N2 phenotype to an antitumor N1 phenotype offers a promising approach to enhancing treatment outcomes in breast cancer. Furthermore, recent advances in immunotherapy and cancer treatment have highlighted the need for more personalized approaches that target specific components of the immune system, including neutrophils. By modulating neutrophil polarization, it may be possible to improve the efficacy of existing therapies, reduce tumor resistance, and overcome the challenges of metastasis.

Review Methodology

This review article was developed through a comprehensive approach, involving an extensive literature search and analysis of relevant studies that explore the role of N1 and N2 neutrophil polarization in breast cancer and their implications for treatment outcomes. The methodology followed several key steps to ensure the synthesis of accurate, current, and relevant information.

Literature Search: A thorough search was conducted using multiple academic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search terms included "N1 neutrophils," "N2 neutrophils," "breast cancer," "tumor microenvironment," "neutrophil polarization," "neutrophils and metastasis," "immunotherapy and neutrophils," and related keywords. Studies published from 2000 to the present were prioritized, with a focus on original research articles, reviews, clinical trials, and meta-analyses.

Selection Criteria: Inclusion criteria for studies were as follows:

- Original research articles and reviews that addressed neutrophil polarization (N1 and N2) in the context of breast cancer.
- Studies that examined the impact of neutrophil polarization on tumor progression, metastasis, and treatment outcomes.
- Research focusing on the mechanisms of neutrophil polarization within the tumor microenvironment and their implications for immunotherapy and other therapeutic strategies.

- Studies published in English with clear methodologies and outcomes.

Exclusion criteria included:

- Articles focusing on neutrophil polarization outside the context of cancer or breast cancer.
- Studies with insufficient data on the role of neutrophils in tumor immunity or treatment response.
- Non-peer-reviewed sources or articles lacking experimental validation.

Neutrophil Polarization and the Tumor Microenvironment

Neutrophil polarization refers to the differentiation of neutrophils into distinct phenotypic states, primarily categorized as N1 (antitumor) and N2 (protumor)[14,15]. This process is profoundly influenced by the tumor microenvironment (TME), which consists of various components such as cancer cells, immune cells, stromal cells, and extracellular matrix elements. In a healthy state, neutrophils are essential for immune defense against infections and tissue repair. However, within the TME, neutrophils undergo polarization that can either promote or inhibit tumor progression, depending on the signals present in the microenvironment[16]. Understanding the regulation of neutrophil polarization and its impact on breast cancer development has important implications for therapeutic strategies. In the context of breast cancer, neutrophils are recruited to the TME in response to various tumor-secreted factors, such as cytokines and chemokines[17]. Once within the tumor, neutrophils can undergo polarization into either N1 or N2 states based on interactions with local signaling molecules. N1 neutrophils are generally considered to be beneficial for antitumor immunity. They exhibit pro-inflammatory characteristics, produce reactive oxygen species (ROS), secrete cytokines like interferon-gamma (IFN-γ), and enhance T cell and natural killer (NK) cell activity[18,19]. These features make N1 neutrophils effective at directly killing tumor cells and promoting tumor clearance. In contrast, N2 neutrophils promote tumor growth by inducing immune suppression, facilitating angiogenesis, and promoting metastasis. They are often associated with poor prognosis in breast cancer and resistance to therapies[15,20].

The polarization of neutrophils in the TME is not a static process but rather is influenced by the dynamic interactions between the tumor, immune cells, and the extracellular matrix. Factors such as cytokines (e.g., interleukins, tumor necrosis factor-alpha), growth factors (e.g., vascular endothelial growth factor), and the presence of specific metabolic conditions (such as hypoxia) all contribute to the polarization of neutrophils[21]. For instance, tumor cells often secrete interleukin-8 (IL-8) and granulocyte-colony stimulating factor (G-CSF), which can shift neutrophils toward an N2 phenotype. On the other hand, factors such as IFN-γ and GM-CSF promote N1 polarization. The intricate balance between these signaling factors in the TME largely determines the functional state of neutrophils and their role in supporting or inhibiting breast cancer progression[2,23]. Neutrophil polarization within the TME also interacts with other immune cells, such as macrophages, dendritic cells, and T cells. For example, N2 neutrophils can interact with tumor-associated macrophages (TAMs) to create an immunosuppressive environment that facilitates tumor growth. In contrast, N1 neutrophils work in concert with activated T cells and NK cells to enhance antitumor immune responses[24]. This cross-talk between neutrophils and other immune cells is a critical factor in shaping the immune landscape of the tumor and ultimately influences the outcome of cancer treatment. Moreover, tumor-associated neutrophils can further influence the metabolic and immune properties of the TME by modulating the secretion of cytokines, growth factors, and other immune modulators[25].

The ability of tumors to modulate neutrophil polarization in their favor represents a significant challenge in cancer therapy. In breast cancer, an overwhelming presence of N2 neutrophils within the TME has been correlated with poor prognosis, increased metastasis, and resistance to conventional treatments such as chemotherapy and immunotherapy. In contrast, promoting N1 neutrophil polarization within the TME could potentially improve the efficacy of current therapeutic strategies[26]. Recent studies have explored therapeutic approaches aimed at shifting the neutrophil balance from the N2 to the N1 phenotype, thereby enhancing the immune response against the tumor and improving treatment outcomes. However, the complexity of the TME and the plasticity of neutrophil polarization pose significant challenges in developing such targeted therapies[26]. Furthermore, neutrophil polarization is not only influenced by tumor-derived signals but also by the systemic immune environment, including the presence of inflammatory cytokines and metabolic stress. For instance, chronic inflammation and increased production of cytokines such as IL-6 can further drive the polarization toward the N2 phenotype, exacerbating the immune suppression within the TME[27]. Therefore, strategies that aim to not only target tumor-derived factors but also modulate systemic inflammatory pathways are needed to achieve a more effective therapeutic outcome. This comprehensive approach could offer novel ways to enhance neutrophil-mediated antitumor immunity and improve the response to existing therapies in breast cancer.

N1 and N2 Neutrophils in Breast Cancer Progression

Neutrophils, the most abundant type of white blood cells, play a critical role in the body's immune response. Their involvement in the tumor microenvironment (TME) is multifaceted, with their polarization into different phenotypes, namely N1 and N2, influencing tumor progression in both protective and destructive ways. The classification of neutrophils into N1 and N2 subtypes stems from their functional properties and their responses to the tumor microenvironment[28,29]. While N1 neutrophils exhibit antitumor properties, N2 neutrophils are associated with tumor promotion. The

balance between these two types is pivotal in determining the progression or suppression of breast cancer[29].

N1 Neutrophils and Antitumor Immunity

N1 neutrophils are generally considered to be the "antitumor" phenotype, associated with an immune response that targets and eliminates tumor cells[30,31]. These neutrophils typically express high levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-12 (IL-12), and interferon-gamma (IFN-γ), which help activate T cells, natural killer (NK) cells, and other immune components essential for tumor destruction. N1 neutrophils also generate reactive oxygen species (ROS) and release cytotoxic granules that can directly damage cancer cells[30]. Their antitumor activity is further enhanced by their ability to present tumor antigens and influence adaptive immune responses. Studies have shown that higher levels of N1 neutrophils in the TME are linked to better clinical outcomes and a more robust antitumor response in breast cancer patients. However, the ability of N1 neutrophils to effectively combat breast cancer is often influenced by the complexity of the TME, which can induce polarization toward the protumor N2 phenotype. Despite their potential, N1 neutrophils are typically short-lived in the TME due to the immunosuppressive factors secreted by tumor cells. This results in a dynamic shift in the balance between N1 and N2 neutrophils, influencing the trajectory of breast cancer progression[31].

N2 Neutrophils and Tumor Promotion

In contrast to N1 neutrophils, N2 neutrophils contribute to tumor progression and metastasis. These neutrophils are associated with the promotion of chronic inflammation, immune suppression, and tissue remodeling, all of which create a favorable microenvironment for tumorgrowth and spread[32]. N2 neutrophils produce immunosuppressive cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which inhibit the function of cytotoxic T cells, NK cells, and dendritic cells. Furthermore, they secrete proteases and pro-angiogenic factors such as vascular endothelial growth factor (VEGF), promoting tumor angiogenesis and facilitating metastasis. The shift toward N2 polarization in the TME is often driven by factors such as hypoxia, the presence of specific cytokines like granulocyte-colony stimulating factor (G-CSF), and tumor-associated macrophages (TAMs)[33]. These factors collectively contribute to an environment where N2 neutrophils outnumber their N1 counterparts, leading to enhanced tumor progression, immune evasion, and resistance to therapies. High numbers of N2 neutrophils are often associated with poor prognosis, metastasis, and chemoresistance in breast cancer patients[34].

The Tumor Microenvironment and Neutrophil Polarization

The TME plays a crucial role in dictating the polarization of neutrophils into either N1 or N2 phenotypes. Tumor cells and stromal cells, through the secretion of cytokines, growth factors, and extracellular matrix remodeling enzymes, create an immunosuppressive and pro-inflammatory environment that influences neutrophil behavior[35]. For example, the release of IL-8, G-CSF, and VEGF by tumor cells can promote N2 polarization, while IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) are known to support N1 polarization. Additionally, factors such as hypoxia, oxidative stress, and metabolic changes within the TME further contribute to the dynamic shift between N1 and N2 phenotypes[12,35,66]. This polarization process is not a static event, but rather a continual reprogramming that can be influenced by various therapeutic interventions. Chemotherapy, radiation, and immunotherapy can impact the polarization state of neutrophils in the TME[15,26,29]. For instance, while chemotherapy may lead to an influx of neutrophils, the treatment's effects on the TME can shift neutrophil polarization toward the N2 phenotype, promoting resistance. Therefore, understanding how neutrophil polarization shifts in response to these treatments is crucial for optimizing therapeutic strategies aimed at reversing the immunosuppressive effects of N2 neutrophils[37].

Impact on Breast Cancer Progression

The polarization of neutrophils toward either N1 or N2 phenotypes has significant implications for the progression of breast cancer. In early stages, the antitumor properties of N1 neutrophils help to limit tumor growth and metastasis[1-7,38]. However, as the tumor progresses, the TME often becomes more immunosuppressive, leading to a shift toward N2 neutrophils, which contribute to tumor growth, immune evasion, and metastasis. N2 neutrophils not only enhance tumor progression by secreting pro-angiogenic and immunosuppressive factors but also help create a niche for tumor cells to invade surrounding tissues and migrate to distant organs[39]. The presence of N2 neutrophils has been linked to increased metastatic potential, poor prognosis, and resistance to conventional therapies. As such, tumors with a high proportion of N2 neutrophils tend to be more aggressive, leading to worse clinical outcomes[40,41]. Studies have suggested that N2 neutrophils may also promote chemoresistance by altering the drug metabolism pathways or by creating a protective tumor niche that reduces drug efficacy. Therefore, the dynamic balance between N1 and N2 neutrophils in breast cancer is a critical determinant of tumor aggressiveness, metastasis, and patient survival[37-39].

Predictive Value of Neutrophil Polarization for Treatment Outcomes in Breast Cancer

Neutrophil polarization, which refers to the differentiation of neutrophils into two distinct phenotypes (N1 and N2), is emerging as an important factor influencing breast cancer progression and treatment outcomes[40]. The tumor microenvironment (TME) plays a crucial role in dictating the polarization of neutrophils, with N1 neutrophils generally exerting antitumor effects and N2 neutrophils promoting tumor

progression, immune evasion, and metastasis. The shift between these two neutrophil phenotypes can influence how the tumor responds to various treatment strategies, making neutrophil polarization a valuable biomarker for predicting therapeutic efficacy and patient prognosis[41,42].

Impact on Chemotherapy Response

Chemotherapy remains one of the most common treatment modalities for breast cancer, but its effectiveness is often limited by tumor heterogeneity, resistance mechanisms, and the immunosuppressive TME[43]. Studies have shown that the polarization of neutrophils plays a significant role in modulating chemotherapy response. Tumors with a higher proportion of N1 neutrophils tend to respond better to chemotherapy, as N1 neutrophils facilitate the activation of cytotoxic T cells and the induction of antitumor immune responses[44]. On the other hand, an N2-dominant neutrophil population in the TME is often associated with chemotherapy resistance, as N2 neutrophils can promote an immunosuppressive environment that limits the effectiveness of chemotherapeutic agents[44,45]. The relationship between N2 neutrophils and chemotherapy resistance is particularly evident in breast cancer subtypes such as triple-negative breast cancer (TNBC), which is known for its aggressive behavior and poor prognosis[46,47,49]. In these cases, the presence of N2 neutrophils can enhance tumor survival and migration by secreting cytokines and growth factors that support immune evasion and metastatic potential. Targeting the N2 phenotype, either by blocking their recruitment or polarizing them towards the N1 phenotype, could be a promising strategy to enhance the efficacy of chemotherapy[48].

Influence on Immunotherapy Outcomes

Immunotherapy, including immune checkpoint inhibitors (ICIs) and immune-modulatory therapies, is a promising treatment approach for certain breast cancer subtypes. However, the response to immunotherapy can be highly variable, and understanding the factors that influence treatment success is critical[19-23,30]. Neutrophil polarization is one such factor that can impact the outcome of immunotherapy. N1 neutrophils are known to promote antitumor immunity through the activation of immune cells such as cytotoxic T cells and NK cells. Therefore, a TME with a higher proportion of N1 neutrophils may enhance the effectiveness of immunotherapy by reinforcing the immune system's ability to recognize and attack tumor cells[49]. Conversely, N2 neutrophils in the TME are often associated with the suppression of immune responses, which can hinder the activity of immunotherapies. By secreting immunosuppressive cytokines like IL-10 and TGF-β, N2 neutrophils inhibit the function of cytotoxic T cells and NK cells, creating an environment where tumor cells can evade immune surveillance[29,50,53]. This highlights the potential for using neutrophil polarization as a predictive marker for immunotherapy outcomes. Manipulating neutrophil polarization to increase the number of N1 neutrophils or reduce the activity of N2 neutrophils may improve the response to immune checkpoint inhibitors and other immunotherapies[52].

Neutrophil Polarization and Targeted Therapies

Targeted therapies, which are designed to specifically target molecular alterations in cancer cells, are becoming increasingly important in the treatment of breast cancer. The predictive value of neutrophil polarization extends to these therapies as well. For example, tumors with a high proportion of N1 neutrophils may be more responsive to targeted therapies that enhance the immune response, such as monoclonal antibodies that activate the immune system or therapies that promote the recruitment of immune cells to the tumor site[53,57]. In contrast, tumors with a predominance of N2 neutrophils may be less responsive to such treatments due to the suppressive effects of N2 neutrophils on immune cell function. The predictive value of neutrophil polarization in targeted therapy outcomes has particular relevance in breast cancer subtypes such as HER2-positive breast cancer. HER2-targeted therapies like trastuzumab have shown significant efficacy, but the presence of immunosuppressive N2 neutrophils can undermine the effectiveness of these therapies by limiting immune activation[54]. Therefore, strategies to modulate neutrophil polarization, such as combining HER2-targeted therapies with agents that promote N1 neutrophil polarization, could enhance the overall therapeutic response and improve patient outcomes.

Neutrophil Polarization as a Biomarker for Prognosis

Beyond its role in predicting treatment outcomes, neutrophil polarization also holds promise as a prognostic biomarker in breast cancer. Studies have shown that tumors with a higher percentage of N1 neutrophils are associated with a better prognosis, as these cells are more likely to elicit an effective immune response that controls tumor growth and metastasis. In contrast, tumors with a predominance of N2 neutrophils are often linked to worse clinical outcomes, including increased metastatic potential, tumor recurrence, and chemoresistance[55,56]. The ability to assess neutrophil polarization in breast cancer patients could provide valuable insights into disease prognosis and help guide treatment decisions. For example, patients with a high N2-to-N1 ratio may benefit from therapies that target the immune microenvironment, such as immunotherapies or agents that promote the reprogramming of N2 neutrophils into N1 neutrophils[56,57]. Conversely, patients with a more favorable N1 neutrophil profile may have a better prognosis and may respond more favorably to standard treatment approaches.

Therapeutic Strategies to Modulate Neutrophil Polarization in Breast Cancer

The modulation of neutrophil polarization from the immunosuppressive N2 phenotype to the antitumor N1 phenotype presents an innovative approach to

enhancing breast cancer treatment. As neutrophils play a pivotal role in the tumor microenvironment (TME), influencing immune responses, tumor growth, and metastasis, strategies to shift neutrophil polarization can potentially improve therapeutic outcomes[8,57]. The ability to manipulate neutrophils to favor a more favorable N1 phenotype, which promotes antitumor immunity, offers a promising avenue for enhancing cancer therapies, particularly in conjunction with traditional treatments such as chemotherapy, immunotherapy, and targeted therapies[13.26]. Below are some potential therapeutic strategies aimed at modulating neutrophil polarization in breast cancer.

1. Cytokine Modulation

Cytokines are key regulators of neutrophil polarization, and their manipulation can direct neutrophils toward either the N1 or N2 phenotype. For example, cytokines such as IL-12 and IFN-γ are known to favor the polarization of neutrophils toward the N1 phenotype, which enhances antitumor immune responses. These cytokines activate neutrophils to secrete pro-inflammatory molecules and engage other immune cells, such as T cells and natural killer (NK) cells, in the fight against tumor cells[44,45]. Conversely, cytokines like IL-10 and TGF-β promote the N2 phenotype, which is immunosuppressive and can contribute to tumor progression and metastasis. Therapeutic strategies that involve the administration of cytokines like IL-12 or IFN-γ could encourage the recruitment and activation of N1 neutrophils in the TME, leading to enhanced tumor cell killing. Additionally, neutralizing or blocking N2-polarizing cytokines such as IL-10 and TGF-β could help reduce the immunosuppressive effects of N2 neutrophils, thereby improving the efficacy of other cancer therapies[12,27].

2. Targeting Neutrophil Chemoattractants

Neutrophil migration to the tumor site is facilitated by chemoattractants, such as chemokines and growth factors, which play a key role in regulating neutrophil polarization within the TME. For instance, CXCL8 (IL-8) is a well-known chemokine that attracts neutrophils to the tumor and has been implicated in the induction of the N2 phenotype[10,51]. Strategies aimed at blocking or neutralizing the activity of chemoattractants like CXCL8 can limit the recruitment of neutrophils to the tumor site or alter the balance of N1 to N2 polarization. This could potentially decrease the number of N2 neutrophils, thus reducing their immunosuppressive effect, and allow for the expansion of N1 neutrophils that support antitumor immunity. Targeting specific chemokine receptors, such as CXCR2 (the receptor for CXCL8), is a promising therapeutic approach. Inhibition of CXCR2 can prevent the recruitment of N2 neutrophils, enhance N1 polarization, and improve the overall immune response against the tumor[16,53].

3. Modulation of the Tumor Microenvironment (TME)

The TME significantly influences neutrophil polarization. In breast cancer, the presence of tumour-associated macrophages (TAMs), regulatory T cells (Tregs), and other immune cells contribute to a pro-tumour, immunosuppressive environment that favors the development of N2 neutrophils. Strategies to alter the TME to reduce immune suppression and promote a more pro-inflammatory, immune-activating environment can help shift the balance towards N1 neutrophil polarisation[31,49]. One approach to modifying the TME is the use of agents that target immune-suppressive cells, such as TAMs and Tregs. For example, the inhibition of TAMs using agents like CSF1R inhibitors can reduce the immunosuppressive effects within the TME and facilitate the recruitment of N1 neutrophils. Similarly, the depletion of Tregs, which inhibit immune responses, could allow for a more robust activation of N1 neutrophils[32-35].

4. Neutrophil Reprogramming

A promising approach to modulating neutrophil polarization involves directly reprogramming neutrophils from the N2 phenotype to the N1 phenotype. This can be achieved through the use of small molecules or antibodies that influence key signaling pathways involved in neutrophil activation and polarization. For example, targeting the Akt/mTOR signaling pathway has been shown to regulate neutrophil activation, and pharmacological agents that modulate this pathway could favor the N1 polarization of neutrophils[36,44]. Similarly, inhibiting the suppressive effects of molecules such as PD-1 or CTLA-4 on immune cells, including neutrophils, can enhance antitumor responses and promote N1 neutrophil activity. Gene-editing technologies, such as CRISPR-Cas9, may also provide a novel means of reprogramming neutrophils at the molecular level to enhance their N1 phenotype. By targeting key regulatory genes involved in neutrophil polarization, these technologies have the potential to shift neutrophils toward a more antitumor state[53-57].

5. Combination with Immunotherapy

The combination of neutrophil modulation with existing immunotherapies, such as immune checkpoint inhibitors (ICIs), offers an exciting strategy for enhancing breast cancer treatment. Immune checkpoint inhibitors like anti-PD-1 and anti-CTLA-4 antibodies work by blocking inhibitory signals that prevent T cells from attacking cancer cells[1-4,38]. However, their effectiveness can be limited by the immunosuppressive TME, which is often characterized by a high presence of N2 neutrophils. By combining ICIs with strategies that promote N1 neutrophil polarization, it may be possible to enhance the overall antitumor immune response and improve patient outcomes[39]. Furthermore, the combination of neutrophil modulation with other immunotherapeutic agents, such as monoclonal antibodies or cancer vaccines, could create a more comprehensive immune activation, improving the efficacy of treatment and potentially overcoming resistance mechanisms.

6. Use of Nanoparticles and Drug Delivery Systems

Nanotechnology has revolutionized the way therapeutic agents are delivered to the TME. Nanoparticles designed to carry cytokines, chemokines, or small molecule

inhibitors can be used to selectively target and modulate neutrophil polarization[40]. For instance, nanoparticles loaded with pro-inflammatory cytokines like IL-12 or IFN-γ could be used to directly deliver these molecules to the tumor, promoting N1 neutrophil polarization and enhancing antitumor immunity. Conversely, nanoparticles could be engineered to deliver inhibitors that block the N2-promoting cytokines or signaling pathways, helping to shift the neutrophil population toward a more beneficial N1 phenotype[41,57]. Additionally, the use of liposomes and other drug delivery systems can improve the specificity and efficiency of neutrophil-targeted therapies, reducing off-target effects and minimizing potential toxicity.

7. Dietary and Lifestyle Interventions

Emerging evidence suggests that dietary and lifestyle factors may also influence neutrophil polarization. For example, the consumption of certain nutrients, such as omega-3 fatty acids, has been linked to the promotion of N1 neutrophil activity, while a high-fat diet may favor N2 polarization[23,46]. As such, dietary interventions aimed at promoting N1 polarization could provide an adjunctive therapy to conventional cancer treatments. Incorporating lifestyle changes, such as exercise and stress reduction, could further help in modulating the immune system and enhancing neutrophil-mediated tumor control. These interventions, while still under investigation, present a novel and non-invasive means of supporting cancer therapy[50,55].

Conclusion

The polarization of neutrophils within the tumor microenvironment plays a crucial role in shaping the immune response and influencing the progression of breast cancer. N1 neutrophils, with their antitumor properties, offer a promising target for therapeutic strategies aimed at enhancing the body's immune defense against cancer. However, the presence of immunosuppressive N2 neutrophils complicates the tumor microenvironment, contributing to tumor growth, metastasis, and resistance to treatment. Therefore, shifting the balance towards N1 neutrophils could significantly improve the efficacy of breast cancer therapies. Several therapeutic approaches, such as cytokine modulation, targeting neutrophil chemoattractants, and reprogramming neutrophils, show potential in altering neutrophil polarization in favor of antitumor immunity. Additionally, combining these strategies with immunotherapies and other treatment modalities, like chemotherapy, may further enhance the overall immune response. However, challenges such as the complexity of the tumor microenvironment, the heterogeneity of neutrophils, and the need for more specific and targeted interventions remain significant barriers.

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References

1. Elyasinia F, Keramati MR, Ahmadi F, Rezaei S, Ashouri M, Parsaei R, Yaghoubi M, Elyasinia F, Aboutorabi A, Kaviani A. Neutrophil-lymphocyte ratio in different stages of breast cancer. Acta MedicaIranica. 2017 :228-32.

2. Wu L, Saxena S, Awaji M, Singh RK. Tumor-associated neutrophils in cancer: going pro. Cancers. 2019 ;11(4):564. https://doi.org/10.3390/cancers11040564 PMid:31010242 PMCid:PMC6520693

3. Jaillon S, Ponzetta A, Di Mitri D, Santoni A, Bonecchi R, Mantovani A. Neutrophil diversity and plasticity in tumour progression and therapy. Nature Reviews Cancer. 2020 ;20(9):485-503. https://doi.org/10.1038/s41568-020-0281-y PMid:32694624

4. Schernberg A, Mezquita L, Boros A, Botticella A, Caramella C, Besse B, Escande A, Planchard D, Le Péchoux C, Deutsch E. Neutrophilia as prognostic biomarker in locally advanced stage III lung cancer. PloS one. 2018 ;13(10):e0204490. https://doi.org/10.1371/journal.pone.0204490 PMid:30304046 PMCid:PMC6179235

5. Chung JY, Tang PC, Chan MK, Xue VW, Huang XR, Ng CS, Zhang D, Leung KT, Wong CK, Lee TL, Lam EW. Smad3 is essential for polarization of tumor-associated neutrophils in non-small cell lung carcinoma. Nature Communications. 2023 Mar 31;14(1):1794. https://doi.org/10.1038/s41467-023-37515-8 PMid:37002229 PMCid:PMC10066366

6. Shaul ME, Fridlender ZG. Neutrophils as active regulators of the immune system in the tumor microenvironment. Journal of leukocyte biology. 2017 Aug;102(2):343-9. https://doi.org/10.1189/jlb.5MR1216-508R PMid:28264904

7. Wang J, Ocadiz-Ruiz R, Hall MS, Bushnell GG, Orbach SM, Decker JT, Raghani RM, Zhang Y, Morris AH, Jeruss JS, Shea LD. A synthetic metastatic niche reveals antitumor neutrophils drive breast cancer metastatic dormancy in the lungs. Nature communications. 2023 Aug 8;14(1):4790. https://doi.org/10.1038/s41467-023-40478-5 PMid:37553342 PMCid:PMC10409732

8. Tabariès S, Ouellet V, Hsu BE, Annis MG, Rose AA, Meunier L, Carmona E, Tam CE, Mes-Masson AM, Siegel PM. Granulocytic immune infiltrates are essential for the efficient formation of breast cancer liver metastases. Breast cancer research. 2015 Dec;17:1-8. https://doi.org/10.1186/s13058-015-0558-3 PMid:25882816 PMCid:PMC4413545

9. Henkels KM, Muppani NR, Gomez-Cambronero J. PLD-specific small-molecule inhibitors decrease tumor-associated macrophages and neutrophils infiltration in breast tumors and lung and liver metastases. PLoS One. 2016 Nov 16;11(11):e0166553. https://doi.org/10.1371/journal.pone.0166553 PMid:27851813 PMCid:PMC5112812

10. Wu G, Pan B, Shi H, Yi Y, Zheng X, Ma H, Zhao M, Zhang Z, Cheng L, Huang Y, Guo W. Neutrophils' dual role in cancer: from tumor progression to immunotherapeutic potential. International Immunopharmacology. 2024 Oct 25;140:112788. https://doi.org/10.1016/j.intimp.2024.112788 PMid:39083923

11. Mahmud Z, Rahman A, Mishu ID, Kabir Y. Mechanistic insights into the interplays between neutrophils and other immune cells in cancer development and progression. Cancer and Metastasis Reviews. 2022 Jun;41(2):405-432. https://doi.org/10.1007/s10555-022-10024-8 PMid:35314951

12. Tyagi A, Wu SY, Sharma S, Wu K, Zhao D, Deshpande R, Singh R, Li W, Topaloglu U, Ruiz J, Watabe K. Exosomal miR-4466 from nicotine-activated neutrophils promotes tumor cell stemness and

metabolism in lung cancer metastasis. Oncogene. 2022 May 27;41(22):3079-3092. https://doi.org/10.1038/s41388-022-02322-w PMid:35461327 PMCid:PMC9135627

13. Bonavita O, Massara M, Bonecchi R. Chemokine regulation of neutrophil function in tumors. Cytokine & growth factor reviews. 2016 Aug 1;30:81-86. https://doi.org/10.1016/j.cytogfr.2016.03.012 PMid:27021826

14. Zhong J, Zong S, Wang J, Feng M, Wang J, Zhang H, Xiong L. Role of neutrophils on cancer cells and other immune cells in the tumor microenvironment. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2023 Oct 1;1870(7):119493. https://doi.org/10.1016/j.bbamcr.2023.119493 PMid:37201766

15. Powell DR, Huttenlocher A. Neutrophils in the tumor microenvironment. Trends in immunology. 2016 Jan 1;37(1):41-52. https://doi.org/10.1016/j.it.2015.11.008 PMid:26700397 PMCid:PMC4707100

16. Vazquez Rodriguez G, Abrahamsson A, Jensen LD, Dabrosin C. Estradiol promotes breast cancer cell migration via recruitment and activation of neutrophils. Cancer immunology research. 2017 Mar 1;5(3):234-247. https://doi.org/10.1158/2326-6066.CIR-16-0150 PMid:28159748

17. Galdiero MR, Garlanda C, Jaillon S, Marone G, Mantovani A. Tumor associated macrophages and neutrophils in tumor progression. Journal of cellular physiology. 2013 Jul;228(7):1404-1412. https://doi.org/10.1002/jcp.24260 PMid:23065796

18. Zhang Y, Guoqiang L, Sun M, Lu X. Targeting and exploitation of tumor-associated neutrophils to enhance immunotherapy and drug delivery for cancer treatment. Cancer biology & medicine. 2020 Feb 2;17(1):32. https://doi.org/10.20892/j.issn.2095-3941.2019.0372 PMid:32296575 PMCid:PMC7142839

19. Wang P, Xu MH, Xu WX, Dong ZY, Shen YH, Qin WZ. CXCL9 Overexpression Predicts Better HCC Response to Anti-PD-1 Therapy and Promotes N1 Polarization of Neutrophils. Journal of Hepatocellular Carcinoma. 2024 Dec 31:787-800. https://doi.org/10.2147/JHC.S450468 PMid:38737384 PMCid:PMC11088828

20. Huang X, Nepovimova E, Adam V, Sivak L, Heger Z, Valko M, Wu Q, Kuca K. Neutrophils in Cancer immunotherapy: friends or foes?. Molecular Cancer. 2024 May 18;23(1):107. https://doi.org/10.1186/s12943-024-02004-z PMid:38760815 PMCid:PMC11102125

21. Timaxian C, Vogel CF, Orcel C, Vetter D, Durochat C, Chinal C, NGuyen P, Aknin ML, Mercier-Nomé F, Davy M, Raymond-Letron I. Pivotal role for Cxcr2 in regulating tumor-associated neutrophil in breast cancer. Cancers. 2021 May 25;13(11):2584. https://doi.org/10.3390/cancers13112584 PMid:34070438 PMCid:PMC8197482

22. Siwicki M, Pittet MJ. Versatile neutrophil functions in cancer. InSeminars in Immunology 2021;57:101538). Academic Press. https://doi.org/10.1016/j.smim.2021.101538 PMid:34876331

23. Peng H, Shen J, Long X, Zhou X, Zhang J, Xu X, Huang T, Xu H, Sun S, Li C, Lei P. Local release of TGF-β inhibitor modulates tumor-associated neutrophils and enhances pancreatic cancer response to combined irreversible electroporation and immunotherapy. Advanced Science. 2022 Apr;9(10):2105240. https://doi.org/10.1002/advs.202105240 PMid:35128843 PMCid:PMC8981446

24. Arvanitakis K, Mitroulis I, Germanidis G. Tumor-associated neutrophils in hepatocellular carcinoma pathogenesis, prognosis, and therapy. Cancers. 2021 Jun 10;13(12):2899. https://doi.org/10.3390/cancers13122899 PMid:34200529 PMCid:PMC8228651

25. Mizuno R, Kawada K, Itatani Y, Ogawa R, Kiyasu Y, Sakai Y. The role of tumor-associated neutrophils in colorectal cancer. International journal of molecular sciences. 2019 Jan 27;20(3):529. https://doi.org/10.3390/ijms20030529 PMid:30691207 PMCid:PMC6386937

26. Xu W, Weng J, Xu M, Zhou Q, Liu S, Hu Z, Ren N, Zhou C, Shen Y. Chemokine CCL21 determines immunotherapy response in hepatocellular carcinoma by affecting neutrophil polarization. Cancer Immunology, Immunotherapy. 2024 Feb 17;73(3):56. https://doi.org/10.1007/s00262-024-03650-4 PMid:38367070 PMCid:PMC10874310

27. Barreno L, Sevane N, Valdivia G, Alonso-Miguel D, Suarez-Redondo M, Alonso-Diez A, Fiering S, Beiss V, Steinmetz NF, Perez-Alenza MD, Peña L. Transcriptomics of canine inflammatory mammary cancer treated with empty cowpea mosaic virus implicates neutrophils in anti-tumor immunity. International Journal of Molecular Sciences. 2023 Sep 13;24(18):14034. https://doi.org/10.3390/ijms241814034 PMid:37762335 PMCid:PMC10531449

28. Cuartero MI, Ballesteros I, Moraga A, Nombela F, Vivancos J, Hamilton JA, Corbí ÁL, Lizasoain I, Moro MA. N2 neutrophils, novel players in brain inflammation after stroke: modulation by the PPARγ agonist rosiglitazone. Stroke. 2013 Dec;44(12):3498-3508. https://doi.org/10.1161/STROKEAHA.113.002470 PMid:24135932

29. Pan YC, Nishikawa T, Chang CY, Tai JA, Kaneda Y. CXCL2 combined with HVJ-E suppresses tumor growth and lung metastasis in breast cancer and enhances anti-PD-1 antibody therapy. Molecular Therapy-Oncolytics. 2021 Mar 26;20:175-186. https://doi.org/10.1016/j.omto.2020.12.011 PMid:33575480 PMCid:PMC7851488

30. Zou JM, Qin J, Li YC, Wang Y, Li D, Shu Y, Luo C, Wang SS, Chi G, Guo F, Zhang GM. IL-35 induces N2 phenotype of neutrophils to promote tumor growth. Oncotarget. 2017 May 5;8(20):33501. https://doi.org/10.18632/oncotarget.16819 PMid:28432279 PMCid:PMC5464885

31. Reichardt CM, Muñoz-Becerra M, RiusRigau A, Rückert M, Fietkau R, Schett G, Gaipl US, Frey B, Muñoz LE. Neutrophils seeking new neighbors: radiotherapy affects the cellular framework and the spatial organization in a murine breast cancer model. Cancer Immunology, Immunotherapy. 2024 Mar 2;73(4):67. https://doi.org/10.1007/s00262-024-03653-1 PMid:38430241 PMCid:PMC10908631

32. Yang J, Xie Y, Xia Z, Ji S, Yang X, Yue D, Liu Y, Yang R, Fan Y. HucMSC-Exo Induced N2 Polarization of Neutrophils: Implications for Angiogenesis and Tissue Restoration in Wound Healing. International Journal of Nanomedicine. 2024 Dec 31:3555-3575. https://doi.org/10.2147/IJN.S458295 PMid:38638364 PMCid:PMC11024985

33. Wu Q, Mao H, Jiang Z, Tang D. Tumour-associated neutrophils: Potential therapeutic targets in pancreatic cancer immunotherapy. Immunology. 2024 Jul;172(3):343-361. https://doi.org/10.1111/imm.13765 PMid:38402904

34. Zhang L, Pan J, Wang M, Yang J, Zhu S, Li L, Hu X, Wang Z, Pang L, Li P, Jia F. Chronic Stress-Induced and Tumor Derived SP1+ Exosomes Polarizing IL-1β+ Neutrophils to Increase Lung Metastasis of Breast Cancer. Advanced Science. 2024:2310266. https://doi.org/10.1002/advs.202310266 PMid:39630109 PMCid:PMC11789585

35. Hajizadeh F, Maleki LA, Alexander M, Mikhailova MV, Masjedi A, Ahmadpour M, Hashemi V, Jadidi-Niaragh F. Tumor-associated neutrophils as new players in immunosuppressive process of the tumor microenvironment in breast cancer. Life sciences. 2021 ;264:118699. https://doi.org/10.1016/j.lfs.2020.118699 PMid:33137368

36. Al Qutami F, Al Halabi W, Hachim MY. Identification of breast cancer LCK proto-oncogene as a master regulator of TNBC neutrophil enrichment and polarization. International journal of molecular sciences. 2023 ;24(17):13269. https://doi.org/10.3390/ijms241713269 PMid:37686072 PMCid:PMC10487917

37. Zheng C, Xu X, Wu M, Xue L, Zhu J, Xia H, Ding S, Fu S, Wang X, Wang Y, He G. Neutrophils in triple-negative breast cancer: an underestimated player with increasingly recognized importance. Breast Cancer Research. 2023 ;25(1):88. https://doi.org/10.1186/s13058-023-01676-7 PMid:37496019 PMCid:PMC10373263

38. Shaul ME, Fridlender ZG. Tumour-associated neutrophils in patients with cancer. Nature reviews Clinical oncology. 2019

;16(10):601-620. https://doi.org/10.1038/s41571-019-0222-4 PMid:31160735

39. Schernberg A, Blanchard P, Chargari C, Deutsch E. Neutrophils, a candidate biomarker and target for radiation therapy?. Acta oncologica. 2017 ;56(11):1522-1530. https://doi.org/10.1080/0284186X.2017.1348623 PMid:28835188

40. Li Z, Zhao R, Cui Y, Zhou Y, Wu X. The dynamic change of neutrophil to lymphocyte ratio can predict clinical outcome in stage I-III colon cancer. Scientific reports. 2018 ;8(1):9453. https://doi.org/10.1038/s41598-018-27896-y PMid:29930287 PMCid:PMC6013456

41. Wang P, Xu MH, Xu WX, Dong ZY, Shen YH, Qin WZ. CXCL9 Overexpression Predicts Better HCC Response to Anti-PD-1 Therapy and Promotes N1 Polarization of Neutrophils. Journal of Hepatocellular Carcinoma. 2024 :787-800. https://doi.org/10.2147/JHC.S450468 PMid:38737384 PMCid:PMC11088828

42. Masucci MT, Minopoli M, Carriero MV. Tumor associated neutrophils. Their role in tumorigenesis, metastasis, prognosis and therapy. Frontiers in oncology. 2019 ;9:1146. https://doi.org/10.3389/fonc.2019.01146 PMid:31799175 PMCid:PMC6874146

43. Senovilla L, Vacchelli E, Galon J, Adjemian S, Eggermont A, Fridman WH, Sautès-Fridman C, Ma Y, Tartour E, Zitvogel L, Kroemer G. Trial watch: Prognostic and predictive value of the immune infiltrate in cancer. Oncoimmunology. 2012 ;1(8):1323-1343. https://doi.org/10.4161/onci.22009 PMid:23243596 PMCid:PMC3518505

44. Bruni D, Angell HK, Galon J. The immune contexture and Immunoscore in cancer prognosis and therapeutic efficacy. Nature Reviews Cancer. 2020 ;20(11):662-680. https://doi.org/10.1038/s41568-020-0285-7 PMid:32753728

45. Xu W, Weng J, Xu M, Zhou Q, Liu S, Hu Z, Ren N, Zhou C, Shen Y. Chemokine CCL21 determines immunotherapy response in hepatocellular carcinoma by affecting neutrophil polarization. Cancer Immunology, Immunotherapy. 2024 ;73(3):56. https://doi.org/10.1007/s00262-024-03650-4 PMid:38367070 PMCid:PMC10874310

46. Huang YC, Chang CY, Wu YY, Wu KL, Tsai YM, Lee HC, Tsai EM, Hsu YL. Single-cell transcriptomic profiles of lung pre-metastatic niche reveal neutrophil and lymphatic endothelial cell roles in breast cancer. Cancers. 2022 ;15(1):176. https://doi.org/10.3390/cancers15010176 PMid:36612175 PMCid:PMC9818165

47. Wu Y, Liu H, Sun Z, Liu J, Li K, Fan R, Dai F, Tang H, Hou Q, Li J, Tang X. The adhesion-GPCR ADGRF5 fuels breast cancer progression by suppressing the MMP8-mediated antitumorigenic effects. Cell Death & Disease. 2024 ;15(6):455. https://doi.org/10.1038/s41419-024-06855-8 PMid:38937435 PMCid:PMC11211477

48. Gianni C, Palleschi M, Schepisi G, Casadei C, Bleve S, Merloni F, Sirico M, Sarti S, Cecconetto L, Di Menna G, Schettini F. Circulating inflammatory cells in patients with metastatic breast cancer: Implications for treatment. Frontiers in oncology. 2022 ;12:882896. https://doi.org/10.3389/fonc.2022.882896 PMid:36003772 PMCid:PMC9393759

49. Jadoon, S.K., Soomro, R., Ahsan, M.N., Khan, R.M.I., Iqbal, S., Yasmin, F., Najeeb, H., Saleem, N., Cho, N., Shaikh, T.G. and Hasan, S.F.S., 2023. Association of neutrophil-to-lymphocyte ratio with clinical, pathological, radiological, laboratory features and disease outcomes of invasive breast cancer patients: A retrospective observational cohort study. Medicine, 102(20), p.e33811. https://doi.org/10.1097/MD.0000000000033811 PMid:37335707 PMCid:PMC10194494

50. Tabariès S, Ouellet V, Hsu BE, Annis MG, Rose AA, Meunier L, Carmona E, Tam CE, Mes-Masson AM, Siegel PM. Granulocytic immune infiltrates are essential for the efficient formation of breast cancer liver metastases. Breast cancer research. 2015 ;17:1-8. https://doi.org/10.1186/s13058-015-0558-3 PMid:25882816 PMCid:PMC4413545

51. Hu P, Liu Q, Deng G, Zhang J, Liang N, Xie J, Zhang J. Radiosensitivity nomogram based on circulating neutrophils in thoracic cancer. Future Oncology. 2019 ;15(7):727-737. https://doi.org/10.2217/fon-2018-0398 PMid:30693787

52. Wang J, Ocadiz-Ruiz R, Hall MS, Bushnell GG, Orbach SM, Decker JT, Raghani RM, Zhang Y, Morris AH, Jeruss JS, Shea LD. A synthetic metastatic niche reveals antitumor neutrophils drive breast cancer metastatic dormancy in the lungs. Nature communications. 2023 ;14(1):4790. https://doi.org/10.1038/s41467-023-40478-5 PMid:37553342 PMCid:PMC10409732

53. Schmidt E, Distel L, Erber R, Büttner-Herold M, Rosahl MC, Ott OJ, Strnad V, Hack CC, Hartmann A, Hecht M, Fietkau R. Tumor-Associated Neutrophils Are a Negative Prognostic Factor in Early Luminal Breast Cancers Lacking Immunosuppressive Macrophage Recruitment. Cancers. 2024 ;16(18):3160. https://doi.org/10.3390/cancers16183160 PMid:39335132 PMCid:PMC11430230

54. Grassadonia A, Graziano V, Iezzi L, Vici P, Barba M, Pizzuti L, Cicero G, Krasniqi E, Mazzotta M, Marinelli D. Prognostic relevance of neutrophil to lymphocyte ratio (NLR) in luminal breast cancer: a retrospective analysis in the neoadjuvant setting. Cells. 2021;10(7):1685. https://doi.org/10.3390/cells10071685 PMid:34359855 PMCid:PMC8303552

55. Liu S, Wu W, Du Y, Yin H, Chen Q, Yu W, Wang W, Yu J, Liu L, Lou W, Pu N. The evolution and heterogeneity of neutrophils in cancers: origins, subsets, functions, orchestrations and clinical applications. Molecular Cancer. 2023 ;22(1):148. https://doi.org/10.1186/s12943-023-01843-6 PMid:37679744 PMCid:PMC10483725

56. Azab BN, Bhatt VR, Vonfrolio S, Bachir R, Rubinshteyn V, Alkaied H, Habeshy A, Patel J, Picon AI, Bloom SW. Value of the pretreatment albumin to globulin ratio in predicting long-term mortality in breast cancer patients. The American Journal of Surgery. 2013 ;206(5):764-770. https://doi.org/10.1016/j.amjsurg.2013.03.007 PMid:23866764

57. Zhang J, Yu D, Ji C, Wang M, Fu M, Qian Y, Zhang X, Ji R, Li C, Gu J, Zhang X. Exosomal miR-4745-5p/3911 from N2-polarized tumor-associated neutrophils promotes gastric cancer metastasis by regulating SLIT2. Molecular Cancer. 2024 ;23(1):198. https://doi.org/10.1186/s12943-024-02116-6 PMid:39272149 PMCid:PMC11396805