Unraveling the complex role of neutrophils in lymphoma: From pathogenesis to therapeutic approaches (Review)

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Abstract. Lymphoma, a malignancy of the lymphatic system, which is critical for maintaining the body's immune defenses, has become a focal point in recent research due to its intricate interplay with neutrophils-white blood cells essential for combating infections and inflammation. Unlike prior perceptions associating neutrophils only with tumor support, contemporary studies underscore their intricate and multifaceted involvement in the immune response to lymphoma. Recognizing the nuanced participation of neutrophils in lymphoma is crucial for developing innovative treatments to improve patient outcomes.

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1. Neutrophils' dual role in lymphoma: A paradigm shift

Contemporary research is redefining the traditional view of neutrophils only as tumor supporters. Current studies underscore their nuanced participation in the immune response to lymphoma, going beyond conventional associations with inflammation and infection defense (1). Recognizing this complexity is pivotal for pioneering novel treatments to enhance patient outcomes (2).

Defining neutrophils: Guardians of the immune frontline. Neutrophils, a subtype of white blood cells, are vital contributors to the immune system, acting as frontline defenders against infections and injuries (3). Their fundamental role centers around engulfing and destroying harmful bacteria and other pathogens, making them indispensable components of the body's initial defense mechanism against foreign invaders (4). As key participants in the innate immune response, these cells are generated in the bone marrow and exist in abundant numbers in the bloodstream and various tissues throughout the body (5). Neutrophils also play a pivotal role in the inflammatory process, which is the body's orchestrated response to tissue damage or infection (6,7).

While the intricate functions of neutrophils in immune surveillance and response have been extensively studied, their precise involvement in lymphoma, a cancer that affects the immune system, remains enigmatic. However, research studies are shedding light on the potential roles of neutrophils in lymphoma progression (8-10). While traditionally recognized for their role in combating infections, neutrophils are now being examined to reveal their possible contributions or influences in the intricate landscape of lymphoma development (11,12).

Understanding the nuanced interactions between neutrophils and lymphoma cells may be key to unraveling the mysteries surrounding lymphoma progression (13). Further insights may emerge as ongoing research endeavors delve into the complex interplay between these immune cells and lymphoma (9), opening new therapeutic avenues and advancing our comprehension of the intricate dynamics within the immune system.

Lymphoma unveiled: Categories, symptoms and diagnosis. Lymphoma, a formidable type of cancer, takes its toll on

the lymphatic system, a crucial component responsible for supporting the body's immune response against infections (14). This malignancy develops when white blood cells, specifically lymphocytes and plasma cells, undergo a chaotic process of uncontrolled growth, culminating in the formation of tumors (15). Lymphoma presents in two primary forms: Hodgkin lymphoma, distinguished by the presence of Reed-Sternberg cells, and non-Hodgkin lymphoma, a diverse array of subtypes, each requiring tailored treatment (16).

Recognizing the onset of lymphoma involves an awareness of its symptoms, which may manifest as swollen lymph nodes, fatigue, persistent fever, night sweats and unexplained weight loss (17). The diagnostic process, integral to effective intervention, typically entails a comprehensive combination of blood tests, imaging scans and biopsy procedures targeting affected tissue. The treatment approach is multifaceted, comprising chemotherapy, radiation therapy, targeted therapies and stem cell transplantation (18).

This complex nature of lymphoma and its diverse manifestations and treatment modalities underscores the complexity of tackling this challenging disease. As research continues to delve into the intricate details of lymphoma subtypes and their unique characteristics, innovative treatments and therapeutic strategies are poised to emerge, promising improved outcomes and enhanced quality of life for those affected by this challenging disease (19,20).

Navigating neutrophils in lymphoma: Current understanding and ongoing research. As the most abundant white blood cells in the human body, neutrophils traditionally stand at the forefront of the immune system, undertaking a critical role in the defense against infections (21). However, the narrative surrounding neutrophils is evolving, with recent studies illuminating an unexpected dimension to their function-one that extends beyond infection control to encompass a substantial role in lymphoma development and progression (22).

Of note, neutrophils are not mere bystanders in lymphoma; they actively engage with lymphoma cells, influencing the complex milieu known as the tumor microenvironment (TME) (21,22). This influence has multiple facets, with neutrophils acting as architects of inflammation and wielders of immune response suppression within the TME (23,24). The consequences of these interactions extend beyond the immediate cellular level, potentially contributing to the overall progression of lymphoma (25).

Despite the pivotal insights from recent studies, the precise mechanisms orchestrating these interactions between neutrophils and lymphoma cells remain enigmatic. The research community is presently engaged in a dynamic pursuit to unravel the intricate relationship between neutrophils and lymphoma (26). This ongoing exploration is poised to uncover the molecular intricacies and signaling pathways that govern this interplay, potentially unlocking novel avenues for therapeutic intervention and refining our understanding of the complex dynamics involved.

As the scientific community delves deeper into the multifaceted roles of neutrophils in lymphoma, the evolving research landscape holds promise for a paradigm shift in our comprehension of lymphoma (27,28). This review serves as a snapshot of the current understanding, recognizing that the journey of discovery is far from completed, with ongoing research poised to shape the future landscape of lymphoma diagnostics and therapeutics.

The neutrophil-to-lymphocyte ratio (NLR) in lymphoma prognosis. In recent studies, the NLR has garnered attention as a critical prognostic indicator (29). The NLR is calculated by dividing the number of neutrophils by the number of lymphocytes in the blood, and it has been shown to hold significant prognostic value across various cancer types, including lymphoma.

Clinical significance of the NLR. An elevated NLR is generally associated with a poor prognosis. In patients with lymphoma, a higher NLR may reflect a heightened inflammatory response, which is often associated with tumor progression and their overall immune status (30). High NLRs may indicate a more substantial tumor burden and a worse therapeutic response (31). Specifically, a high NLR may indicate several key factors. Firstly, the inflammatory state of the TME, often indicated by an increase in neutrophils, can promote tumor cell growth and metastasis. Secondly, a suppressed immune state, often reflected by a high NLR indicating a relative decrease in lymphocytes, can weaken the immune response against the tumor since lymphocytes, particularly T cells, are crucial for anti-tumor immunity. Thirdly, the therapeutic response, often associated with a high NLR, which some studies suggest is linked to a worse response to treatments such as chemotherapy or radiotherapy in patients with lymphoma, affects their overall survival (30,31).

Application of the NLR as a prognostic indicator. Given these reasons, the NLR can serve as a simple and effective prognostic indicator to assist clinicians in risk assessment during treatment planning. For instance, at the initial diagnosis stage, measuring the NLR can provide a preliminary prognosis and help tailor treatment strategies. During treatment, monitoring changes in the NLR can provide insights into treatment efficacy, allowing timely adjustments to therapeutic approaches. In addition, the simplicity of measuring the NLR, which requires no complex equipment or technical support, adds to its clinical utility (32,33).

In conclusion, as an important prognostic indicator, the NLR holds significant potential in lymphoma. Future research should further explore the specific mechanisms of the NLR in different types and stages of lymphoma to validate its reliability and effectiveness as a prognostic tool.

By redefining the role of neutrophils in lymphoma, a comprehensive understanding of their multifaceted functions within the TME may be gained. Neutrophils are not only simple immune cells but are actively involved in tumor initiation and progression. Understanding these complex functions is crucial for developing novel therapeutic strategies.

Investigation of the relationship between neutrophils and lymphoma. Research on the relationship between neutrophils and lymphoma has a long history, evolving from early fundamental discoveries to current, in-depth explorations of their mechanisms, gradually revealing their complex roles in tumorigenesis and progression.

Early discoveries. In the mid-20th century, researchers first observed the abnormal accumulation of neutrophils in tumor tissues, sparking interest in the role of neutrophils in tumor biology. Early studies focused on neutrophils' inflammatory response and their role within the TME. Histological analyses showed high densities of neutrophils surrounding and infiltrating tumors, suggesting their involvement in the immune response to tumors (34).

Progress in the late-20th century. During the 1980s and 1990s, significant advancements were made in understanding the relationship between neutrophils and tumors. Researchers found that neutrophils were not only inflammatory cells but could directly influence tumor cell growth and metastasis by secreting various cytokines and growth factors. For instance, studies showed that neutrophils could promote tumor angiogenesis by secreting vascular endothelial growth factors, providing nutrients and oxygen to tumor cells. Neutrophils were also found to facilitate tumor cell invasion and metastasis by releasing matrix metalloproteinases (35,36).

Modern research focus. At the start of the 21st century, advances in molecular biology techniques have deepened our understanding of neutrophils' roles within the TME. Modern research has revealed that neutrophils not only support tumor growth but also participate in immune suppression and tumor immune evasion. Specific mechanisms include neutrophils suppressing T cell anti-tumor activity by secreting inhibitory cytokines such as interleukin (IL)-10 and chemokines such as C-X-C motif chemokine ligand 8, aiding tumor cells in evading immune surveillance (37-40).

The recent discovery of neutrophil extracellular traps (NETs) added another layer of complexity to neutrophils' roles in cancer. Initially identified as structures for trapping and killing pathogens, NETs were found to promote tumor cell migration and metastasis, providing new insights into neutrophils' complex functions in cancer (41).

Clinical research and applications. As basic research progressed, the potential of neutrophils in cancer therapy began to emerge. Clinical studies indicated that modulating neutrophil functions could significantly impact tumor progression and treatment outcomes. For instance, certain drugs targeting neutrophils are being evaluated in clinical trials to inhibit their tumor-promoting activities or enhance their anti-tumor functions to improve patient prognosis (42,43).

In summary, research on the relationship between neutrophils and lymphoma reflects continuous efforts to explore this complex field. From early discoveries to modern mechanistic studies, the evolving understanding of neutrophils in the TME underscores their multifaceted roles. These historical data not only provide essential background information for current research but also guide future studies. By comprehensively understanding neutrophils' roles in lymphoma, it may be possible to develop more effective therapeutic strategies and improve patient survival and quality of life.

Reviewing the historical progress in the research on neutrophils and lymphoma may improve the understanding of the significance and complexity of this field. Future studies should continue to explore neutrophils' specific roles within the TME to provide a solid foundation for developing new therapeutic approaches.

2. Neutrophils and lymphoma pathogenesis: A complex interplay

The intricate interplay between neutrophils and lymphoma pathogenesis presents as a complex relationship with both promotional and inhibitory influences on the disease trajectory (27,44). Neutrophils, traditionally regarded as immune warriors, can induce DNA damage in lymphoma cells, potentially triggering apoptosis and providing a therapeutic avenue for impeding uncontrolled growth (26,45). Conversely, their secretion of pro-inflammatory cytokines paradoxically enhances lymphoma growth and contributes to tumor angiogenesis (27,46). The real-world manifestation of neutrophil influence through tissue infiltration is a potential biomarker and target for therapeutic intervention, indicating active involvement in tumorigenesis (47). Despite significant findings, the role of neutrophils in lymphoma pathogenesis is still incompletely understood and further investigations into the underlying mechanisms are required. The ongoing journey of exploration holds the promise of revealing novel therapeutic strategies and refining approaches to lymphoma treatment, advancing our comprehension of the complexities of neutrophil involvement and lymphoma pathogenesis.

Inflammation: Balancing act in the immune response. As a fundamental biological response to injury or infection, inflammation involves intricate molecular reactions orchestrated by neutrophils, key contributors to the immune system's response (48,49). While acute inflammation is a transient and protective defense, chronic inflammation, characterized by prolonged neutrophil engagement, may lead to sustained tissue damage and contribute to diseases such as cancer, including lymphoma (50). Research has revealed that neutrophils actively promote tumor growth and ensure cancer cell survival in lymphoma by releasing cytokines and chemokines (34,51). The complex interplay among neutrophils, inflammation and lymphoma goes beyond conventional immune responses, providing crucial insights into lymphoma's pathophysiology and potential therapeutic targets (52). Delving deeper into the molecular intricacies of neutrophil-mediated inflammation offers a tangible prospect of unveiling novel therapeutic avenues, signifying a crucial step in translating scientific understanding into practical applications that could revolutionize the treatment landscape for inflammatory diseases, including lymphoma.

Types of inflammation. Inflammation, a fundamental and natural process, is the body's orchestrated response to tissue injury or infection. This dynamic phenomenon is categorized into two primary types, acute and chronic, each characterized by distinct temporal and molecular features (53,54).

Acute inflammation is characterized by its rapid onset and short-lived nature, unfolding over seconds to minutes. This immediate response involves the release of chemical mediators, including histamine and cytokines, triggering a cascade of events aimed at restoring tissue homeostasis (55,56). A hallmark of acute inflammation is the swift migration of neutrophils to the site of injury or infection (52,57). These white blood cells play a crucial role in the immune response, phagocytizing and destroying invading microorganisms, thereby preventing the spread of infection (58).

In contrast, chronic inflammation represents a protracted and enduring response, persisting over weeks, months or even years (59). This sustained reaction involves the infiltration of immune cells, such as macrophages and lymphocytes, into the affected tissue (49). While these immune cells are essential components of the body's defense mechanism, their prolonged presence in chronic inflammation can lead to tissue damage. Notably, chronic inflammation is implicated in the development of various diseases, including cancer (46,50).

Within the cancer context, chronic inflammation creates an environment conducive to the initiation and progression of malignant processes (46,50). The infiltrating immune cells release pro-inflammatory signals, contributing to the formation of a TME that supports the survival and growth of cancer cells (60). Understanding the intricate dynamics of acute and chronic inflammation is crucial not only for deciphering the body's response to injury and infection but also for unraveling the complexities underlying the development of diseases, particularly those with an inflammatory component, such as cancer.

Cytokine signaling during inflammation. In the intricate landscape of inflammation, cytokines emerge as pivotal orchestrators, playing a crucial role in the complex signaling processes that facilitate communication between cells (61,62). Cytokines are small proteins secreted by various cell types, particularly immune cells, in response to infection or injury. Their release, a dynamic and tightly regulated process, serves as a molecular communication network that coordinates the immune response and contributes significantly to the inflammatory milieu (62,63).

During inflammation, neutrophils and other immune cells release cytokines as part of their concerted effort to activate and recruit additional immune cells to the site of injury or infection (64,65). This orchestrated recruitment is fundamental to the inflammatory response, where immune cells collaborate to neutralize threats and restore tissue homeostasis (65). The dysregulation of cytokine signaling has been implicated in lymphoma development, with their uncontrolled release fostering a TME conducive to tumor growth and metastasis (50,66).

The significance of understanding the intricate role of cytokine signaling during inflammation extends beyond lymphoma and encompasses a broader spectrum of cancers (67). Unraveling the molecular intricacies of cytokine-mediated signaling pathways not only sheds light on the pathophysiology of cancer but also holds the promise of identifying novel therapeutic targets (68,69). Targeting cytokine signaling pathways offers a potential avenue for intervention, aiming to mitigate the pro-tumorigenic effects associated with uncontrolled cytokine release (70).

In summary, exploring cytokine signaling during inflammation is at the frontier of cancer research, providing a foundation for developing innovative and targeted treatments. As our comprehension of these molecular pathways advances, so too does the potential for transformative therapeutic strategies in the fight against lymphoma and other malignancies.

TME: Neutrophils' symphony in lymphoma progression. The TME is a complex ecosystem surrounding tumors, comprising various cell types such as immune cells, stromal cells and blood vessels (71). Traditionally known for combatting infections, neutrophils have gained attention for their active role in the TME, influencing molecular and cellular interactions that shape cancer progression, particularly in lymphoma development (51). Understanding neutrophils' contribution to the intricate interplay within the TME is crucial for unraveling the intricacies of lymphoma. Beyond comprehension, this knowledge paves the way for innovative therapeutic strategies. By deciphering neutrophil interactions and their impact on the broader TME, researchers may identify novel targets for intervention, offering potential avenues to disrupt pro-tumorigenic influences and enhance treatment outcomes. Exploring neutrophils in the TME represents a frontier in cancer research, providing a deeper understanding of the molecular intricacies driving lymphoma development, with the promise of transformative therapeutic strategies to disrupt the TME's role in cancer progression.

Composition of the TME. The TME is a dynamic and heterogeneous milieu comprising diverse cell types, including cancer, immune and stromal cells, as well as extracellular matrix (ECM) components (71). The intricate interactions between these components are pivotal in shaping tumor progression, influencing metastatic potential and determining the response to therapy. Within this complex landscape, neutrophils, a vital type of immune cell, have recently emerged as key players in modulating the TME, particularly in lymphoma (72,73).

Traditionally recognized for their role in the innate immune response against infections, neutrophils are now gaining recognition for their critical involvement in the TME of lymphoma (72). The TME is a dynamic environment in which various cell populations interact and communicate, influencing the behavior of cancer cells (73). Understanding the nuanced interactions between neutrophils and other cell types within the TME is pivotal for unraveling the complexities of lymphoma progression.

Research has shown neutrophils can significantly impact the TME by releasing signaling molecules and enzymes (74,75). These mediators help create an inflammatory TME, either supporting or inhibiting tumor growth. The specific mechanisms by which neutrophils modulate the TME in lymphoma are still being actively investigated, highlighting their complexity.

Appreciating the dynamics of the TME and the role of neutrophils within it may provide valuable insights into potential therapeutic strategies for lymphoma and other cancers (76). Targeting the interplay between neutrophils and the broader TME could offer new therapeutic avenues to disrupt the supportive environment that drives cancer progression (10).

In conclusion, the TME represents a complex ecosystem in which the orchestration of various cell types influences tumor behavior. Neutrophils, once considered primarily first responders to infections, are now recognized as influential contributors to the TME in lymphoma. Deciphering the intricacies of these interactions opens up new possibilities for therapeutic interventions, offering hope for more effective strategies to combat lymphoma and improve patient outcomes.

Role of neutrophils in the TME. Classically acknowledged for their crucial role in combating infections, neutrophils are now recognized as key contributors to the TME in lymphoma. Recent studies have revealed their substantial impact on TME

dynamics, shedding light on their involvement in tumor growth and metastasis (77).

One notable aspect of neutrophil-mediated influence on the TME is their ability to release specific signaling molecules and enzymes (9). These mediators contribute to establishing an inflammatory milieu within the tumor, fostering a TME conducive to tumor progression. The intricate molecular interactions orchestrated by neutrophils are pivotal in shaping the landscape of the TME, influencing the behavior of cancer cells.

Furthermore, the interactions between neutrophils and other cell types within the TME further accentuate their significance (78,79). Neutrophils engage in crosstalk with tumor and immune cells, creating a communication network that can amplify the support for tumor growth and progression. Understanding the complexities of these interactions is essential for deciphering the mechanisms underlying lymphoma development.

Collectively, the findings from these studies suggest that targeting neutrophils in the TME is a promising potential therapeutic avenue for improving the outcomes of patients with lymphoma. Novel therapeutic strategies may emerge that disrupt the pro-tumorigenic effects orchestrated by neutrophils. However, it is imperative to delve deeper into the molecular mechanisms and signaling pathways involved in the interplay between neutrophils and the TME to develop targeted interventions that effectively impede lymphoma progression.

In conclusion, the role of neutrophils in the lymphoma TME extends beyond their classical function in infection defense. Their influence on signaling pathways and interactions within the TME underscores their significance as potential therapeutic targets. Unraveling the intricacies of neutrophil-mediated effects on the TME holds promise for devising innovative strategies to improve the outcomes for patients with lymphoma.

Molecular mechanisms regulating neutrophil behavior. Understanding the complex roles of neutrophils in lymphoma requires thoroughly exploring the molecular mechanisms that govern their behavior. These mechanisms include signaling pathways, transcriptional regulation and epigenetic modifications, all of which collectively determine neutrophil function within the TME (Fig. 1).

Signaling pathways. Several critical signaling pathways regulate neutrophil activation and function in lymphoma. The nuclear factor kappa B (NF-κB) pathway is one of the most crucial in mediating inflammatory and immune responses in lymphogenesis with neutrophil participation. NF-κB is a transcription factor activated in response to infection or inflammation, translocating to the nucleus to initiate the expression of multiple inflammatory genes, including cytokines, chemokines and adhesion molecules. These genes are essential for the inflammatory response and neutrophil recruitment (80-82). This pathway is pivotal in maintaining the pro-tumorigenic environment often seen in lymphoma.

Another vital pathway is the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. This pathway is activated through cytokine receptors, such as the IL-6 receptor, promoting the phosphorylation and activation of STAT proteins, which then enter the nucleus to regulate gene expression. The JAK/STAT pathway is critical for neutrophil survival, proliferation and function within the lymphoma TME (82-84). This pathway is integral to the role of neutrophils in supporting lymphoma progression.

The phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway also plays a significant role in regulating neutrophil behavior in lymphogenesis, influencing cell survival, metabolism and migration. For instance, activating the PI3K/AKT pathway can enhance neutrophil migration and their release of inflammatory mediators, contributing to the maintenance of a TME conducive to lymphogenesis (85-87). This signaling cascade underscores the dual role of neutrophils in promoting inflammation and facilitating tumor growth.

Transcriptional regulation. In lymphoma, transcription factors are essential for regulating neutrophil gene expression. Beyond NF-κB and STAT transcription factor families, the CCAAT/enhancer-binding protein (C/EBP) family plays a crucial role in neutrophil differentiation and function. C/EBP alpha (CEBPA) and beta (CEBPB) are key regulators of neutrophil development and control the expression of numerous genes involved in inflammation and immune responses within the lymphoma TME (88-90).

GATA binding protein 1 (GATA1) and Spi-1 proto-oncogene (SPI1/PU.1) are two other significant transcription factors with complementary roles in neutrophil development and function. GATA1 primarily promotes neutrophil differentiation, while PU.1 is crucial for maintaining and activating neutrophil functions within the lymphoma TME. The interactions and regulatory networks of these transcription factors constitute a complex regulatory mechanism for neutrophil gene expression that drives neutrophil behavior in lymphoma, highlighting their involvement in both tumor-promoting and anti-tumor activities (91-93).

Epigenetic modifications. Epigenetic modifications, including DNA methylation and histone modifications, play vital roles in regulating neutrophil function in lymphoma. DNA methylation is generally associated with gene silencing, while histone acetylation and methylation can activate or repress gene expression related to lymphogenesis.

In lymphoma, the epigenetic state of neutrophils can significantly impact their inflammatory responses and interactions within the TME. For instance, histone deacetylase inhibitors can enhance neutrophils' inflammatory response, potentially exacerbating lymphoma-promoting activities, by increasing histone acetylation levels. Conversely, DNA methyltransferase inhibitors can modulate neutrophil gene expression, influencing their role in either supporting or suppressing lymphoma progression (94-96).

The multifaceted roles of neutrophils in lymphoma pathogenesis are complex and critical. Investigating their molecular mechanisms can enhance the understanding of their functions in the TME, offering valuable insights for developing targeted therapeutic approaches.

3. Neutrophils and lymphoma progression: Unveiling the culprits

Traditionally seen as immune defenders against infections, neutrophils have been revealed to have a dual role, implicated

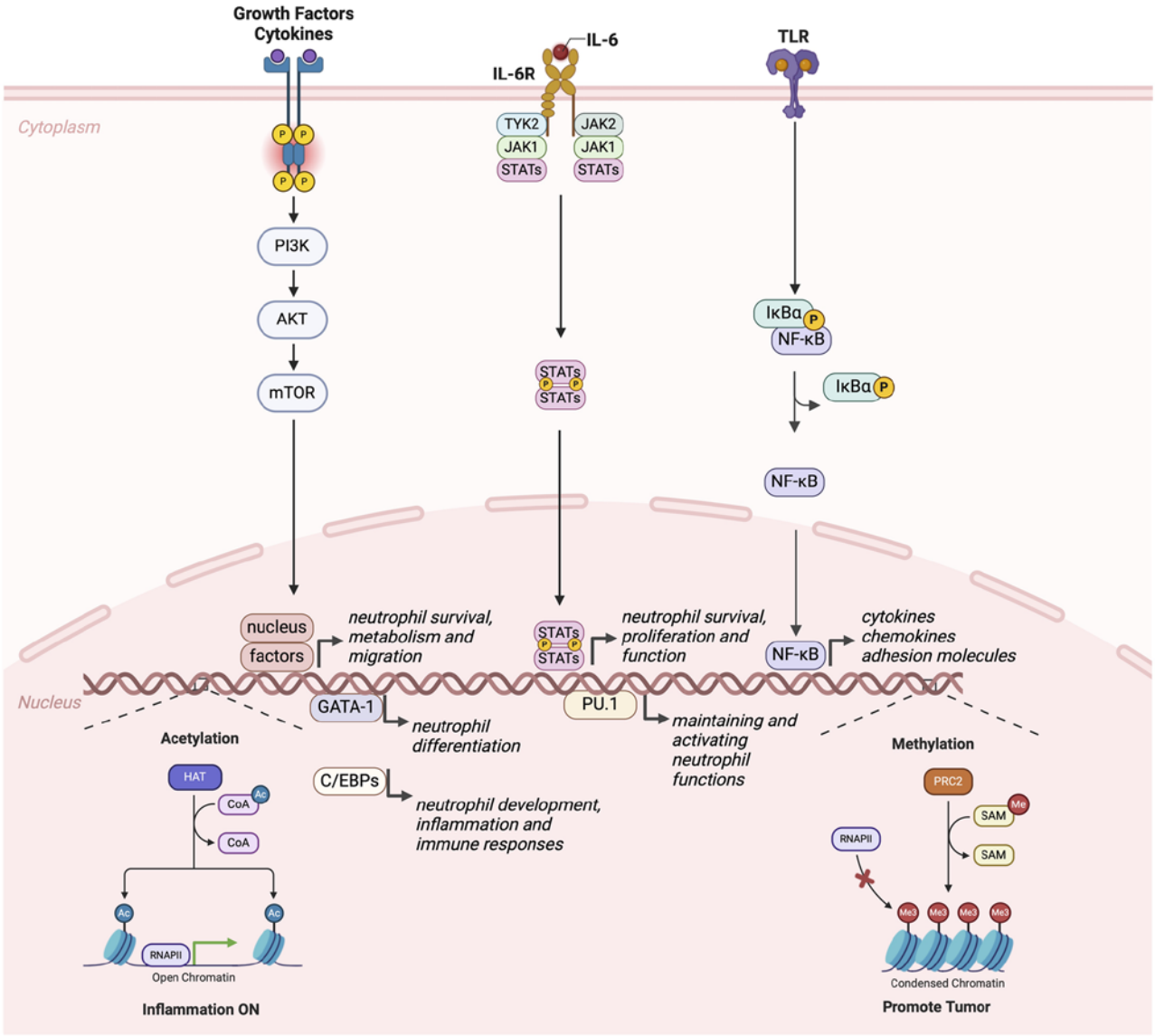

Figure 1. Molecular mechanisms regulating neutrophil behavior in lymphoma. Schematic diagram illustrating the NF-κB, JAK/STAT and PI3K/AKT signaling pathways, key transcription factors and epigenetic modification processes involved in regulating neutrophil behavior within the lymphoma microenvironment. NF-κB, nuclear factor K-light-chain-enhancer of activated B cells; IκBα, Inhibitor of κBα; PRC2, polycomb repressive complex 2; SAM, S-adenosylmethionine; Me, methyl group; RNAPII, RNA polymerase II; HAT, histone acetyltransferase; CoA, coenzyme A; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; TLR, Toll-like receptor; STATs, signal transducers and activators of transcription; IL-6R, interleukin-6 receptor; JAK1, Janus kinase 1; TYK2, tyrosine kinase 2; GATA-1, GATA binding protein 1; PU.1, Spi-1 proto-oncogene.

in the progression of lymphoma, a cancer affecting the immune system (9). Recent research has revealed their active contribution to tumor progression, promoting tumor growth through intricate molecular interactions in the TME. Neutrophils promote angiogenesis, sustaining lymphoma cells by creating a vascular network (97). Their immunosuppressive role aids cancer cell evasion from surveillance mechanisms, contributing to unchecked lymphoma growth. Collaborative interactions with other immune cells within the TME further enhance cancer progression (98). Recognizing these diverse contributions opens avenues for novel therapeutic strategies, with targeting neutrophils as a promising approach to impede lymphoma progression. However, a comprehensive understanding of the specific molecular mechanisms is crucial for developing effective and targeted therapies. The emerging understanding of neutrophils in lymphoma progression necessitates further research to unravel the specific mechanisms and holds promise for reshaping the landscape of lymphoma treatment.

Neutrophils and tumor growth: A complex interplay. Traditionally merely considered defenders against infections, neutrophils are now known to play a key role in tumor biology, having a dual impact on tumor growth (13). Recent studies suggest their potential to impede tumor growth, adding a counterintuitive aspect to their conventional function (99). However, their pro-metastatic and tumor-promoting capabilities create a dualistic nature in the TME. Neutrophils contribute to angiogenesis, forming new blood vessels crucial for tumor sustenance (10). They also orchestrate a pro-inflammatory milieu by releasing cytokines, fostering conditions for tumor progression and metastasis, which is crucial in aggressive cancers such as lymphoma. Furthermore, neutrophils

suppress the immune system, facilitating immune evasion by tumor cells. The intricate interplay between neutrophils and various immune cells within the TME adds complexity, emphasizing the need for a nuanced understanding. Unraveling this interplay is imperative for advancing cancer therapies, particularly for lymphoma. As research progresses, targeting neutrophil-tumor interactions may offer a promising avenue for innovative and effective cancer therapies.

Neutrophils and tumor initiation. Neutrophils have recently come under greater scrutiny in tumor biology. Contrary to their conventional role, emerging research suggests that neutrophils may have a dual role, potentially contributing to tumor initiation and growth (78), thus opening new avenues for exploring the challenging landscape of cancers such as lymphoma.

One aspect of neutrophil involvement in tumor biology centers around their ability to produce reactive oxygen species and other inflammatory factors (24). When released by neutrophils, these molecular entities can damage cellular DNA. In the tumor context, this DNA damage can stimulate aberrant cellular responses, promoting the survival and uncontrolled proliferation of tumor cells (24). This revelation underscores the complex interplay between neutrophils and the genomic integrity of cells within the TME, providing a compelling rationale for investigating their role in initiating malignancies such as lymphoma.

Furthermore, neutrophils contribute to the formation of blood vessels through a process known as angiogenesis. By promoting the growth of new blood vessels, neutrophils facilitate the supply of oxygen and nutrients to the growing tumor, creating a TME supportive of sustained tumor growth (97). In lymphoma research, understanding how neutrophils influence angiogenesis within lymphomatous tissues remains an active area of investigation. Insights into this process may be vital to deciphering the mechanisms underlying lymphoma progression and could potentially inform the development of targeted therapeutic interventions.

While the precise nature of neutrophil involvement in lymphoma is still under investigation, ongoing research is unraveling the intricacies of their interactions with lymphoma cells (79). Determining the role of neutrophils in tumor initiation and progression, particularly in the context of lymphoma, is a dynamic field that presents promising opportunities for developing innovative treatments.

Understanding these complex interactions provides a foundation for devising novel therapeutic strategies tailored to the unique challenges posed by lymphoma. By deciphering the intricate language of neutrophil-tumor crosstalk, researchers aim to unveil potential vulnerabilities that can be exploited to develop targeted therapies (99). As research progresses, the evolving narrative of neutrophils in tumor biology holds the promise of not only enhancing our understanding of cancer initiation and progression but also paving the way for more effective and tailored treatments for lymphoma.

Neutrophils and tumor promotion. Long heralded as guardians of the immune system, neutrophils are central players in the intricate process of cancer progression (13). While their conventional role involves combating cancer cells, recent research has revealed a paradoxical dimension wherein neutrophils can, under certain conditions, promote tumor growth and metastasis. This revelation underscores the complexity of the immune response within the TME and necessitates a nuanced understanding to develop effective strategies for countering their pro-tumor effects and ultimately improving cancer outcomes.

In the context of tumor promotion, inflammation emerges as a pivotal player in orchestrating the behavior of neutrophils within the TME (10). The chronic inflammatory milieu in cancer tissues stimulates neutrophils to release diverse pro-tumor factors that exert multifaceted effects, enhancing angiogenesis, suppressing immune cell activity, and fostering the survival and migration of cancer cells. The net result is the creation of a TME that drives tumor growth and facilitates metastasis.

Angiogenesis, the formation of new blood vessels, is a critical process for sustaining tumor growth and metastasis (97). In response to signals from the inflamed TME, neutrophils release factors that promote angiogenesis. These newly formed blood vessels provide the growing tumor with a dedicated supply of oxygen and nutrients, supporting its relentless growth. Understanding the intricate interplay between neutrophils and angiogenesis is essential for developing interventions that disrupt this supportive network and slow tumor expansion.

Designed to recognize and eliminate aberrant cells, the immune system paradoxically experiences suppression when confronted with neutrophil-driven tumor promotion (98). Neutrophils release factors that attenuate the activity of immune cells, creating an immunosuppressive TME conducive to tumor immune evasion. Unraveling the mechanisms underlying neutrophil-mediated immune suppression holds promise for devising strategies that enhance the immune response against cancer cells.

The survival and migration of cancer cells, crucial determinants of metastasis, are also influenced by neutrophil-derived factors (9,10,97). By fostering a TME that shields cancer cells from immune surveillance and promotes their mobility, neutrophils contribute significantly to the metastatic process. Targeting these specific aspects of neutrophil involvement in tumor promotion may offer novel therapeutic avenues for impeding metastasis and improving overall cancer outcomes.

In conclusion, while neutrophils are stalwart defenders in the immune system's arsenal, their dynamic role in the TME introduces complexities that demand careful consideration. Understanding the dual nature of neutrophil behavior-as guardians and inadvertent promoters of tumor growth-is pivotal for advancing cancer research and therapeutic development. Harnessing this understanding to modulate neutrophil behavior within the TME holds promise for refining treatment strategies, ultimately improving outcomes for patients with cancer.

Neutrophils and tumor metastasis. The intricate interplay between neutrophils and tumor metastasis involves molecular interactions that significantly shape cancer progression (10,13,78). Once considered foot soldiers in the body's immune defense, neutrophils have emerged as pivotal orchestrators of the metastatic process, controlling events that pave the way for cancer cells to colonize distant organs.

Central to this process is the activation of neutrophils by tumor cells, which sets off a cascade of events, with neutrophils releasing various factors crucial in metastasis (10,97,98). One such factor is the promotion of blood vessel formation, a

process known as angiogenesis. Driven by signals from tumor cells, neutrophils release pro-angiogenic factors that induce the formation of new blood vessels. This neo-vascular network provides an essential conduit for cancer cell migration, facilitating their journey to distant organs.

Moreover, the interaction between neutrophils and cancer cells goes beyond merely creating a structural support system. Neutrophils actively help to suppress the immune response, tipping the balance in favor of cancer cells (98). By releasing factors that inhibit the immune system's vigilance, neutrophils mask cancer cells, allowing them to evade immune surveillance and establish footholds in new tissues.

The establishment of a favorable TME for cancer cell growth and survival is another aspect of neutrophil involvement in metastasis (99). By secreting factors that create a nurturing milieu, neutrophils contribute to the proliferation and survival of cancer cells in distant organs. This supportive TME enhances the adaptability and resilience of cancer cells, further driving metastatic progression.

Understanding the intricate mechanisms that govern the interplay between neutrophils and tumor metastasis is paramount in developing effective anti-cancer strategies (10). Targeting specific steps in this process, such as neutrophil activation or their pro-angiogenic activities, may provide novel therapeutic opportunities (98). Furthermore, unraveling the complex network of molecular signals exchanged between neutrophils and cancer cells may offer insight into disrupting the immune evasion strategies used by metastatic cancer cells.

In conclusion, the role of neutrophils in tumor metastasis extends beyond their conventional function in immune defense. Instead, they emerge as active participants in the complex process of cancer progression, influencing key events that underpin metastasis. As research delves deeper into this intricate relationship, new avenues for therapeutic interventions may emerge, holding the promise of more effective strategies to prevent the metastatic spread of cancer.

NETs: Unraveling a paradox. Initially celebrated for their role in immune defense, the intricate web of NETs is now being scrutinized for its potential involvement in cancer development, notably in lymphoma (100,101). NETs comprise DNA, histones and antimicrobial proteins. Initially recognized for their role in combating infections, NETs are now known to be implicated in the complex landscape of cancer pathogenesis (102,103). Their ability to promote inflammation, particularly in lymphoma, suggests a role in creating a TME conducive to tumor progression (104,105). NETs also contribute to forming supportive niches for tumor growth and metastasis, acting as scaffolding for cell migration (106,107). Understanding this interplay offers avenues for therapeutic interventions, targeting NETs to disrupt pro-inflammatory and pro-metastatic effects (108). Deciphering molecular signals driving NET deployment may reveal potential biomarkers for disease prognosis or therapeutic responsiveness. Exploring the dual nature of NETs provides a fresh perspective on cancer dynamics, particularly in lymphoma, with the potential to improve treatment strategies and patient outcomes through targeted interventions.

Function of NETs. NETs are a dynamic and crucial component of the body's immune response, having contradictory roles that safeguard against pathogens and, paradoxically, contribute to tissue damage and inflammation (109). These intricate structures, composed of chromatin and antimicrobial peptides, are deployed in response to infection, inflammation or various stimuli (110).

NETs are designed as a defense mechanism, acting as a formidable barrier against invading pathogens (111). When faced with microbial threats, neutrophils undergo a specialized form of cell death called NETosis. During NETosis, the neutrophil releases its chromatin, decorated with antimicrobial peptides, into the extracellular space (109). The resulting web-like structures effectively trap and immobilize pathogens, preventing their further spread and facilitating their destruction. This process is a crucial first line of defense against infections, exemplifying the proactive nature of the immune system.

Beyond their role in pathogen containment, NETs are also pivotal in modulating the immune response (112). The release of NETs activates nearby immune cells, orchestrating a coordinated effort to eliminate the threat. This immune activation is a finely tuned response that involves the recruitment and activation of various immune components to the site of infection or inflammation. In this context, NETs act as signals that engage the immune system in a targeted and localized manner.

However, the multifaceted nature of NETs becomes apparent when considering their potential to contribute to tissue damage and inflammation (113). Under certain conditions, the release of NETs can exacerbate inflammation, leading to damage to healthy tissues. This dual role-protective against pathogens, yet potentially harmful to host tissues-underscores the delicate balance within the immune system.

In diseases such as cancer, including lymphoma, the role of NETs takes on additional complexity (114). While NETs are traditionally associated with microbial defense, emerging research suggests their involvement in shaping the TME and influencing cancer progression. The pro-inflammatory nature of NETs may contribute to chronic inflammation, a known driver of cancer development (115). Furthermore, the ability of NETs to create a TME conducive to tumor growth and metastasis adds another layer of complexity to their role in cancer biology.

In conclusion, NETs represent a sophisticated arm of the immune system, exhibiting a nuanced interplay between protective and potentially detrimental effects. The intricate interplay of NETs in the immune response reflects the adaptive and responsive nature of the body's defense mechanisms. As our understanding of NETs deepens, so too does the potential for harnessing their power for therapeutic interventions, not only in the context of infections but also in the intricate landscape of cancer, including lymphoma.

Role of NETs in lymphoma progression. NETs have emerged as intricate players in the complex landscape of inflammation, with recent studies revealing their involvement in the progression of lymphoma, a cancer originating in lymphocytes (116). These web-like structures, composed of chromatin and antimicrobial peptides, contribute to various aspects of lymphoma development, including cancer cell migration, invasion and metastasis, while fostering an immunosuppressive TME (104) (Fig. 2).

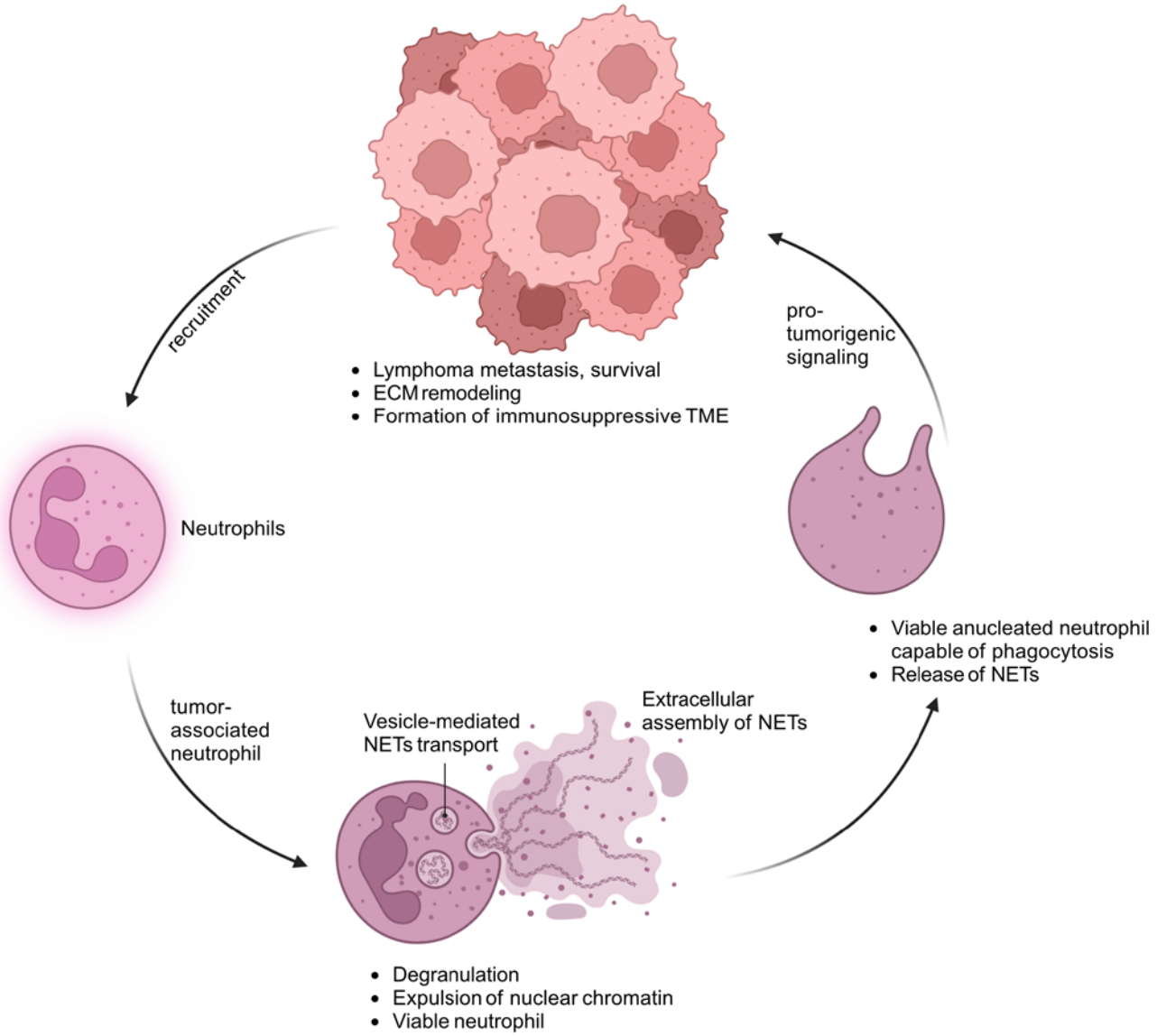

Figure 2. Role of tumor-associated neutrophils and neutrophil extracellular traps in lymphoma progression. Schematic diagram illustrating the interplay between neutrophils, tumor-associated neutrophils and lymphoma cells, highlighting the role of NETs in lymphoma progression. Lymphoma cells recruit neutrophils from the bloodstream into the TME, where they differentiate into tumor-associated neutrophils. Tumor-associated neutrophils undergo vesicle-mediated NETs transport, releasing chromatin into the extracellular space while remaining viable. NETs are then extracellularly assembled, composed of DNA and antimicrobial peptides. The NETs interact with lymphoma cells, promoting tumorigenic signaling. These interactions contribute to the survival and metastasis of lymphoma cells, ECM remodeling and the formation of an immunosuppressive TME. The pro-tumorigenic signaling from the NETs reinforces further recruitment of neutrophils to the tumor site, perpetuating the cycle of tumor progression. NTEs, neutrophil extracellular traps; TME, tumor microenvironment; ECM, extracellular matrix.

One key aspect of NET-mediated lymphoma progression is their ability to influence cancer cell behavior (117). NETs have been implicated in facilitating the migration and invasion of cancer cells, thereby promoting the metastatic spread of lymphoma (104). This phenomenon is intricately connected to the immunosuppressive characteristics of the TME orchestrated by NETs.

The mechanism through which NETs drive lymphoma progression involves the activation of inflammatory signaling pathways and the remodeling of ECM proteins (114). Inflammatory signaling pathways are crucial orchestrators of cancer development and NETs appear to drive this process by activating pathways that sustain a pro-tumorigenic TME (107). Simultaneously, the remodeling of ECM proteins by NETs may create a favorable niche for cancer cell survival, proliferation and invasion, a critical determinant in the metastatic process.

Remarkably, the relationship between cancer cells and neutrophils appears to be reciprocal, as cancer cells can induce the production of NETs by neutrophils (101), creating a feedback loop that amplifies the pro-tumorigenic effects of NETs, contributing to a TME conducive to tumor growth (105). Understanding the intricate interplay between cancer cells and neutrophils and the role of NETs in this communication opens new avenues for therapeutic exploration.

Modulating NET formation and function emerges as a promising strategy to intervene in lymphoma progression and potentially improve patient outcomes (116). Strategies aimed at targeting NETs could involve developing drugs that inhibit

NET formation or neutralize the pro-tumorigenic factors released by these structures (118). Gaining insights into the specific signaling pathways activated by NETs in the context of lymphoma could also reveal potential targets for precision therapies.

In conclusion, the discovery of NETs as active participants in lymphoma progression adds complexity to our understanding of cancer biology. Unraveling the intricacies of the interplay between NETs, cancer cells and the TME provides a foundation for developing innovative therapeutic approaches. Targeting NETs may not only offer a means to slow cancer progression but also represent a novel avenue for immunomodulation in the fight against lymphoma. As research progresses, the potential for translating these findings into tangible clinical benefits for patients with lymphoma becomes an exciting prospect in cancer therapeutics.

4. Neutrophil-mediated therapeutic approaches in lymphoma: A promising frontier

Neutrophil-mediated therapeutic strategies have garnered significant attention as innovative approaches in treating lymphoma (119). These strategies aim to harness the natural immune response and enhance neutrophil activity to increase the destruction of tumor cells. Several promising avenues have emerged, showcasing the potential for improved treatment outcomes and potentially reducing the need for more aggressive interventions (78).

One notable approach involves leveraging antibodies to mediate tumor cell destruction, effectively recruiting neutrophils to engage in targeted and specific anti-tumor activities. Designed to recognize and bind to specific markers on lymphoma cells, antibodies serve as guiding signals for neutrophils. Neutrophils become activated once bound to the target tumor cells, leading to the latter's destruction. This targeted antibody-mediated approach holds promise in minimizing collateral damage to healthy tissues and enhancing the precision of therapeutic interventions (120).

Combination therapies represent another frontier in neutrophil-mediated strategies for lymphoma treatment. Integrating neutrophil-targeted approaches with conventional chemotherapy aims to capitalize on the synergistic effects of both modalities. By enhancing the recruitment and activation of neutrophils in the TME, these combination therapies seek to enhance the overall treatment efficacy (121). This approach not only maximizes the impact on cancer cells but may also contribute to minimizing drug resistance and expanding the therapeutic window.

NETs have emerged as a particularly intriguing target for therapeutic intervention in lymphoma (114). As web-like structures composed of chromatin and antimicrobial peptides released by neutrophils, NETs have been implicated in lymphoma progression. Targeting NETs as a therapeutic strategy involves modulating their formation or function to disrupt their pro-tumorigenic effects (101). Preventing the ability of NETs to facilitate cancer cell migration, invasion and immune evasion aims to impede lymphoma progression.

In the context of NETs, another potential avenue involves understanding and manipulating the interaction between cancer cells and neutrophils (117). Disrupting the feedback loop where cancer cells induce NET formation by neutrophils may represent a novel therapeutic approach (105), which could involve developing drugs that specifically inhibit this induction, potentially attenuating the pro-tumorigenic effects associated with NETs.

Using neutrophil-mediated therapeutic approaches to treat lymphoma reflects a paradigm shift towards exploiting the body's defenses to fight cancer (122). By enhancing the role of neutrophils in recognizing and destroying cancer cells, these strategies offer a more nuanced and targeted approach to treatment (123). As research in this field progresses, there is optimism that these innovative approaches may contribute to improved treatment outcomes for patients with lymphoma, potentially reducing the reliance on more aggressive and potentially debilitating interventions (124). Continued exploration of the complex interplay between neutrophils and lymphoma cells is vital to unlocking the full therapeutic potential of these immune-mediated strategies.

5. Conclusions: Neutrophils in lymphoma - a continuing journey of discovery

In summary, neutrophils have complex and multifaceted roles in lymphoma. The existing evidence indicates their dual potential in promoting and inhibiting lymphoma growth, emphasizing the need for ongoing research to unravel the intricacies of their role. The recognition of neutrophils as potential prognostic markers and therapeutic targets highlights the importance of sustained research in this area. As our comprehension of the interactions between neutrophils and lymphoma improves, these cells are poised to maintain a central role in shaping the trajectory of lymphoma research and refining treatment strategies.

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Authors' contributions

KW wrote most of the manuscript. XW helped with the topic selection and wrote a draft of the manuscript. KW and XW edited the manuscript. LS edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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