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The heterogeneous roles of neutrophils in gastric cancer: scaffold or target?

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Abstract

Gastric cancer (GC) is a significant challenge for global health. Neutrophils, the predominant white blood cells in the innate immune system, are increasingly becoming known as potential contributors to either tumor-promoting or tumor-suppressive activities within different tumor biology settings. This review highlights such dual roles of neutrophils in GC, where complex interactions occur within the tumor microenvironment. Specifically, we focus on the formation and function of neutrophil extracellular traps (NETs), which have emerged as critical players in GC progression. NETs influence key processes such as inflammation, angiogenesis, and metastasis. This review offers a comprehensive analysis of the polarization of neutrophils into two of its distinct subtypes, namely N1 and N2, which exert opposing influences on tumor biology. While N1 neutrophils exert anti-tumor properties, N2 neutrophils are generally regarded as pro-tumor. We uniquely discuss how these subtypes interact with cancer cells, affecting epithelial–mesenchymal transition and immune evasion mechanisms. These interactions change the tumor microenvironment and impact overall GC progression. In addition, we underscore the potential of neutrophils and their associated molecules as biomarkers and therapeutic targets. Specific neutrophil-derived markers and neutrophil-associated signaling pathways, along with their perspectives in personalized medicine that would pave the way for neutrophil-based anti-GC therapy, have been discussed in this review. Through the integration of these perspectives, we aim to guide future research involving neutrophils and their therapeutic implications, thus establishing strategies to precisely and effectively treat GC and improve prognosis.

Keywords: Gastric cancer, Neutrophil, Tumor microenvironment, Neutrophil extracellular trap (NET), Therapeutic target

Introduction

Gastric cancer (GC) represents a major health threat and an urgent concern that necessitates active and sustained attention [1–3]. The latest global cancer statistics indicate that GC has the fifth highest incidence and mortality rate [4]. GC exhibits a distinct geographic distribution pattern, with East Asia and East Europe remaining high-risk regions [4]. The latest China cancer statistics indicate that GC is the fifth most common type of cancer and the third most common cause of death in China [5]. The disparate

geographical distribution of GC reflects the complex interplay between GC pathology, immunity, environmental factors, and genetic predisposition [6].

Helicobacter pylori (*Hp*), a Gram-negative bacterium, is the most significant risk factor and a primary driver of chronic inflammation and subsequent carcinogenesis, particularly in the distal stomach. Meta-analyses revealed a strong positive association between *Hp* infection and cardia GC (CGC) in East Asia, but an inverse association of *Hp* infection with CGC in Europe and America [7, 8]. Furthermore, dietary factors such as elevated salt intake and high-fat diets exacerbate *Hp*-induced gastric inflammation, further promoting cancer development [9–11].

Chronic inflammation triggered by *Hp* infection recruits immune cells, including neutrophils, to the gastric mucosa. Neutrophils, which stand at the vanguard of cancer immunology research, are polymorphonuclear white blood cells that constitute a vital component of the body's innate immune system. Upon encountering external factors and pathogen invasion, the organism can swiftly mobilize neutrophils to translocate to the site of infection or injury, where neutrophils engage in various processes including degranulation, phagocytosis, and generation of reactive oxygen species (ROS). Neutrophils release a variety of cytokines and chemokines to orchestrate the immune response. They are capable of effectively expressing proinflammatory mediators (e.g., leukotrienes and prostaglandins), which augment their chemotaxis and phagocytosis [12]. Neutrophil extracellular traps (NETs) can form as a result of either neutrophil apoptosis or necrosis. They are equally capable of participating in immune defense, recognizing and binding to pathogens, and exerting cytotoxic effects [13]. The composition of NETs is diverse, comprising DNA, proteins, and granzymes. The proportions of individual components of NETs may differ markedly between different tissues in different organisms. However, an assessment of the heterogeneity of NETs at multiple age levels demonstrated that the protein and DNA contents of NETs remained consistent and that there were no significant differences in cytokine content or activity [14]. The immunological microenvironment exerts a greater effect on changes in NET component composition [15]. There is complex interplay between neutrophils, the tumor microenvironment (TME), microbiota, alternative splicing, and cancer progression in GC [16].

Neutrophils closely interact with cancer cells in GC [17]. Neutrophil-rich carcinoma represents a distinctive morphological variant of GC [18, 19]. Neutrophils display both pro-tumor and anti-tumor properties, with a subset of neutrophils involved in tumor response and known as tumor-associated neutrophils (TANs). TANs have been demonstrated to facilitate tumor formation, invasion, and angiogenesis [20]. They can release cytokines that induce epithelial-to-mesenchymal transition (EMT) to enhance GC invasion and metastasis [21, 22]. TANs in regional lymph nodes promote the invasion of lymph nodes by cancer cells via augmenting lymphangiogenesis and thereby contribute to GC progression [23]. Neutrophil-to-lymphocyte ratio (NLR) has emerged as a prominent biomarker for GC, offering insights into the balance between TAN-mediated pro-tumor effects and lymphocyte-mediated anti-tumor effects [24]. Elucidating the mechanisms underlying neutrophil behavior in GC may aid in the identification of novel therapeutic targets [25].

This review offers a detailed analysis of neutrophils, particularly NETs, in GC. Although a previous review broadly discussed neutrophils' roles in the progression of

non-GC cancers, the current work focuses on specific mechanisms by which neutrophils influence GC bidirectionally [26]. Unlike the earlier study, which emphasized general TME dynamics and neutrophil recruitment, the present review investigates neutrophil heterogeneity, activation, polarization, and their interactions with GC cells, driving EMT and immune evasion [26]. A key distinction of this review is its in-depth analysis of NETs in GC, a topic only superficially covered in prior reviews [27, 28]. The article discusses how NETs affect inflammation, angiogenesis, and metastasis, with a focus on signaling pathways such as Janus kinase–signal transducer and activator of transcription (JAK-STAT), NF-κB, and phosphoinositide 3-kinase (PI3K)/AKT that modulate neutrophils. It also examines neutrophils as biomarkers and therapeutic targets, an area that has received little attention in previous research [26], including the clinical significance of the NLR and neutrophil-derived exosomal microRNAs (miRNAs) [29, 30]. This paper also examines interactions between neutrophils, tumor-associated macrophages (TAMs), and cancer-associated fibroblasts (CAFs) in the GC TME, a degree of cellular crosstalk analysis not seen in the earlier review [26]. These insights advance the understanding of neutrophil biology in GC and identify therapeutic strategies, such as targeting NET formation or neutrophil polarization, underscoring the need for precise regulation of neutrophil behavior in the TME.

Localization and activation of neutrophils in GC TME

Neutrophils are essential innate immune cells of the TME, which comprises cancer cells, immune cells, stromal cells, and extracellular matrix (ECM). Neutrophils are highly heterogeneous, and can be categorized into anti-tumor (N1-like) and pro-tumor (N2-like) neutrophils [27]. Neutrophils are frequently observed within gastric stroma, epithelium, and glands, and are ubiquitously distributed in the GC TME [31, 32]. Neutrophil infiltration in the stomach is associated with an increased GC risk [33]. Tumor-associated neutrophils are associated with the tumor–stroma ratio in advanced GC [34]. In GC tissues, neutrophils are often densely concentrated in marginal tissues. Notably, in diffuse-type GC tissues, neutrophils exhibit a mixed and homogeneous distribution closely associated with GC cells. Neutrophils can also infiltrate the glandular lumen formed by epithelial cells of GC tissues [35]. This contrasts with the characteristics of some other digestive tract cancers, such as bowel cancer, where neutrophils are clustered in cancerous tissue.

This close proximity to tumor cells suggests that neutrophils are likely influenced by the TME, which plays a critical role in their activation. The anti-tumor or pro-tumor effects exerted by neutrophils need their activation in the TME, which is governed by the integrated regulation of immune cells, stromal cells, ECM, hypoxia, and nutrient deficiency in the GC TME. The hypoxic environment of GC can induce neutrophils to form NETs, which contribute to tumor progression through the Toll-like receptor (TLR) pathway [36]. There was a notable elevation in the number of neutrophils within the GC TME in mice subjected to chronic stress over an extended period [37]. The concentration of the cytokine interleukin (IL)-1α also rose, promoting tumor growth and metastasis. Neutrophils in GC are particularly sensitive to ADP-heptose, an important *Hp* metabolite and neutrophil activator [38]. *Fusobacterium nucleatum*-induced neutrophil

transcriptional activation might also be implicated in GC via several candidate genes (e.g., *DNAJB1*, *EHD1*, *IER2*, *CANX*, and *PH4B*) [39].

The GC TME promotes the development of GC by disrupting the balance of neutrophil activation, which impairs the function of immune checkpoints [40]. Malignant epithelial cells and M2 macrophages are involved in neutrophil activation in GC, specifically through multiple chemokines (e.g., macrophage colony-stimulating factor [GM-CSF]) and associated signaling pathways (e.g., MAPK) [41]. The crosstalk between these cell populations could represent a potential target for the treatment of GC. The JAK-STAT3 pathway is key in immune responses and tumor progression, activating neutrophils and regulating B7 homologs B7-H3 and B7-H4. B7-H3 promotes tumor cell apoptosis, while B7-H4 inhibits T-cell mediated tumor killing. *Hp* recognition by TLR2 activates JAK/STAT signaling, boosting GC growth [42–44]. GM-CSF upregulates B7-H4 via JAK-STAT3, which is linked to GC progression and poor survival [42–44]. The expression of this factor by neutrophils suppresses the anti-tumor effects of T and NK cells, thereby promoting tumor metastasis. Moreover, the IL-6–STAT3 axis mediates a reciprocal crosstalk between cancer-derived mesenchymal stem cells and neutrophils to synergistically prompt GC progression [45].

The chemokine CXCL5 may trigger interleukin (IL) activation of neutrophils, and amplify cytokine secretion by neutrophils involved in inflammatory signaling, angiogenesis, and immunosuppression [46]. Neutrophils within the TME can also be activated toward an anti-tumor direction. TOB1, a signal transduction protein that suppresses GC progression, was highly enriched in $CD66b^{+}$ neutrophils. Upon contact with tumor tissues, it boosted the anti-tumor activation of neutrophils and extended the duration of interaction with GC tissues, thereby enhancing the viability of resistance to GC tissues [47]. These further highlight the complexity of the GC TME.

N1/N2 neutrophil polarization

Neutrophil polarization can result in neutrophil heterogeneity, and is initiated by the formation of pseudopods, which is accompanied by increases in intracellular calcium ion concentration and mosein expression [48]. Neutrophils exhibit functional plasticity, polarizing into anti-tumor N1 (pro-inflammatory, tumor-suppressive) or pro-tumor N2 (immunosuppressive, tumor-promoting) states. In early GC, suppressed N1 activity and delayed dominance of N2 may create a transitional state. TME-derived factors are implicated in neutrophil polarization. Transforming growth factor (TGF)-β, IL-13, and G-CSF are pivotal stimulators of N2 cells, while interferon (IFN)-β promotes neutrophil polarization toward N1 cells [49, 50]. The release of exosomal circ-CTNNB1 can inhibit neutrophil apoptosis and promote N2 polarization, which may be related to activation of the proliferative pathway [51]. NOD-like receptor family pyrin domain containing 3 (NLRP3) is an inflammasome that promotes the formation of several interleukins. It can drive neutrophil chemotaxis towards the TME and participates in polarization [52]. Nuclear factor erythroid 2 (NFE2) binds to the promoter of peptidylarginine deiminase 4 (PAD4) to promote neutrophil polarization and the synthesis of NETs [53]. Moreover, extracellular adenosine exerts an immunosuppressive effect while binding to receptors on the neutrophil surface, which promotes the polarization from N1 to N2 cells [54].

N1 neutrophils inhibit GC progression by promoting antigen presentation, cytotoxicity, and ROS

N1 cells suppress tumors primarily through cytotoxicity and ROS, while also playing a role in tumor-associated antigen presentation [55]. Leucine metabolism represents a crucial pathway regulating antigen presentation in N1 cells. Leucine activates and promotes the expression of human leukocyte antigen (HLA) and the major histocompatibility complex (MHC) class II complex, which are indispensable effectors for recognition and binding [56, 57]. The MHC class II complex binds to $CD4^+$ T cells, enhancing the anti-tumor effects. Further research is required to elucidate the effects of leucine metabolism on the differentiation, activation, and migration of neutrophils, and the chemotaxis of other antigen-presenting cells. It remains unclear whether leucine metabolism operates independently of type 1 regulatory T cells (Tr1) to alter the antigen-presenting activity or it promotes synergistic effects between Tr1 and dendritic cells (DC) in antigen presentation. Furthermore, a diet high in leucine can alter the TME. Leucine metabolism may affect the levels of metabolites, such as lactate in the TME, which in turn affects Tr1 function [58]. There is also a pressing need to elucidate the role of the metabolism of other amino acids in this regulatory process and their interaction with leucine metabolism. These innovative findings provide a new rationale for developing new immunotherapies, suggesting that leucine dietary metabolism therapy, in combination with chemotherapy, radiotherapy, and/or other immune-modulating therapies, might improve survival outcomes of patients with GC.

In addition to antigen presentation, N1 neutrophils enhance the recognition of tumor cells by immune cells, including T and B cells, which is essential for initiating antibody-dependent cell-mediated cytotoxicity (ADCC). N1 cells exhibit anti-tumor properties through ADCC against tumors, accompanied by the recognition of different molecules by a variety of Fc receptors, which enhances the ADCC effect. Src kinase-associated phosphoprotein 2 (SKAP2) in N1 cells regulates myosin rearrangements and influences the stability of the CD18 complex, thereby enhancing ADCC and increasing NADPH oxidase activity, ultimately contributing to anti-tumor effects [59]. Similarly, disruption of the CD47–SIRPα checkpoint significantly enhances ADCC in neutrophils. The integrin-associated protein kindlin-3 can directly interact with CD18, regulating cytopharynx formation and the dependence of kindlin-3 on the process by which CD47-SIRPα mediates the formation of cytotoxic synapses in neutrophils [60]. Importantly, inhibition of the CD47–SIRPα checkpoint facilitates neutrophil anti-tumor activity [61, 62]. Immunoglobulin-like lectins inhibit tumor immunity. Galactose lectin-9 (Gal-9) and silencing of the Fc receptor of Siglec-9 augmented anti-tumor ADCC effects in neutrophils, suggesting a promising therapeutic target for GC [63, 64]. However, the clinical relevance of these findings should be verified using clinical samples in the future, and clinical trials need to be performed to evaluate the effects of Gal-9 treatment.

The Fc region has a high affinity for FcγRIII, serving as the foundation for the development of anti-tumor drugs [65]. Comprehensive hierarchical genetic analysis revealed a direct correlation between enhanced FcγRIIa polymorphism and the anti-tumor ADCC effect of neutrophils, representing a novel approach to improving the efficacy of cancer antibody therapy [66]. Targeting the immunoglobulin A (IgA) Fc receptor FcαRI could further enhance the ADCC effect of neutrophils, offering

a novel therapeutic strategy [67]. Notably, a YAP/TAZ–CD54 axis is required for $CXCR2^{-}CD44^{-}$ tumor-specific neutrophils to suppress GC, and neutrophils highly expressing CD44 have a critical impact on immunotherapy outcomes in GC [68, 69].

N1 neutrophils rely on ROS and nitric oxide (NO) to inhibit GC cell proliferation. Hydrogen peroxide (H_2O_2) released by neutrophils can kill tumor cells by causing calcium ion dysregulation in tumor cells via transient receptor potential cation channel, subfamily M, member 2 (TRPM2) [70]. However, H_2O_2 in low concentrations may exert a pro-tumorigenic effect, enhancing tumor growth [70]. Superoxide generation by neutrophils was suppressed in GC [71]. Neutrophils promote monocyte activation through ROS, collaboratively exerting anti-tumor effects [72]. NO released by neutrophils can limit the proliferation of tumor cells, modulate the function of p53, and promote ROS production, further mediating tumor suppression. Preoperative detection of the myeloperoxidase- and NADPH-dependent production of active oxygen could be prognostic and predictive of severe infectious complications during the postoperative period [73]. The activity of neutrophils might also be associated with the exocytosis of lysosomal enzymes in GC [74].

Together, enhancing the N1 transition of neutrophils and the function of N1 neutrophils may represent a potential therapeutic strategy for GC (Fig. 1). By leveraging their roles in antigen presentation, ADCC, and ROS production, N1 neutrophils present multiple tracks for anti-cancer properties. Further study should be focused on

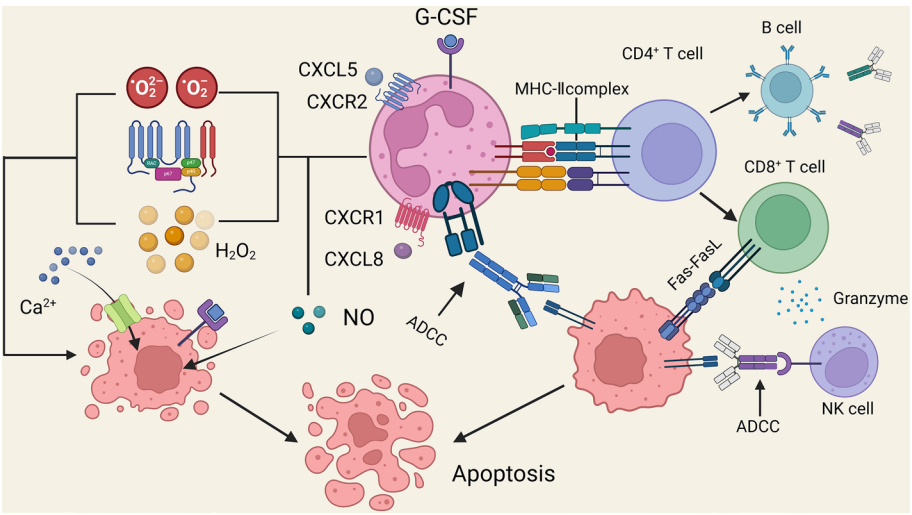

Fig. 1 N1 neutrophils inhibit gastric cancer (GC) progression by promoting antigen presentation and reactive oxygen species (ROS) generation. Neutrophils exert anti-tumor effects through the generation of ROS and NO and antibody-dependent cell-mediated cytotoxicity (ADCC) after continuous stimulation by G-CSF and chemokines. (1) ROS, H_2O_2, and NADPH oxidase 2 (NOX2) released by neutrophils promote the entry of excess calcium ions into GC cells via TRPM2, resulting in intracellular calcium disorders. ROS destabilizes the fluidity and physical state of GC cell membranes through peroxidation. (2) NO released by neutrophils limits the action of p53, which inhibits the proliferation of GC cells. (3) MHC II complexes are formed between neutrophils and $CD4^{+}$T cells, which activate B and $CD8^{+}$T cells. (4) B cells release antibodies against specific antigens on the surface of tumor cells, which are involved in ADCC. The FcγRIII on the surface of the antibody and the Fc on the surface of the neutrophil have high affinity, which allows neutrophils and NK cells to exert ADCC. (5) $CD8^{+}$T cells kill GC cells by releasing perforin, granzyme, and forming Fas–FasL complexes on the surface of tumor cells

validating these aspects in clinical settings and confirming their therapeutic potential in combination with existing treatments.

N2 neutrophils promote GC cell proliferation, invasion, and EMT

N2 neutrophils activate mesenchymal stem cells (MSCs) by secreting specific inflammatory factors in the GC microenvironment, leading to their transformation into tumor-associated fibroblasts (CAFs) [75]. This promotes invasion and metastasis of GC. EMT is a key process in the metastasis of GC, where epithelial cells acquire the characteristics of mesenchymal cells with enhanced motility and migration, thereby promoting GC invasion and metastasis. The interaction of GC cells with neutrophils promotes GC cell migration and invasion through ERK pathway activation and EMT induction [76].

Inflammatory angiogenesis with massive neutrophil infiltration is active in GC [77]. Previously, we found that in GC tissues, neutrophils were predominantly enriched in the invasive margin. IL-17$^+$ neutrophils constitute a large portion of IL-17-producing cells in human GC. Proinflammatory IL-17 is a critical mediator of the recruitment of neutrophils into the invasive margin by CXC chemokines. Moreover, neutrophils at the invasive margin are a major source of matrix metalloproteinase (MMP)-9, a secreted protein that stimulates the proangiogenic activity of GC cells. Accordingly, high levels of infiltrated neutrophils at the invasive margin are positively correlated with angiogenesis and progression in patients with GC. These data directly support the pivotal role of neutrophils in GC progression, revealing a novel immune escape mechanism driven by precise collaboration between cancer cells and immune cells in the TME. They also suggest that IL-17-producing neutrophils link inflammation to cancer progression by promoting angiogenesis in GC [78, 79]. Tumor-associated neutrophils also induce EMT by IL-17a to promote the migration and invasion of GC cells [80].

Notably, EMT is not a binary process. While the "endpoint" of EMT, a strong mesenchymal-like phenotype of cancer cells, increases invasive and migratory abilities of the cancer cells, it does not necessarily increase metastasis, as it diminishes cell–cell interactions and significantly decreases collective migration [81]. Thus, generally, intermediate states are more metastatic. Cancer cells exhibiting a predominantly epithelial phenotype, concomitant with mesenchymal characteristics, demonstrate augmented invasive and migratory capacities and heightened aggressiveness; epithelial-type cancer cells with a restricted mesenchymal transition are a major source of metastasis [82]. It is imperative to direct our attention toward the impact of neutrophils on intermediate-state cancer cells and the underlying mechanisms.

In addition to these pro-inflammatory and angiogenic factors, neutrophils also produce other signaling molecules that contribute to tumor progression. For example, family with sequence similarity 3, member C (FAM3C), produced by neutrophils and cancer-associated adipocytes (CAAs), is a metabolic regulatory signaling molecule. GC cells activate FAM3C via TGFβ1-Smad2/3 signaling, promoting EMT and lymph node metastasis [83]. Local infiltration of CD15$^+$ tumor-associated neutrophils (TANs) might be correlated with inflammation in tumor-draining lymph nodes and systemic responses to cause metastasis in GC [84]. The presence of CD15$^+$ tumor-infiltrating neutrophils is an independent and unfavorable prognostic factor in patients with gastric adenocarcinoma [85]. Neutrophil metalloproteinases drive inflammation and cancer [86]. The

role of lipocalin-2 (LCN2) in regulating the behavior of neutrophils and GC cells within the TME is complex. When LCN2 levels are high, neutrophil activation is inhibited and MMP-2 levels are reduced, resulting in an inhibitory effect on GC progression [87]. Conversely, low LCN2 levels may drive EMT in GC cells, enhance their proliferation and invasion, and ultimately contribute to the progression of GC [88]. Moreover, exosomal miR-4745-5p/3911 from N2-polarized tumor-associated neutrophils promotes GC metastasis via regulation of SLIT2 [89]. EFHD1 expression is correlated with tumor-infiltrating neutrophils and predicts prognosis in GC [90].

The CXCL family of chemokines plays a pivotal role in the interconnection between neutrophils, GC, and EMT. CXCL5, an epithelium-derived neutrophil-activating peptide, functions as a chemokine that activates the ERK pathway, inducing EMT in GC cells [46]. CXCL8 also induces EMT and neutrophil activation in GC, while CXCL6 may promote neutrophil mobilization and GC angiogenesis [91, 92]. GCP-2/CXCL6 synergizes with other endothelial cell-derived chemokines in neutrophil mobilization and is associated with angiogenesis in GC [93].

Together, N2 neutrophils adapt their gene expression in the GC microenvironment, altering the TME through changes in effector activity and interactions with other cells, ultimately affecting GC biology. This process relies on dysregulated signaling pathways that propagate throughout the TME. Downstream molecules, including interleukins, chemokines, and cytokines, drive key processes such as cell proliferation, invasion, EMT, and angiogenesis, contributing to the aggressive behavior of GC (Fig. 2).

Key signaling and molecules of neutrophils associated with immunosuppression in GC

The JAK-STAT3 pathway regulates neutrophil-mediated immunosuppression in GC

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) 3 pathway is widely expressed in immune cells, and regulates immune cell division, differentiation, and apoptosis [94]. JAK is a class of non-receptor tyrosine kinases involved in protein phosphorylation. STAT proteins are phosphorylated by JAK and dimerize to enter the nucleus for signaling [95, 96]. In GC, the TME disrupts the regulation of the neutrophil JAK-STAT pathway, leading to abnormal proliferation, differentiation, and apoptosis of neutrophils, which contributes to tumor growth and metastasis (Fig. 3).

The JAK2-STAT3 axis is actively involved in the proliferation of GC cells, and is strongly associated with the overproduction of multiple interleukins promoting GC growth, including IL-1β/6/11 [97]. The GC-associated pathogen *Hp* can be recognized by TLR2, which triggers a signaling cascade that involves the JAK/STAT pathway, leading to the secretion of CXCL1, CXCL5, and CXCL8 chemokines. These chemokines promote inflammation and potentially facilitate the growth of GC [98]. In addition, GM-CSF could activate signaling pathways that increase the expression of programmed death ligand 1 (PD-L1) in neutrophils, which may initiate the interaction between GC cells and neutrophils [99].

Another key player in this pathway is Cathepsin C (CtsC), which is downregulated in GC cells after *Hp* infection, particularly through the cagA protein and the JAK/STAT3 signaling pathway. This downregulation reduces neutrophil activity; however, inhibition of the JAK/STAT3 pathway restores CtsC levels and enhances the bactericidal capacity

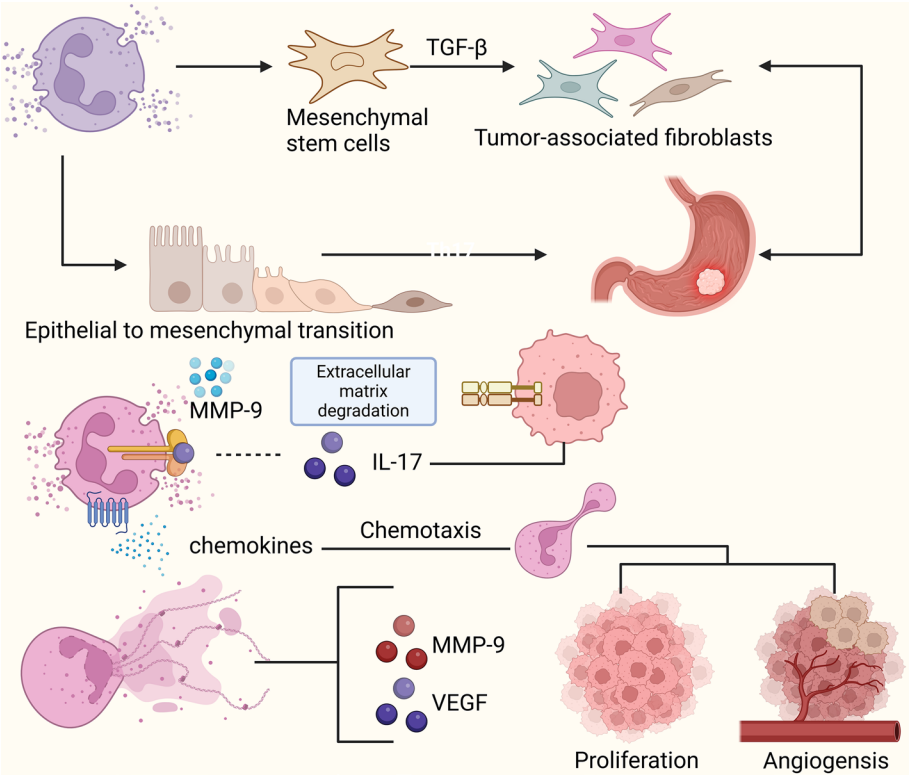

Fig. 2 Major pro-tumor mechanisms of N2 neutrophils in gastric cancer (GC): induction of epithelial-to-mesenchymal transition (EMT), release of enzymes and chemokines, and formation of neutrophil extracellular traps (NETs). (1) N2 neutrophils activate mesenchymal stem cells (MSCs) by secreting specific inflammatory factors into the GC microenvironment. MSCs are then transformed into tumor-associated fibroblasts by TGF-β. N2 neutrophils are actively involved in the EMT process, which allows epithelial cells to gain enhanced motility and migration, promoting the metastasis of GC. (2) Chemokines released by N2 neutrophils can promote tumor cell proliferation, and N2 neutrophils themselves accumulate in the center of the tumor through chemotaxis and participate in GC angiogenesis. MMP-9 released by N2 neutrophils can degrade the extracellular matrix of the tumor and promote metastasis of GC. (3) NETs also release MMP-9 and vascular endothelial growth factor (VEGF), which are involved in GC metastasis and angiogenesis

of neutrophils, which inversely correlates with bacterial colonization. This suggests a potential therapeutic strategy for GC by augmenting N1 neutrophil activation through active CtsC [100]. Furthermore, GM-CSF could specifically upregulate the expression of the neutrophil immunosuppressive molecule B7-H4 via the activation of the JAK/STAT3 pathway, reinforcing the role of the B7 family in gastric carcinogenesis and metastasis [43]. GM-CSF and neutrophils might inhibit T-cell function by expressing elevated levels of FasL and PD-L2 due to JAK/STAT3 hyperactivation [101]. These findings broaden the spectrum of receptors involved in tumor suppression by intrinsic immune cells and underscore the indispensable importance of intrinsic immune cells within the GC TME, opening up new potential avenues for targeted GC therapy.

NF-κB, PI3K/AKT, and MAPK pathways contribute to the tumor-promoting effects of neutrophils either independently or synergistically

The regulatory network involving the interaction between NF-κB, PI3K/AKT, and mitogen-activated protein kinase (MAPK) signaling is of great importance to both

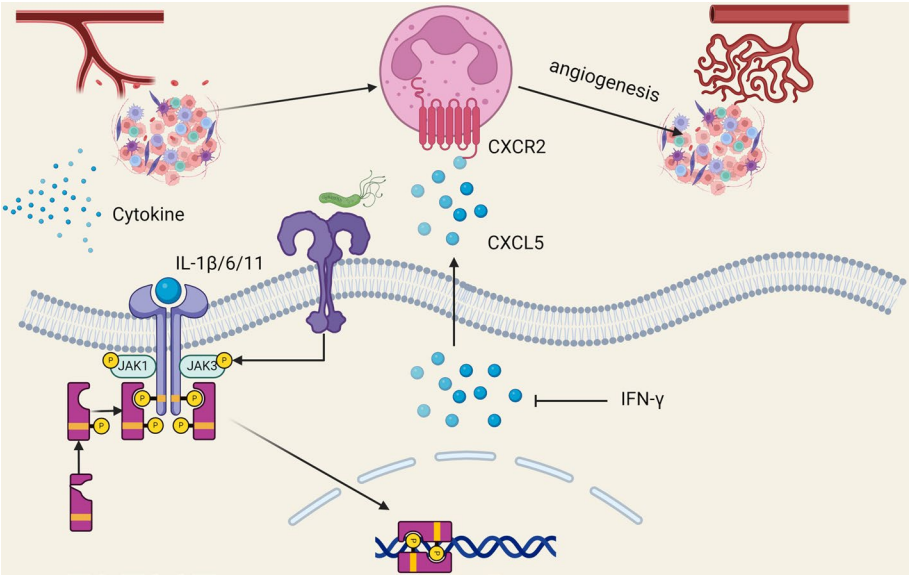

Fig. 3 JAK-STAT pathway associated with immunosuppression in gastric cancer (GC). *Helicobacter pylori* (*Hp*) is recognized by the Toll-like receptor on the surface of GC cells, and interleukins (IL)-1β/6/11 bind to the corresponding receptors on the cell membrane, activating the receptor-associated JAK1/3 tyrosine kinases, whose tyrosine residues are subsequently phosphorylated. The STAT3 protein, with the SH2 domain, binds to the corresponding site on the receptor and is phosphorylated to form a dimer before translocating into the nucleus and binding to specific DNA sequences to regulate the expression of target genes. This pathway leads to the release of chemokine CXCL5 from GC cells, which binds to CXCR2, the corresponding receptor on the surface of neutrophils, and promotes angiogenesis and, ultimately, GC growth and metastasis. IFN-γ can inhibit the release of CXCL5

neutrophils and GC cells. NF-κB is a nuclear factor that responds positively to extracellular signals and regulates a variety of important genes. PI3K phosphorylates and modifies substrates, and AKT acts as a proto-oncogene that influences transcription, cell proliferation, and apoptosis. This pathway typically activates the mammalian target of rapamycin (mTOR), which is involved in the synthesis of intracellular substances, and MAPK, which mediates inflammation, cell growth, and apoptosis [102–104]. Together, these pathways create a complex signaling network between neutrophils and GC cells that drives tumorigenesis.

Exosomes secreted by tumor cells could stimulate neutrophils and enhance neutrophil responses via the NF-κB pathway, contributing to a pro-tumor environment [105]. One of the key factors involved is the high expression of high mobility group box-1 protein (HMGB1), a highly conserved chromosomal protein involved in the inflammatory response. Moreover, complement component 5a receptor 1 (C5AR1), a G protein-coupled receptor for the ligand complement component 5a (C5a), is highly expressed in neutrophils. Binding of C5a, a cleaved fragment of component 5 and the most potent pro-inflammatory allergenic toxin, to its receptor C5AR1 activates various pathways, including PI3K/AKT and MAPK signaling [106]. Knockdown of C5AR1 specifically impedes the proliferation of GC cells and triggers the accumulation of intracellular ROS [107, 108].

In addition to protein-based signaling, neutrophils utilize exosomes containing long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) to modulate the TME and

regulate GC progression by promoting or inhibiting tumor growth, offering potential therapeutic targets [109, 110]. Various lncRNAs promote GC cell proliferation, migration, and angiogenesis by modulating the PI3K/AKT signaling pathway and its downstream targets [111]. Notably, lncRNAs such as LINC01279 and LINC02465 significantly enhance tumorigenesis in GC [112, 113]. These findings provide novel theoretical insights and potential targets for the treatment of GC (Fig. 4).

Overall, the NF-κB, PI3K/AKT, and MAPK pathways interact and synergize to exert tumor-promoting effects in neutrophils. Elucidating the crosstalk between these pathways, as well as the role of exosomal lncRNAs and miRNAs, may provide new avenues for the development of targeted therapies against GC.

Neutrophils and immunosuppressive effects of the B7 family

The B7-CD28 superfamily functions as a regulatory switch and costimulatory molecules that synergistically stimulate T-cell proliferation and activation. This dual role results in

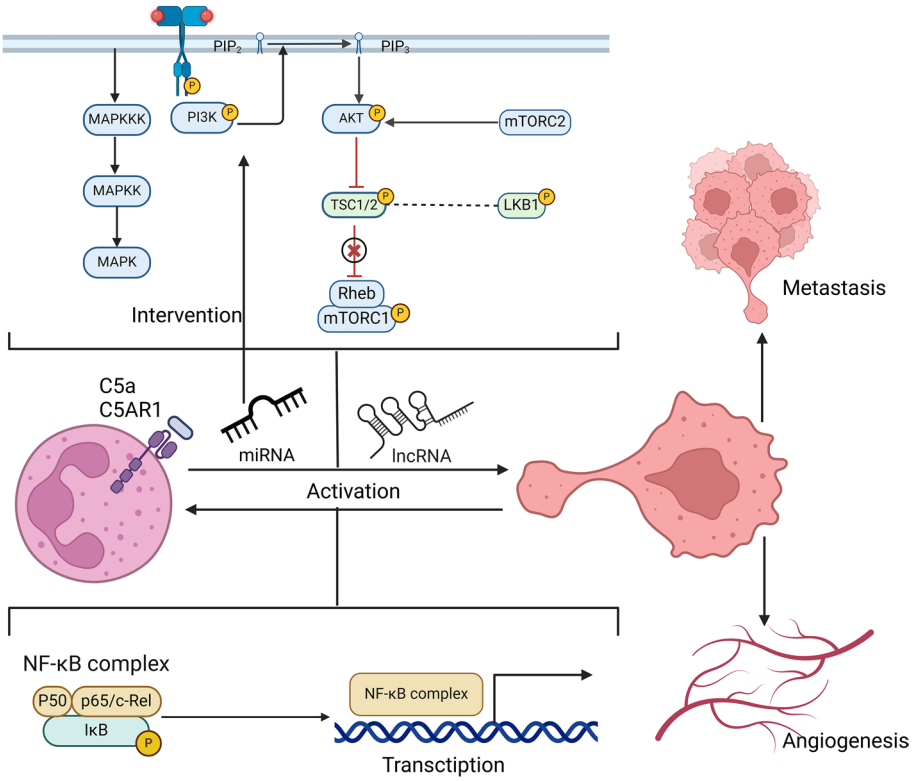

Fig. 4 NF-κB, PI3K/AKT, and MAPK pathways contribute to the pro-tumor effects of neutrophils in gastric cancer (GC). (1) The NF-κB complex is composed of P50, p65/c-Rel, and IκB. IκB prevents entry of the complex into the nucleus. Following IκB phosphorylation and subsequent degradation, the NF-κB complex can translocate into the nucleus, bind to specific DNA sequences, and regulate the expression of target genes. (2) PI3K catalyzes the conversion of PIP_2 to PIP_3, which recruits and activates AKT. The activation of AKT inhibits the mTORC1-inhibiting TSC1/2 complex, thereby enhancing the activity of mTORC1 and promoting the synthesis of intracellular substances. AKT also receives stimulation from mTORC2, contributing to cell survival. (3) The MAPK pathway is initiated by the activation of MAPKKK, which subsequently activates MAPKK and then MAPK. (4) Exosomes derived from tumor cells could activate neutrophils via the NF-κB pathway. When complement C5a binds to the corresponding receptor, neutrophils can promote GC metastasis and angiogenesis via the JAK/STAT and MAPK pathways. Noncoding RNAs in exosomes can interfere with the PI3K/AKT pathway and thus promote tumor growth and metastasis

both immune-stimulating and immune-inhibitory effects, which can either suppress GC cell proliferation or facilitate GC development [114]. The pro-tumorigenic molecules of the B7 family are closely linked to the GC TME, playing a critical role in immune evasion and tumor progression (Fig. 5).

B7-H1, also known as PD-L1, and B7-DC, known as PD-L2, are the primary ligands of PD-1 [114]. Neutrophils are capable of expressing both molecules on their membranes, inhibiting T cells from exerting anti-tumor effects. Neutrophils exhibited elevated levels of B7-H2 expression, with a notable correlation observed between tumor-derived tumor necrosis factor (TNF)-α levels and neutrophil B7-H2 levels [92]. Neutrophils utilize B7-H2 to effectively induce the differentiation of the IL-17A-producing Th cell subpopulation. The secreted IL-17A promotes the proliferation of GC cells.

B7-H3, another immune checkpoint molecule, is rarely expressed in normal tissues but can be abnormally upregulated in GC. Neutrophils in the microenvironment of GC are influenced by GM-CSF, particularly over extended periods and at high concentrations, leading to the sustained high expression of B7-H3 on their surface [42–44]. Elevated expression of B7-H3, an important immune checkpoint molecule, in neutrophils suppresses immune responses in GC. Similarly, B7-H4, another immune checkpoint molecule, is also highly expressed in neutrophils and displays immunosuppressive effects in GC. The high expression of B7-H4 is associated with GC progression and poor patient survival [43]. Collectively, B7 family molecules such as B7-H1, B7-H2, B7-H3,

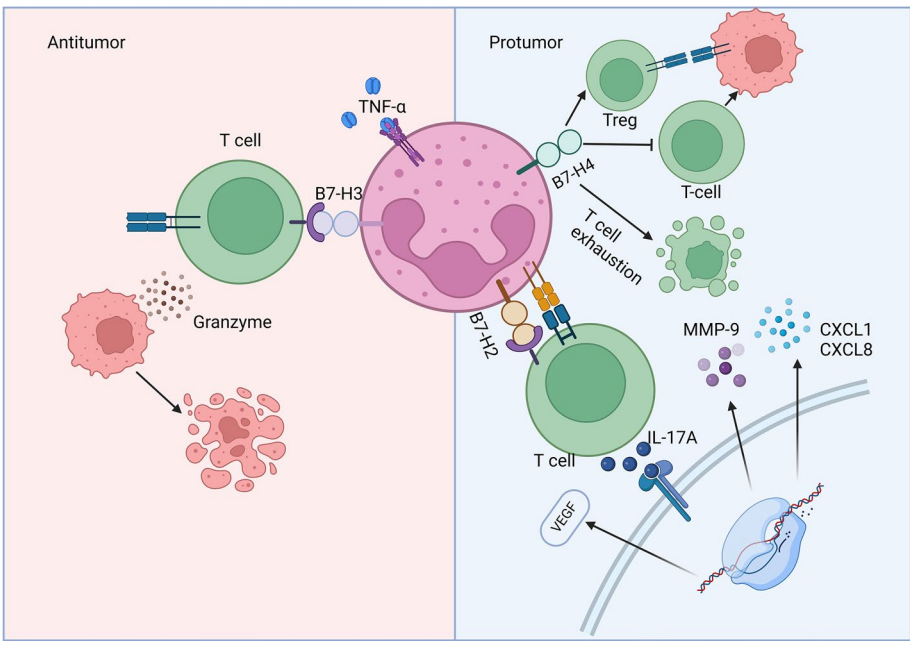

Fig. 5 Roles of B7 family members on the membranes of neutrophils in gastric cancer (GC): both anti-tumor and pro-tumor effects. (1) Sustained stimulation of tumor necrosis factor (TNF)-α increases the amount of B7-H2 on the membrane of neutrophils, and the binding of B7-H2 to the T helper (Th) cell receptor causes the release of IL-17A, which leads to the expression and release of VEGF, MMP-9, and CXCL1/8 by GC cells and promotes tumor cell proliferation. (2) B7-H3 binds to T cells and promotes the release of granzyme, inducing the apoptosis of tumor cells. (3) B7-H4 is one of the most specific markers of GC cells. The binding of B7-H4 to its receptor promotes the transformation of T_{reg} cells, inhibits the killing of GC cells by T cells, and enhances T-cell exhaustion

and B7-H4 play key roles in the GC TME. They suppress T cells, help neutrophils escape immune surveillance, and promote tumor growth, making them promising targets for new GC therapies.

Associations of NETs with GC

NETs have important diagnostic, predictive, and prognostic values in patients with GC [115].

NETs promote inflammation-driven GC development

NETs are primarily composed of DNA fibers modified with histones, granule proteins, and basophils, and are produced through two distinct pathways: NADPH oxidase (NOX)-mediated suicide NETosis and vesicle-mediated vital NETosis [13, 116]. While NETs promote inflammation-driven GC development and form a network that traps pathogens and enhances intrinsic immunity, NETs produced via mitochondrial pathways do not result in the loss of function or death of secretory cells. TREM1 facilitates the development of GC through regulating NETs-mediated macrophage polarization [117]. $CD163^+$ tumor-associated macrophages (TAMs) combined with $CD66b^+$ TANs could precisely predict the prognosis of patients with GC [118].

In the GC microenvironment, activated immune cells exhibit increased energy demands. To support proliferation and angiogenesis, GC cells undergo accelerated oxygen consumption and accumulate mitochondrial mutations. This process, combined with inflammation, creates a hypoxic microenvironment [119]. Neutrophils inhibit the proliferation of GC cells through ROS generation. However, excessive ROS levels result in oxidative damage and further exacerbate the inflammatory response. Notably, the progression from non-malignant mucosa to GC might be linked to the time-dependent effects of *Hp* on the gastric mucosa via neutrophil-produced ROS [120]. Thus, it is important to understand the relationship of NETs with inflammation before exploring their interaction with GC.

This inflammatory response is often accompanied by hypoxia, a common feature of the TME. The hypoxic microenvironment in GC induces the generation of NETs. The HMGB1/TLR4/p38 MAPK pathway is a crucial pathway that induces neutrophil activation and NET formation [36]. High expressions of hypoxia-inducible factor (HIF)-1α and chemokines, along with multiple pathways, further promote NET generation [121]. GC cells can also secrete proteins and exosomes to directly trigger neutrophil activation and subsequent NET formation, even in the absence of hypoxia or other stimuli [122, 123]. Therefore, understanding the relationship of NETs with inflammation is critical for exploring their role in GC progression.

NETs contribute to GC progression and metastasis by promoting inflammation. Persistent bacteria-induced inflammation, mimicked by repeated lipopolysaccharide (LPS) administration, enhances NETosis and cancer metastasis. Inhibition of NETosis or neutrophil depletion significantly reduces cancer incidence and metastasis rate. NETs are frequently observed near affected tissues. *Hp*, a gram-negative bacterium, mimics tissue invasion, engraftment, and inflammation through continuous LPS infusion, suggesting that NETs may drive the progression from *Hp*-induced gastritis to GC. The MMP-9 enzyme within NETs acts as an inflammatory mediator, stimulating carcinogenesis and

cancer metastasis [124]. LPS-induced inflammation can promote NETosis, COX2 upregulation, and tumor angiogenesis, further linking NETs to inflammatory responses in the TME and enhanced cancer cell metastasis [125]. Increased levels of C-reactive protein, a nonspecific marker of inflammation, are found around cancerous tissues, activating the complement system and phagocytosis [126]. ROS released by NETs damages cancer cell mitochondria, thereby inducing the reprogramming of cancerous tissues [127]. Apoptosis-like cancer cell death might especially take place in mitochondria-rich GCs [128]. Interestingly, there exists phagocytosis of apoptotic neutrophils by cancer cells in gastric micropapillary carcinomas [129]. Gastric adenocarcinoma cells could phagocytose apoptotic neutrophils, which suggests a particular mechanism of tumor-immune escape in human GC [130].

Four NET gene-based signatures are robustly predictive of immune infiltration, TME, immunotherapy response, and prognosis in GC [131–134], and a prognostic signature based on NET-associated lncRNAs is strongly predictive of immune infiltration, overall survival (OS), and treatment response [135]. Collectively, NETs stimulate GC formation through inflammation, and facilitate cancer cell metastasis by promoting mitochondrial reprogramming, inflammation, and angiogenesis. These findings highlight the critical role of NETs in GC progression and suggest that targeting NET formation could be a promising therapeutic strategy.

NETs facilitate the invasion of GC

The content and activity of NETs are strongly associated with the activation and proliferation of GC cells. For example, IL-8 can initiate NETosis and subsequently promote the proliferation of GC cells [136]. Neutrophils and NETs located at the margin of GC release IL-17 and CXC chemokines, recruiting neutrophils from the marginal zone toward the tumor center. They also released MMP-9 to promote angiogenesis [78]. MMP-9 can shed MHC-I molecules on the tumor surface, enabling GC cells to evade immune surveillance [137]. MMP-9 also enhances hyaluronic acid production in the ECM and upregulates PD-L1 expression, both of which promote GC metastasis [138]. NETs can capture circulating tumor cells in blood vessels, enhance tumor adhesion, and promote distant metastasis [139]. The likelihood of tumor metastasis was diminished when NETs were inhibited by PAD4 inhibitors in GC [140]. Primary cancers can independently rely on the interactions between CCDC25 and NETs to induce NETs release, thereby promoting distant metastasis through the ILK-β-Parvin pathway [141]. Histones in NETs increase endothelial cell proliferation and accelerate tumor-associated angiogenesis in a dose-dependent manner, acting as key mediators of GC cell migration [142]. Furthermore, histones, which stabilize DNA conformation by acting as spools for DNA winding, may also promote GC metastasis by regulating gene activation or suppression within NETs. NETs also facilitate the migration of GC cells via EMT, characterized by reduced expression of epithelial markers during migration. Both GC EMT and metastasis were inhibited by PAD4, a NETs inhibitor [21]. Destruction of NETs promotes the apoptosis and inhibits the invasion of GC cells by regulating the expression of Bcl-2, Bax, and NF-κB [11].

In addition to proteins and histones, RNAs in NETs are associated with calcium signaling, cAMP signaling, and inflammatory pathways [143]. NETs can upregulate NEAT1 to

promote GC cell invasion and stimulate the expression of von Willebrand factor (vWF), which is involved in damage repair [143]. Moreover, angiopoietin 2 (ANGPT2) expression was elevated in GC, activating tumor cell signaling and suppressing immune cell function. NETs can drive ANGPT2 expression in endothelial cells, further promoting GC metastasis [144]. NETs also rely on the TGF-β pathway to enhance GC metastasis in patients with infection or inflammation, as evidenced by increased levels of RNA transcripts for factors downstream of this pathway [145]. Leukemia inhibitory factor (LIF) expression, driven by TGF-β, contributes to peritoneal metastasis in GC via influencing NETs [146]. In GC, NETs could upregulate cyclooxygenase-2 (*COX-2*) RNA transcripts through TLR2, promoting the metastasis of distal GC [147]. NETs also upregulated the expression of N-acetyltransferase 10 (NAT10) and enhanced the stability of Su(var)3–9, Enhancer of zeste, and Trithorax (SET) and Myeloid, Nervy, and DEAF-1 (MYND) domain-containing 2 (SMYD2), facilitating the invasion and migration of GC cells [148].

Taken together, NETs play a pivotal role in the invasion and migration of GC cells. The diversity and complexity of NETs offer a wide range of potential targets for the precise management of GC (Fig. 6).

NETs influence vascular coagulation in the vicinity of GC

NETs are implicated in not only the pathogenesis of GC (e.g., metastasis and angiogenesis) but also the coagulation cascade. The fibers comprising NETs, including DNA and histones, interconnect to form a network that acts as a scaffold for thrombus formation, primarily to facilitate endothelial dysfunction, platelet activation, and coagulation [149].

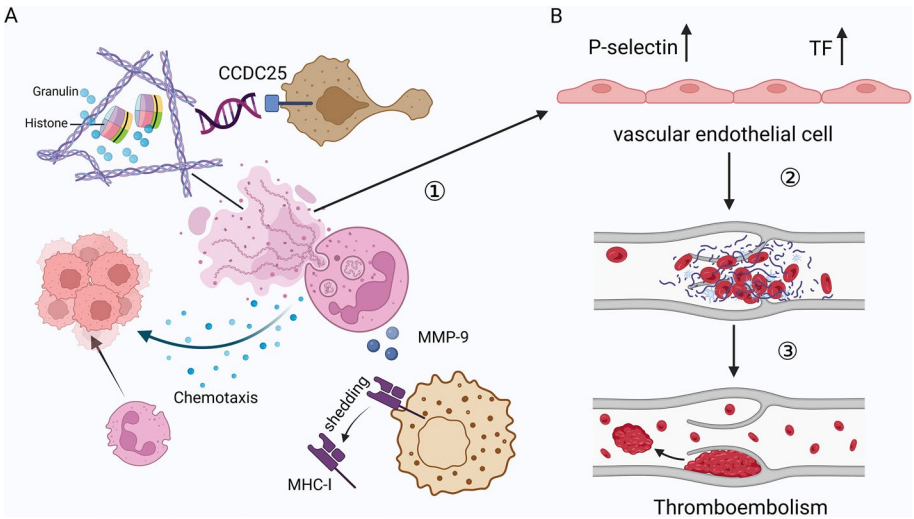

Fig. 6 Composition and mechanism of action of neutrophil extracellular traps (NETs) in gastric cancer (GC). **A** NETs are primarily composed of DNA fibers, along with histones, granulins, and basophils, with fibers interwoven into a network. Chemokines in NETs play a pivotal role in the chemotaxis of neutrophils towards the center of GC. The release of MMP-9 dislodges MHC-I from the membranes of GC cells, thus facilitating the immune escape of these cells. Furthermore, DNA fibers in NETs bind to CCDC25 on the membranes of tumor cells, thereby enabling metastasis of GC through downstream signaling. **B** NETs promote GC-associated thrombus by participating in the coagulation cascade. NETs promote the production of P-selectin and tissue factor (TF) by vascular endothelial cells. The fibrous network in NETs acts as a scaffold for thrombus formation and also promotes fibronectin production in plasma, which, in combination, facilitates the conversion of vascular endothelial cells to a hypercoagulable phenotype and ultimately the formation of a thrombus

NETs promote fibrin production in plasma, establishing a framework for platelet-neutrophil-thrombosis mediated by phosphatidylserine-positive leukocytes in patients with GC [150]. Particles in NETs specifically inhibited complex thrombogenesis and significantly prolonged clotting time in vascular endothelial cells [151]. NETs can upregulate the expression of P-selectin on cells, inducing a hypercoagulable state in platelets. NETs generally downregulate intercellular tight junction expression, while concurrently upregulating tissue factor expression, the latter of which promotes the conversion of vascular endothelial cells to a hypercoagulable phenotype [152].

Together, NETs play a multifaceted role in GC progression, influencing not only tumor angiogenesis and metastasis but also vascular coagulation. Targeting NETs may offer a novel approach for the treatment of GC by disrupting these processes.

Neutrophils can serve as biomarkers for GC

Neutrophils are not only involved in the immune response of the TME but also serve as potential biomarkers for the diagnosis, prognostic assessment, and therapeutic response of GC. A high baseline neutrophil count is associated with a worse prognosis in advanced GC [153]. The glycogen and lipid concentrations in neutrophils in patients with GC are significantly lower than in healthy controls, while the myeloperoxidase and acid phosphatase activities are higher [154–156]. Tumor-infiltrating neutrophils are prognostic and predictive of treatment benefit in patients with resected GC or adenocarcinoma of the esophagogastric junction (AEJ) receiving adjuvant chemotherapy and those with inoperable advanced or metastatic GC treated with first-line chemotherapy [157–159]. In Epstein–Barr (EB) virus-associated GC, a high density of $CD66b^+$ TANs is associated with intestinal-type histology and low frequency of lymph node metastasis [160]. Neutrophil infiltration is associated with metachronous GC following endoscopic submucosal dissection [161]. We previously found that increased neutrophil counts in both the peripheral blood and GC tissues were strongly associated with poor prognosis in patients with GC [78]. There is a sex-specific prognostic effect of tumor-associated neutrophils in GC [162]. Tumor-associated neutrophils might only predict patient outcomes for women [163]. Women appear to have a better prognosis than men with advanced GC, which might be partly due to sex differences in neutrophil function [164]. Here, we evaluate the feasibility and potential applications of neutrophils as biomarkers for GC, offering a novel perspective for precision medicine in this disease (Table 1).

The neutrophil-to-lymphocyte ratio (NLR) is the most classical biomarker for GC

NLR, calculated by dividing the number of neutrophils by the number of lymphocytes in the blood, is a marker of both immunity and inflammation. NLR can reflect the body's response to GC. A higher NLR is associated with more intense GC-associated inflammation and a worse prognosis of GC [24]. NLR is a widely utilized clinical tool for predicting disease progression and prognosis. Owing to its ease of measurement, cost-effectiveness, and strong correlation with clinical outcomes, NLR is widely utilized as a clinical tool for predicting disease progression, treatment response, and prognosis [165, 166]. It is the most commonly employed biomarker in GC and plays a pivotal role in guiding treatment decisions [165, 166]. For example, we previously found that peripheral blood NLR indicated GC progression, and that a high NLR after PD-1 antibody-based

Table 1 Neutrophil and neutrophil-to-lymphocyte ratio (NLR) as biomarkers in gastric cancer (GC)

Key findings	Clinical applications/implications	References
Neutrophil as biomarker		
High baseline neutrophil count correlates with worse prognosis in advanced GC	Prognostic assessment in advanced GC	[153]
Altered neutrophil components (↓ glycogen/lipids, ↑ myeloperoxidase/acid phosphatase) in GC versus healthy controls	Potential diagnostic utility	[154–156]
Tumor-infiltrating neutrophils predict treatment benefit in resected GC/AEJ and metastatic GC	Guides adjuvant/chemotherapy decisions	[157–159]
High $CD66b^+$ TANs in EBV-associated GC correlate with intestinal-type histology and ↓ lymph node metastasis	Stratification of EBV + GC patients	[160]
Neutrophil infiltration linked to metachronous GC after endoscopic submucosal dissection	Monitoring recurrence risk post-treatment	[161]
Sex-specific effects: TANs predict outcomes in women; women have better prognosis due to neutrophil function differences	Sex-stratified prognostic models	[162–164]
NLR as biomarker		
High NLR reflects systemic inflammation and immune response, correlating with poor prognosis	Widely used for predicting disease progression, treatment response, and survival	[24, 165, 166]
Predicts outcomes post-surgery, chemotherapy, and immunotherapy (e.g., poor response to PD-1 inhibitors)	Guides treatment decisions (e.g., adjuvant therapy, immunotherapy)	[41, 167, 168, 213–226]
Correlates with immune escape, angiogenesis (via NETs), and metastasis (lymph node/ovary)	Predicts metastasis risk and guides surveillance	[169–173, 204–212]
Combination with albumin, PLR, or fibrinogen enhances prognostic value	Improves diagnostic/prognostic accuracy in metastatic/advanced GC	[185–196, 203]
Preoperative NLR predicts lymph node metastasis; NLR trajectories during neoadjuvant chemotherapy correlate with complications/recurrence	Surgical planning and monitoring during neoadjuvant therapy	[180–183, 206, 207]
Elevated NLR during *Hp* eradication predicts recurrence; NLR post-transfusion linked to GC recurrence	Monitoring during *Hp* therapy and perioperative care	[227, 228]
Predicts immunotherapy efficacy (e.g., low NLR → better response to ICIs)	Stratification for immunotherapy candidates	[217–226]
Limitation: not predictive in early GC owing to lack of inflammation	Limited utility in early-stage diagnosis	[230]
Novel biomarkers		
IGFBP7: linked to *Hp* infection and neutrophil infiltration; poor prognosis	Diagnostic and prognostic marker for *Hp*-associated GC	[231]
CSF1R, CPZ, DOK5, ITGAL: regulate ECM/neutrophil infiltration via PI3K-AKT/TGF-β pathways	Therapeutic targets and prognostic indicators	[232–235]
NGAL/MMP9: overexpressed in GC; promotes invasion/metastasis	Early GC detection and monitoring metastasis	[240–243]
Neutrophil exosome miRNAs: reflect disease progression	Noninvasive biomarkers for GC subtypes	[244]
Machine learning: identifies TANs as predictors of chemotherapy response	Personalized treatment strategies	[245]

TAN tumor-associated neutrophil, *EBV* Epstein–Barr virus

immunotherapy was significantly associated with poor outcomes of patients with advanced GC [41, 167]. The preoperative and the postoperative NLRs both predict prognosis in patients with GC [168].

NLR exhibits a strong correlation with the degree of immune escape in GC [169–172]. Neutrophils, as well as NETs, promote angiogenesis and coagulation, and can affect platelet and lymphocyte content [173]. A high NLR can independently reflect a poorer prognosis of GC. NLR is a valuable prognostic indicator in patients who have undergone surgical resection and/or chemotherapy, which represent the mainstay of GC care. Our prospective AMONP cohort study demonstrated that preoperative NLR predicts clinical outcomes in patients with resected nonmetastatic Siewert type II/III AEJ [174]. Notably, T-cell infiltration mediates the association between NLR and survival in GC [175].

NLR is a reliable biomarker for predicting overall survival (OS) and significantly correlates with treatment response and prognosis in advanced GC [176]. Although NLR measured before first-line palliative chemotherapy does not independently predict progression-free survival (PFS), NLR measured during second-line chemotherapy is a significant predictor of both OS and PFS in patients with GC [177, 178]. Another study showed that NLR before first-line palliative chemotherapy predicts prognosis following subsequent chemotherapy, highlighting the importance of closely monitoring NLR in patients requiring multiple chemotherapy sessions or palliative treatment, particularly before initiating first-line chemotherapy [179]. Also, in patients with GC receiving neoadjuvant chemotherapy, an elevated NLR combined with lower histological response is strongly associated with reduced OS and PFS [180–182]. During neoadjuvant chemotherapy there are different trajectories of NLR, which are significantly associated with severe postoperative complications, recurrence, and mortality in patients with GC [183]. Neoadjuvant treatment affects spatial distribution and densities of tumor-associated neutrophils and $CD8^+$ lymphocytes in GC [184].

Elevated NLR was linked to a higher Charlson Comorbidity Index, higher body mass index, preoperative systemic inflammation, and worse prognosis of patients with resected GC [185, 186]. Combining NLR with erythrocyte width has a significantly enhanced prognostic value for GC [187]. Similarly, integrating platelet volume and number ratio with NLR harbored a higher predictive factor for PFS [188]. A high NLR and platelet count post-chemotherapy is adversely prognostic in advanced GC treated with chemotherapy [189]. Combining NLR with D-dimer predicts the sensitivity of oxaliplatin-based first-line chemotherapy in patients with unresectable advanced GC [190]. A higher modified neutrophil–platelet score is associated with worse OS and recurrence-free survival (RFS) in patients with GC undergoing curative gastrectomy [191]. Preoperative NLR (combined with albumin or other clinicopathological factors) is usefully prognostic for patients with GC receiving curative gastrectomy, and those with metastatic GC or AEJ treated with trifluridine/tipiracil as third- or later-line chemotherapy [192–195]. Preoperative neutrophil-to-platelet ratio is prognostic for GC with positive peritoneal lavage cytology [196]. Postoperative NLR is usefully predictive of early major complications after total gastrectomy for GC [197]. A neutrophil count 1 month after curative surgery could also reflect long-term prognosis better than a preoperative count [198]. NLR is also usefully prognostic in older ($\geq$75 years) patients with GC [199]. A change in NLR during perioperative periods is a promisingly prognostic in GC [200].

Patients with metastatic GC and with high baseline NLR and elevated NLR after chemotherapy exhibited higher levels of epidermal growth factor receptor and carcinoembryonic antigen and had worse prognoses [201, 202]. NLR significantly correlates with fibrinogen concentration, which is negatively linked to survival in patients with GC [203]. As a marker, NLR reflects coagulation and angiogenesis function, with higher values linked to accelerated proliferation, EMT, and GC progression. NLR is independently associated with GC metastasis and ovary invasion. It can determine the likelihood of ovarian metastasis in high-risk individuals when combined with biomarkers such as estrogen receptors, enabling timely diagnosis and treatment [204]. The preoperative NLR could be utilized as diagnostic markers for GC, or even early GC, and the combination of NLR with the platelet–lymphocyte ratio (PLR) and systemic immune-inflammation index could further improve the diagnostic efficiency [205]. Preoperative NLR could independently and effectively predict lymph node metastasis and the prognosis of patients with GC [206, 207]. NLR (combined with the prognostic nutritional index) could also predict distant metastasis in GC [208, 209]. NLR could help to distinguish precancerous gastric lesions from GC, and predict histological types of early GC [210, 211]. Combined with dual-source computed tomography, NLR could efficaciously differentiate gastric signet ring cell carcinoma (SRC) from mixed SRC (mSRC) and non-SRC (nSRC) [212].

Moreover, NLR responds to the overexpression of PD-L1 receptors in GC cells, and is predictive of tertiary lymphoid structures and the benefit from PD-1 inhibitors in GC [213–215]. Elevated peripheral NLR is associated with an immunosuppressive TME and a decreased benefit of PD-1 antibodies in advanced GC [216]. In patients with GC or AEJ receiving immune checkpoint inhibitors (ICIs), low baseline NLR is effectively predictive of good treatment efficacy and survival [217–220]. A meta-analysis of 16 studies confirms that an elevated NLR is associated with unfavorable OS and PFS in patients with advanced GC or AEJ receiving immunotherapy [221]. Particularly, NLR (combined with albumin) before each chemotherapy line is sensitively predictive of disease progression and prognosis in patients with unresectable or recurrent GC treated with nivolumab [222–224] and ramucirumab [225]. NLR was also significantly predictive of long-term survival in patients with advanced GC treated with first-line trastuzumab [226].

Transfusion operations or inadvertent infections during the perioperative period, with high NLR potentially being a marker, may promote GC recurrence [227]. An elevated NLR at the time of *Hp* clearance may indicate incomplete eradication, which also predicts a high likelihood of GC recurrence [228]. The prognostic value of NLR may also be reflected in the individual density of CAAs within the tumor, as high CAA densities influence the TME through the secretion of cytokines and growth factors [229]. However, pretreatment NLR may not be a suitable biomarker in early GC and is not associated with OS, likely due to the lack of a significant inflammatory response in early-stage disease [230].

Novel neutrophil-associated biomarkers for GC

The complexity of GC biology and the heterogeneity of neutrophil functions suggest that additional biomarkers may be needed to improve diagnostic and prognostic accuracy. Novel neutrophil-associated biomarkers may predict the occurrence, progression,

and prognosis of early GC. For instance, insulin-like growth factor binding protein 7 (*IGFBP7*) mRNA expression is closely associated with neutrophil gene expression in GC. High levels of IGFBP7 may indicate *Hp* infection and neutrophil infiltration, which are associated with a poor prognosis in GC [231]. CSF1R, CPZ, DOK5, and ITGAL can alter the ECM and neutrophil infiltration in the GC TME through the PI3K-AKT and TGF-β signaling pathways, which regulate GC growth and metastasis and reflect tumor prognosis [232–235]. Macrophage migration inhibitory factor (MIF) and human neutrophil peptide (HNP) 1–3 are also potential biomarkers for GC [236]. HNP-1 can serve as a specific molecular probe for the detection of HNP 1–3, with a potential application as a GC tissue marker utilizing MALDI-imaging mass spectrometry, highlighting infiltrated neutrophils as a target in tumors [237].

A negative correlation exists between the expression level of glucosyl xylosyltransferase 2 (GXYLT2) and the level of activated neutrophils [238]. This may reflect a state where the anti-tumor effect of N1 cells is inhibited in early GC, while the pro-tumor effect of N2 cells has not yet become dominant; thus, GXYLT2 may aid in the diagnosis of early GC. Moreover, EFNA3 exhibits a significant inverse correlation with neutrophil levels, suggesting its potential use as a biomarker for early diagnosis of GC. In GC cells, EFNA3 influences ribosome biogenesis and protein translation pathways, highlighting its role as a crucial biomarker for cell cycle checkpoints in GC [239]. Neutrophil gelatinase-associated lipocalin (NGAL) may also serve as a biomarker for early GC [240]. *NGAL* expression is upregulated in gastric mucosal cells of patients infected with *Hp*, thereby enhancing the inflammatory response in the stomach [241]. C/EBPβ expression enhances the activity of the *NGAL* promoter and induces its overexpression by binding to 12-*O*-tetradecanoylphorbol-13-acetate (TPA). NGAL can mediate the activity of MMP-9, which in turn promotes the invasion and migration of GC cells. The expression of the NGAL/MMP-9 complex in GC tissues is significantly greater compared with non-cancerous gastric tissues. There is also a direct positive correlation between the histological level of the NGAL/MMP9 complex and the malignancy grade in GC [242]. Furthermore, NGAL can modify the subcellular localization of E-calmodulin and connexin, reducing cell adhesion to enhance tumor invasion [243]. In addition, neutrophil exosome miRNAs could be utilized as biomarkers [244]. The abundance of various mRNAs in exosomes can distinguish patients with different types of GC and reflect disease progression.

Overall, the use of neutrophils and their associated markers as biomarkers for GC holds promise. However, further validation in large clinical trials is required to establish their clinical utility and improve the accuracy of gastric cancer diagnosis and prognosis. Notably, machine learning could advance personalized medicine for GC by identifying tumor-associated neutrophils and their subgroups as key indicators of chemotherapy response [245].

Neutrophil-targeting anti-GC therapeutic strategies

Clinical research targeting neutrophils in GC is one of the cutting-edge fields of tumor immunotherapy in recent years. The complex role of neutrophils in the microenvironment of GC (both pro-tumor and anti-tumor) makes them a potential therapeutic target. The targeted strategies lie in inhibiting the tumor-promoting properties and activating

the anticancer activities of neutrophils in GC [25, 246]. Inhibition of the pro-tumor neutrophils could be achieved through the following:

Targeting chemotaxis and recruitment: CXCR1/2 inhibitors, such as AZD5069 (AstraZeneca) and SX-682 (Synthrix), block the IL-8/CXCR1/2 signaling pathway and reduce neutrophil infiltration (multiple phase I/II trials are underway; e.g., NCT02499328). IL-8 monoclonal antibody (BMS-986253) shows a synergistic effect in combination with PD-1 inhibitors in advanced GC, with overall response rate (ORR) increased to 25% (NCT03400332).

Blocking the formation of NETs: PAD4 inhibitors (such as GSK484) inhibit histone citrullination and reduce NETs release (in preclinical studies). DNase I could degrade the DNA backbone in NETs and inhibit metastasis (effective in animal models).

Reversing immune suppression: arginase inhibitor (CB-1158) could restore T-cell function (in phase I trial).

Activation of anticancer neutrophils could be achieved through the following:

Cytokine regulation: IFN-γ could enhance the phagocytic and antigen presentation functions of neutrophils (being tested in combination with a PD-1/PD-L1 inhibitor). GM-CSF could induce neutrophil differentiation toward an anti-tumor phenotype (N1 subtype).

Engineering transformation: CAR-neutrophils could be achieved through expression of chimeric antigen receptors targeting HER2 or CEA using gene editing (in preclinical study).

Targeting neutrophils provides a novel approach for the treatment of GC, but its dual role and functional complexity require more precise strategies. In the future, it is necessary to combine multiple omics technologies, new engineering methods, and combination therapies to balance efficacy and safety. At present, multiple clinical trials (such as CXCR2/IL-8 inhibitor combined with immunotherapy) have entered the critical stage, and are expected to bring breakthrough treatment options for patients with advanced GC [25, 246].

Future perspectives

The majority of cancer-related deaths are due to cancer metastasis. The common metastatic sites for GC include the liver, peritoneum, lungs, bones, and distant lymph nodes, with liver and peritoneal metastases being the most frequent and clinically impactful because of their association with poor prognoses [247, 248]. The susceptibility of the liver is attributed to hematogenous dissemination through the portal venous system, while peritoneal metastasis often arises from direct invasion or spreading of cancer cells.

Neutrophils play critical roles in the pre-metastatic niche and represent a pivotal component of the pre-metastatic niche in GC, preparing secondary sites for the colonization of cancer cells. N2 neutrophils can release a variety of inflammatory factors in preparation for GC metastasis. Neutrophils facilitate ECM remodeling through MMP secretion, promote angiogenesis via vascular endothelial growth factor (VEGF) and IL-8, and augment immunosuppression through arginase-1 and ROS. The formation of the pre-metastatic niche is also facilitated by HIF-1, which is crucially involved in the chemotaxis of peripheral neutrophils to the TME [249]. Notably, NETs are involved in trapping circulating cancer cells and activating pro-metastatic signaling cascades in distant organs.

Within the pre-metastatic niche, the release of G-CSF, the secretion of interleukins, and the upregulation of hydroxyacid oxidase 1 (HAO1) expression promote the production of NETs, which act as a scaffold for GC cells, promote angiogenesis, and assist in GC metastasis [250]. Moreover, neutrophil-derived LCN2 and S100A8/A9 proteins foster a permissive microenvironment for GC metastasis, underscoring their dual roles as both effector and regulator in the preparation of pre-metastatic niches. In the pre-metastatic niche of GC, neutrophil metabolism is also altered, with the expression level of fatty acid transporter protein (FATP)-2 increasing, which can result in increased uptake of fatty acids and the production of more prostaglandin E2, which in turn inhibits T cells [251]. Targeting neutrophil recruitment and/or function may thus represent a promising therapeutic strategy to inhibit the metastatic progression of GC.

Neutrophil-associated GC treatment is promising but challenging. Neutrophil elastase is related to the immune cell infiltration in the tumor immune microenvironment (TIME) and prognosis in GC [252]. Chamomile (*Matricaria recutita* L.) infusion can inhibit neutrophil elastase and MMP-9 of human gastric adenocarcinoma cells [253]. The specific neutrophil elastase inhibitor sivelestat, which may block the release of transforming growth factor-α, can inhibit GC cell proliferation [254, 255]. This discovery opens new avenues for GC treatment. However, it remains at the animal experiment stage and does not take into account infection and secondary disease episodes. Enhanced photodynamic therapy and anti-PD-1 therapy could synergistically inhibit GC cell proliferation. The TOB1 protein functions as a modulator of neutrophil phenotypes, potentially acting as a tumor suppressor by influencing the activation and proliferation of neutrophils in GC progression, indicating its potential as a target (and efficacy-predictive marker) for immunotherapy [47]. Particularly, tumor-infiltrating neutrophils may be potential therapeutic targets for $HER2^-$ GC [256].

In addition to targeting specific neutrophil functions, understanding the broader interactions between neutrophils and other cell types in the TME is crucial for developing effective therapies. Neutrophils in GC undergo spontaneous ferroptosis, a process that releases oxidized lipids, inhibiting T-cell mediated tumor suppression [257]. Loss of purinergic receptor P2X 1 (P2RX1) in neutrophils can induce $CD8^+$ T-cell dysfunction in GC [258]. The ratio of intratumoral $CD15^+$ neutrophils to $CD8^+$ lymphocytes predicts recurrence in patients with GC after curative resection [259]. Neutrophils in GC tissue inhibit the proliferation of $CD4^+$ T cells and may form a local immunosuppressive environment through the PD-1/PD-L1 pathway [260]. Extracellular vesicles from GC cells induce PD-L1 expression in neutrophils, suppressing T-cell immunity [261]. The combination of $CD66b^+$ tumor-associated neutrophils and $\alpha\text{-SMA}^+$ CAFs could independently predict patient outcomes and identify patients with GC who might benefit from postoperative chemotherapy [262]. Mast cells also interact with neutrophils in human GC [263]. It is imperative and challenging to comprehensively elucidate how neutrophils interact with other cell types within the complex GC TME, such as TAMs and CAFs, and how these interactions influence GC progression [264, 265]. This presents a considerable technical hurdle, necessitating the development of novel methodologies for the precise functional characterization and identification of neutrophil subpopulations.

Notably, we previously found that subclusters of neutrophils activated by cancer cells and M2 macrophages promote GC progression during PD-1 antibody-based

immunotherapy [41] Single-cell RNA sequencing (scRNA-seq) analysis revealed an increased number of circulating neutrophils in peripheral blood after treatment, with neutrophil cluster 1 (NE-1) as the major subcluster. NE-1 displayed an activated neutrophil phenotype, marked by elevated expression levels of MMP-9, S100A8/9, PORK2, and TGF-β1. In pseudo-time trajectory analysis, NE-1 occupied an intermediate position, with gene functions enriched in neutrophil activation, leukocyte chemotaxis, and the negative regulation of MAP kinase activity. Cellular interaction analysis revealed that chemokine signaling is the primary pathway associated with the interactions of NE-1 with subclusters of malignant epithelial cells (EP-4) and M2 macrophages (M2-1 and M2-2). In addition, the MAPK signaling and JAK-STAT signaling of EP-4, which include the IL1B/IL1RAP, OSM/OSMR, and TGFB1/TGFBR2 axes, were interacting pathways between EP-4 and NE-1. Notably, high expression of OSMR in tumor cells was closely associated with lymph node metastasis in GC. These key interaction pathways require further validation and may represent promising therapeutic targets for GC.

The relationship between neutrophils and GC is complex. Research should prioritize stimulating the anti-tumor roles of neutrophils while inhibiting their pro-tumor effects. The heterogeneity and multifunctionality of neutrophils play a crucial role in GC growth, invasion, metastasis, and angiogenesis. Ongoing research efforts should include continued investigation of the role of NETs, analysis of the predictive values of combined neutrophil-based biomarkers, identification of innovative therapeutic targets, and development of new neutrophil-targeting drugs for GC. Furthermore, with full consideration of spatiotemporal specificity, transforming N2 into N1 neutrophils and guiding neutrophils to differentiate in the N1 direction to exert anticancer functions in the GC TME is a key area that warrants further exploration.

The contradictory results found in the literature, such as the dual functions of neutrophils (both tumor-promoting and tumor-suppressing) and the variations in NET formation among different GC subtypes, underscore the necessity for more detailed research. These inconsistencies may stem from disparities in experimental models, patient cohorts, or the particular GC microenvironment (e.g., levels of hypoxia and inflammation). Notably, the role of NETs in facilitating metastasis as opposed to their capacity to augment immune surveillance may be contingent on the context, and future research should strive to clarify these contexts with greater precision.

Future research should focus on crucial areas to further our understanding of neutrophils in GC. scRNA-seq reveals neutrophil diversity, identifying particular subpopulations and their contributions to tumor development or suppression. Inhibiting NETs using drugs such as PAD4 inhibitors, especially in advanced instances when NETs induce metastasis, may be coupled with immune checkpoint inhibition therapy. Another method is to convert pro-tumor N2 neutrophils to anti-tumor N1 neutrophils by targeting pathways such as JAK-STAT or NF-κB, or by metabolic treatments. Investigating neutrophil-derived exosomes and their function in immune evasion and metastasis may yield new diagnostic and therapy approaches. These strategies show the potential to improve GC treatment.

Several therapeutic strategies could be considered on the basis of current evidence, including combination therapies that pair neutrophil-targeting approaches, such as NET or neutrophil elastase inhibitors, with immune checkpoint inhibitors such as PD-1/

PD-L1 antibodies, to enhance anti-tumor immunity. A neoadjuvant chemotherapy strategy based on abraxane/human neutrophil cytopharmaceuticals with radiotherapy may provide new opportunities for advanced GC treatment, revealing the huge clinical potential of human neutrophils as drug delivery vectors [266]. There might exist a correcting effect of the combined treatment of electron-beam intraoperative radiotherapy with sanazole administration on the functional activity of neutrophils [267]. In addition, targeting neutrophil polarization by developing drugs that selectively inhibit the N2 phenotype and promote the N1 phenotype could be promising, potentially through targeting specific cytokines such as TGF-β or IL-17, or metabolic pathways such as lactate and leucine metabolism. Last but not least, utilizing neutrophil-related biomarkers, such as NLR or NET-associated proteins, to stratify patients for personalized therapy might precisely improve treatment outcomes, with patients exhibiting high NLR or elevated NET levels potentially benefiting more from neutrophil-targeting therapies.

Conclusions

This review provides a comprehensive and in-depth exploration of the role of neutrophils in GC. Neutrophils play a complex and crucial role in the occurrence and development of GC. Within the TME, neutrophils display functional diversity, being classified into anti-tumorigenic (N1-like) and pro-tumorigenic (N2-like) subtypes. Notably, N1-like neutrophils exhibit inhibitory effects on GC progression by enhancing antigen presentation, exerting cytotoxicity, and producing ROS, whereas N2-like neutrophils foster tumor development by inhibiting anti-cancer immunity, inducing tumor immune evasion, activating mesenchymal stem cells, and promoting EMT. Neutrophils also participate in immunosuppression through key signaling pathways, such as the JAK-STAT and NF-κB pathways, which promote tumor growth and metastasis. NETs can not only trigger inflammation to promote the occurrence of GC but also play an important role in tumor invasion and vascular coagulation. As for neutrophil-associated biomarkers, NLR is a classic one, and some emerging ones also show potential predictive and prognostic values. While neutrophil-based GC treatment is promising, it still faces many challenges and remains at the experimental stage. The interaction between neutrophils and other cells is complex. Future research needs to focus on understanding how to regulate the function of neutrophils, transform their subtypes, and develop novel neutrophil-targeted drugs. By elucidating the mechanisms underlying the plasticity and interaction of neutrophils within the TME, precise targets could be identified to enhance the anti-tumor effects while suppressing the pro-tumor activities. In addition, advancing the development of neutrophil-specific therapies could improve treatment outcomes and reduce off-target effects, offering a more personalized approach to the care of patients with GC.

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Author contributions

Conception or design: Zou WB, Li Z, and Huang L. Drafting of the manuscript: Qin Y, Liu Y, Dong P, and Huang L. Critical revision of the manuscript for important intellectual content: Qin Y, Liu Y, Dong P, Zou WB, Li Z, and Huang L. Administrative, technical, or material support: Li Z and Huang L. All authors have approved the current manuscript version for submission and publication.

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Competing interests
We declare that there are no competing interests.

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