Activation of neutrophils as potential therapeutic targets for cancer treatment.

Md Abdus Subhan*

Department of Chemistry, Shahjalal University of Science and Technology, Bangladesh

Abstract

Neutrophils are essential for host protection against microbial infections and can be used as a mode of cancer therapy. They play dual role in cancer either as tumor promoting or anti-tumor. Neutrophil cytotoxicity is deceptive at the time of metastatic seeding and possibly at early stages of tumorigenesis but not in the microenvironment of a matured tumor. Application of neutrophils and their membranes for improved drug delivery and novel therapeutics as already attained inspiring results in preclinical settings.

Keywords: Neutrophils, NETs, PMN-MDSCs, Anti-cancer, Cytotoxicity, TME.

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Introduction

Neutrophils play dual and conflicting roles in cancer. Both tumor promoting and anti-tumor functions of neutrophils are executed by specific molecular mediators [1-4]. The tumor promoting functions include promotion of tumor cell dissemination by degradation of the ECM (extracellular matrix) at the primary and premetastatic sites and progression of tumor cell seeding by deploying neuroendocrine tumors. Promotion of angiogenesis is mediated by secretion of Vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF) and the release of angiogenic factors from the ECM by neutrophil derived Matrix metallopeptidase9 (MMP9). Neutrophil mediate immune suppression via the secretion of ROS and Arginase 1 to impede T cell dependent anti-tumor immunity. On the other hand, anti-tumor roles of neutrophils include limitation of tumor growth and metastatic progression by eliminating tumor cells either directly or via antibody dependent mechanisms (e.g., antibody-dependent cellular cytotoxicity (ADCC)), stimulation of anti-tumor adaptive immune by acting as antigen presenting cells, secretion of TNFα, secretion of Elastase and secretion of Cathepsin G (Cath G) (Figure 1).

Human neutrophils transit from bone marrow into circulation within six to seven days after the last cell division. Based on morphological features including cell size, nuclear condensation and granule content, their different stages are classified from granulocyte–monocyte progenitors (GMPs). Several studies have identified an increase in the neutrophil–lymphocyte ratio (NLR), a ratio of absolute neutrophil to absolute lymphocyte numbers in cancer patient peripheral blood and an association of higher NLR with more advanced or aggressive cancer. High blood neutrophil counts and high neutrophil-to-lymphocyte ratios in patients with advanced cancer generally correlate with a poor prognosis. Therefore, tumor-associated neutrophils (TANs) have emerged as important players in tumor microenvironment (TME).

The tumor promoting functions of neutrophils

An aggressive tumor phenotype is regulated by the expression

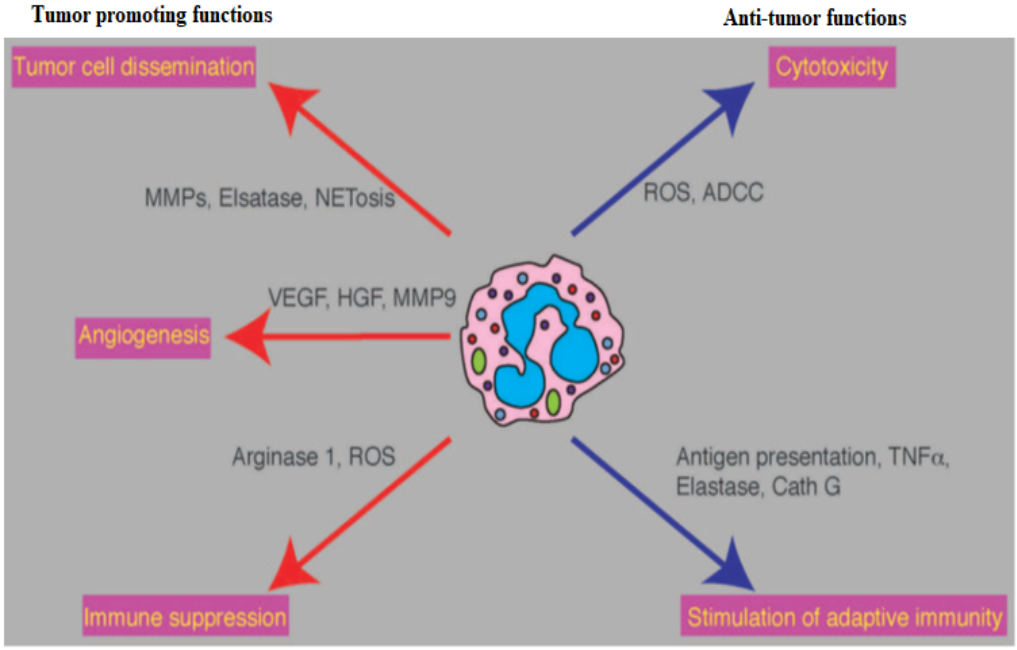

Figure 1. *Tumor promoting functions (red arrows) and anti-tumor functions (blue arrows) of neutrophils (adapted from an open access article ref 2).*

of angiogenic factors such as VEGF [5]. Thus, targeting angiogenesis should serve to inhibit tumor growth in certain types of cancer [2,6]. In TME, neutrophils, together with other stromal cells provide pro-angiogenic factors and actively promote tumor angiogenesis. Explicitly, neutrophils provide MMP9, VEGF and HGF. Neutrophils also provide factors that evade common anti-angiogenic therapies targeting VEGF [7]. These observations emphasized a key role for neutrophils in propagating tumor angiogenesis and suggest that targeting of neutrophil mediated angiogenesis or the angiogenic neutrophil subpopulation may be used as an anti-angiogenic therapeutic approach.

Polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) are known as pathologically activated neutrophils [3]. They are crucial for the regulation of immune responses in cancer. These cells are responsible for the failure of cancer therapies. However, the mechanisms of the pathological activation of neutrophils are not clear, which confines the selective targeting of these cells. Veglia et al. showed that FATP2 deficient neutrophils lose their immunosuppressive properties leading to a delay in tumor progression [3]. Mouse as well as human PMN-MDSCs exclusively upregulate fatty acid transport protein 2 (FATP2). Overexpression of FATP2 in PMN-MDSCs was controlled by granulocyte–macrophage colony-stimulating factor through the activation of the STAT5 transcription factor. Removal of FATP2 rescinded the suppressive activity of PMN-MDSCs. The mechanism of FATP2-mediated suppressive activity involved the uptake of arachidonic acid and the synthesis of prostaglandin E2. The selective pharmacological inhibition of FATP2 revoked the activity of PMN-MDSCs and delayed tumor progression. In combination with checkpoint inhibitors, FATP2 inhibition impeded tumor progression in mice. FATP2 mediates the acquisition of immunosuppressive activity by PMN-MDSCs and represents a target to inhibit the functions of PMN-MDSCs selectively and to improve the efficiency of cancer therapy [3].

Metastasis is the final and deadly stage in cancer progression. Tumor cells acquire unique features that support the transition from the primary site, their survival in the circulation and the successful metastatic seeding in a distant organ to metastasize. Neutrophils play various roles to promote the intravasation of tumor cells, their survival in the circulation, their adherence to the endothelium at the future site of metastasis through priming of the pre-metastatic niche, and the process of extravasation [8]. Neutrophils play a critical role in the triggering of dormant tumor cells and the initiation of metastases growth [9]. Thus, targeting of neutrophil function in each of these stages of metastatic dissemination may have significant consequences on metastatic progression. Albrengues et al. showed that neutrophil extracellular traps (NETs) are required for promoting the exit from dormancy and the establishment of marcometastases. The formation NETs, known as NETosis, was first observed as a novel immune response to bacterial infection. NETs form when activated neutrophils release DNA, histones, and granular content, exposing antimicrobial and pro-inflammatory proteins. NETosis occurs abnormally in a variety of other inflammatory disease including cancer. In woman breast cancer, NETosis has been linked to increased disease progression, metastasis, and complications such as venous thromboembolism [10]. NET-targeted therapies have shown success in preclinical cancer models and may be a valuable clinical target in slowing or halting tumor progression in breast cancer. Administration of DNAse eliminate NETs to maintain tumor cells dormant and seize metastasis [9].

Myeloid Derived Suppressor Cells (MDSC) involves a wide range of myeloid cells which possess immunosuppressive properties [2,11]. These cells have the capacity to suppress cytotoxic T cells and promote immune evasion. The immunosuppressive neutrophils are propagated to promote the resolution of an inflammatory process. The propagation of immunosuppressive neutrophils serves the resolution of tumor associated inflammation in cancer. Suppressive neutrophils are mobilized excessively to the point where they become the dominant subpopulation of neutrophils. The overall neutrophil contribution is pro-tumorigenic. Immunosuppressive neutrophils, referred to as g-MDSC contain large amounts of arginase I, which suppresses T cell proliferation through deficiency of L-arginine [11,12]. These neutrophils generate high levels of hydrogen peroxide and thus block T cell proliferation [13,14]. Neutrophils play role for maintaining an immunosuppressive TME and facilitate metastatic spread through suppression of adaptive immune components [2,13,15]. Thus, inhibition of neutrophil-mediated immunosuppression may further potentiate anti-tumor adaptive immunity.

Stimulation of adaptive immune responses by neutrophils

Adaptive immunity is the major effector in anti-tumor immune responses. However, there is evidence supporting a role for neutrophils in this context. For example, neutrophils interact with T cells and are required for proper anti-tumor CD4+ and CD8+ T-cell responses [16-19]. Neutrophils present antigens and provide accessory signals for T cell activation [20,21]. In addition, N1 tumor associated neutrophils require T cells for their anti-tumor activity at the primary site, which may indicate possible stimulation of T cells by neutrophils [16]. Neutrophils can recruit and activate T-cells via secretion of cytokines, including TNF-α, Cathepsin G and neutrophil elastase [15]. Neutrophils may exist with either tumor promoting or tumor limiting properties depending on the context. It is not yet clear whether this is a manifestation of distinct subsets or the extreme ends of a diverse functional spectrum. Neutrophils are the first responders of the immune system and as such are equipped with a wide variety of receptors. This makes neutrophils highly responsive to signals in their microenvironment. Neutrophils function one way at the primary tumor and in a completely different way in the pre-metastatic niche. The Neutrophil function was found to be dramatically modified by factors such as TGF-β and type I interferons.

TGF-β is a highly versatile molecule which may act as both tumor suppressor and oncogene. TGF-β plays a dual role behaving as a suppressor factor at early stages but contributing later to tumor progression once cells escape from its cytostatic effects. The effect of TGF-β on neutrophil function in cancer is regarded as pro-tumoral. Fridlender et al. showed that TGF-β in the TME functions to inhibit neutrophil cytotoxicity [16]. The study investigated the "N1" antitumor and "N2" pro-tumor terminology to describe neutrophil function in cancer. Their study showed that TGF-β inhibit the anti-tumor function of

neutrophils and restricted their entry into the tumor [16]. TGF-β directly blocks the production of H2O2, a significant mediator of neutrophil cytotoxicity by activated neutrophils. TGF-β also block the migration of tumor neutrophils toward tumor cells. Moreover, TGF-β was found to change the ratio between HDN (high density neutrophils) and LDN (low density neutrophils). Collectively, these observations demonstrate that TGF-β not only blocks the anti-tumor functions of neutrophils, it also increases the proportion of tumor promoting neutrophils supporting tumor growth. Since TGF-β is ample at the primary and metastatic tumors, neutrophil cytotoxicity is not evident in these sites but rather the pro-tumor functions are manifested [20-21]. In contrast, during the early stages of metastatic dissemination, circulating tumor cells arriving to the future site of metastasis are not protected by high levels of TGF-β and are susceptible to neutrophil cytotoxicity. Hence neutrophil cytotoxicity is evident at the time of metastatic seeding and possibly at early stages of tumorigenesis but not in the microenvironment of an established tumor.

Type I interferons influence neutrophil function that opposes that of TGF-β. IFNs were first identified as having anti-viral functions and later were found to play an anti-tumorigenic role. IFNs mediate an anti-tumor immune response by prompting various immune cells [22]. On modulating the function of lymphocytes and macrophages, IFN-β was found to suppress the expression of pro-angiogenic factors, such as VEGF and MMP9, thereby limiting tumor growth [23]. In addition to modifying the expression of pro-tumorigenic factors, IFN-β enhances the recruitment of neutrophils and their life span in primary tumors [24, 25]. Type I IFN activity was found to inhibit neutrophil-mediated priming of a receptive premetastatic niche [26]. These observations support the view that neutrophil function in cancer is dictated by the specific microenvironment. These data suggest that rather than modifying the function of neutrophils or depleting specific subsets, therapeutic benefit mediated by neutrophils via modulation of the TME can be achieved. Blocking TGF-β activity or enhancing IFNs activity at the TME may facilitate neutrophil anti-tumor cytotoxicity of immunotherapy.

Anti-tumor functions of neutrophils

Different strategies of targeting immunosuppressive neutrophils for cancer therapy have been developed as shown in (Figure- 2) [4].

A. Depletion of existing PMN-MDSCs:

1. Chemotherapeutic drugs, gemcitabine and 5-fluorouracil (5FU), directly induce apoptosis;

2. The anti-CD33 antibody, AMV564, induces NK cell-mediated ADCC; (3) LXRβ agonists activate ApoE and induce apoptosis.

B. Inhibition of the development of PMN-MDSCs:

1.The differentiation process from myeloid progenitor cells in bone marrow to MDSCs is blocked by ATRA, IL-12, or anti-G-CSF antibody;

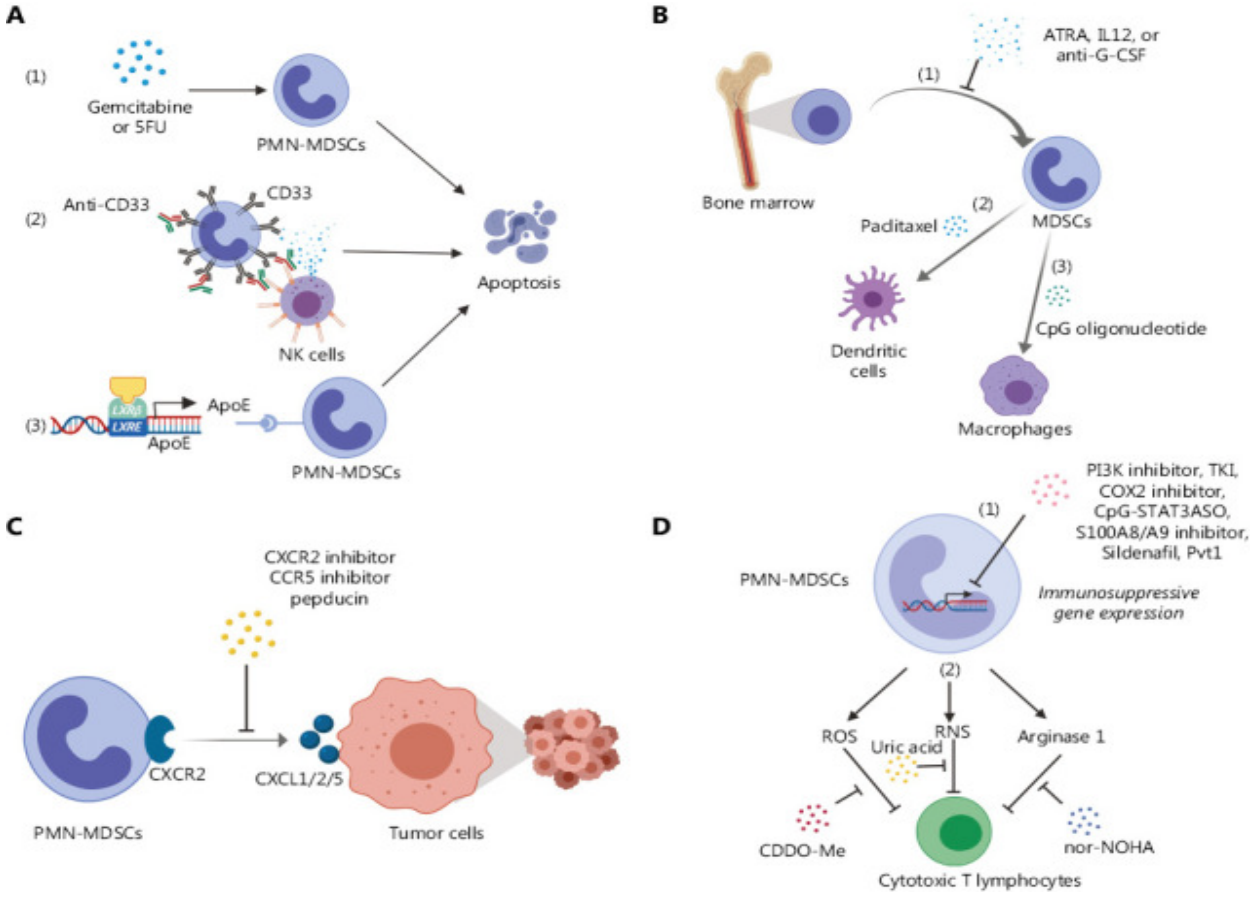

Figure 2. *Different strategies of targeting immunosuppressive neutrophils. (A) Depletion of existing PMN-MDSCs (B) Blockade of the development of PMN-MDSCs (C) Blockade of PMN-MDSC recruitment and (D) Inhibition of PMN-MDSC immunosuppressive potential.(Adapted from open access article ref 4)*

2. Ultra-low doses of paclitaxel induce differentiation of MDSCs into non-immunosuppressive dendritic cells;

3. CpG oligonucleotide induces MDSC to differentiate into non-immunosuppressive macrophages.

C. Blockade of PMN-MDSC recruitment: Delivery of PMN-MDSCs into the tumor microenvironment via chemotaxis is effectively blocked by CXCR2 inhibitors (such as SB225002 and SX-682), neutralizing antibody or peptide (pepducin), mCCR5-Ig or other agents.

D. Inhibition of PMN-MDSC immunosuppressive potential:

1.Immunosuppressive gene expression programs in PMN-MDSCs are blocked by PI3K inhibitors, RTK inhibitors, COX2 inhibitors, CpG-STAT3ASO, S100A8/A9 inhibitors, the PDE5 inhibitor sildenafil or long noncoding RNA Pvt1;

2. Immunosuppressive products from PMN-MDSCs, such as ROS, RNS and Arginase 1, are neutralized by nor-NOHA, uric acid, and bardoxolone methyl.

Inhibition of receptor tyrosine kinase c-MET in neutrophils improve the efficacy of immunotherapy by limiting the recruitment of immunosuppressive neutrophils [27]. The c-MET inhibition enhances adoptive T Cell transfer immunotherapy, increases the number of tumor-infiltrating T Cells, and impairs the reactive recruitment of tumor-infiltrating neutrophils in response to immunotherapy. The c-MET inhibitor capmatinib was found to be effective against HCmel12 melanoma cell line in mice [27]. In patients with metastatic melanoma undergoing anti-PD-1 immunotherapy in combination with capmatinib was found their blood neutrophil counts and serum HGF levels increase in lesser extent than non-responders [27].

Neutrophil has a pro-tumorigenic role in cancer. On the other hand, neutrophil also eliminate cancerous cells and limit metastatic seeding. Neutrophil cytotoxicity requires a high level of specificity. Neutrophils need to be activated, attracted to tumor cells. They must identify tumor cells as a target, form physical contact with tumor cells and must secrete cytotoxic mediators (H2O2) to induce tumor cell apoptosis. Neutrophil recognition of tumor cells mediated either directly (RAGE-Cathepsin G) or in an antibody dependent fashion (ADCC) [28,29]. Tumor cells must be susceptible to neutrophil cytotoxicity (i.e., express the H2O2-dependent TRPM2 Ca2+ channel) for the neutrophils to exert anti-tumor function [30]. Cytotoxic neutrophils may be detected throughout the course of the disease, neutrophil cytotoxicity is mostly evident in early stages of tumor progression. TRPM2 expression in tumor cells varies, and not all tumor cells are equally susceptible to neutrophil cytotoxicity. Preventing the transition from HDN to LDN enhance the proportion of anti-tumor neutrophils. Thus, the transfusion of cytotoxic neutrophils is challenging.

The inflammatory TME impaired by tumor-recognizing therapeutic antibodies, photosensitization or surgery enhances the recruitment of drug/NP-loaded neutrophils or neutrophil membrane-derived nanovesicles, which is the most essential prerequisite for neutrophil-based drug delivery (Figure-3).

Neutrophils carrying therapeutic liposomes, albumins or CD11b antibody-coated NPs travel into the TME to deliver the drugs following chemoattraction by pro-inflammatory signals. The neutrophils penetrate the blood brain barrier (BBB) to exert their effects (Figure 3A). Nanovesicles generated using neutrophil membranes loaded with drugs (such as piceatannol) to forms neutrophil-mimicking NPs (NM-NPs) have been used. The neutrophil-derived properties of nanovesicles allow homing to the tumor microenvironment for therapeutic delivery (Figure 3B).

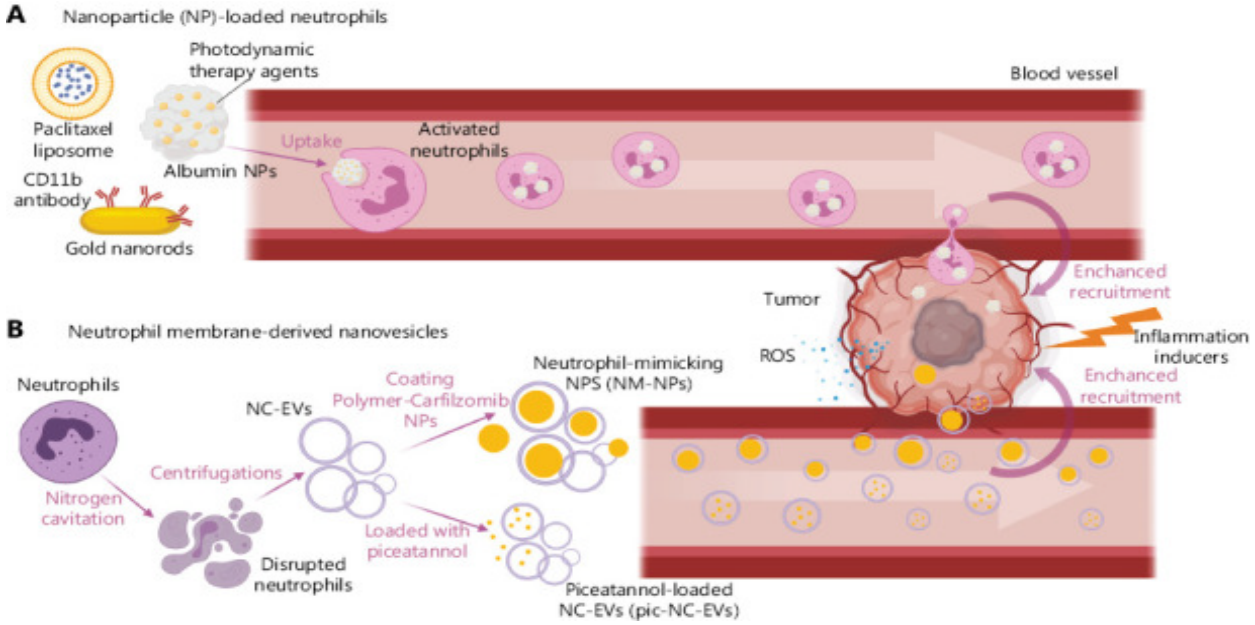

Figure 3. *Neutrophil-based drug delivery system. (A) NP-loaded neutrophils. Neutrophils carrying therapeutic liposomes (loaded ex vivo), albumins or CD11b antibody-coated NPs (engulfed by circulating neutrophils) and travel into the tumor microenvironment to deliver the drugs following chemoattraction by tumor-emitted pro-inflammatory signals. The neutrophils penetrate the blood brain barrier (BBB) to exert their effects. (B) Neutrophil membrane-derived nanovesicles. Nanovesicles generated using neutrophil membranes, loaded with drugs (such as piceatannol) or form neutrophil-mimicking NPs (NM-NPs). The neutrophil-derived properties of nanovesicles allow homing to the tumor microenvironment for therapeutic delivery.*

(Adapted from open access article ref 4)

Conclusion and future perspective

Neutrophils are essential for host protection against microbial infections and may be used as a mode of therapy. Neutrophils are not a homogeneous population of cells, which open new opportunities for targeting neutrophils as a mode of cancer therapy. Better characterization of neutrophils, their different subsets and distinct functions may serve to precisely deplete harmful populations and enhance neutrophils' favorable functions [31]. However, this requires continuous administration of antibodies. This therapeutic approach is not risk free and previous studies using antibodies to deplete neutrophils show that ultimately the deployed antibodies lose their efficacy. A different strategy for the manipulation of neutrophil function in cancer is via the modulation of the TME in a fashion that would permit neutrophil anti-tumor functions. Indeed, using small molecules to block TGF-β showed a dramatic effect on tumor growth that was dependent on neutrophils. Furthermore, tumor growth and metastatic spread can be blocked in myeloid-specific deletion of TGFβR2 in mouse. Thus, modifying TGF-β activity in neutrophils in vivo may be useful for stimulating a robust anti-tumor response. However, current therapies targeting TGF-β signaling are toxic and not tolerated well. A possible alternative for circumventing the toxicity of systemic administration of small molecule TGF-β blockers is a targeted approach.

Neutrophils present with either tumor promoting or tumor limiting properties depending on the context. Neutrophils function one way at the primary tumor and in an entirely different way in the pre-metastatic niche. The only characteristic that discriminates granulocytic g-MDSCs from mature neutrophils is their suppressive capacity. It raising the question whether human g-MDSCs and neutrophils are actually different cell types or whether they are one plastic cell type that can functionally polarize from microbial killers to immunosuppressor cells, depending on local conditions. Neutrophil cytotoxicity is apparent at the time of metastatic seeding and possibly at early stages of tumorigenesis but not in the microenvironment of a solid tumor. Blocking TGF-β activity or enhancing IFNs activity in TME may facilitate neutrophil anti-tumor cytotoxicity of immunotherapy. For targeting immunosuppressive neutrophils, depletion, redirection of differentiation, blockage of recruitment and efficient inactivation of PMN-MDSCs shows promising results. Uses of neutrophils and their membranes for better drug delivery and novel therapeutics has already obtained inspiring results in preclinical models, and neutrophil- based therapeutics present a rapidly mounting area of cancer therapy. Neutrophils carrying therapeutic liposomes, albumins or CD11b antibody-coated NPs transportable into the TME to deliver the drugs following chemoattraction by pro-inflammatory signals. Inhibition MET in neutrophils improve the efficacy of immunotherapy by restraining the recruitment of immunosuppressive neutrophils. Future knowledge on neutrophil biology and advanced therapies using neutrophil specific drug delivery are expected to harness neutrophils toward fighting cancer more effectively.

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Conflict of Interest

The author declares no competing interest.

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***Correspondence to:**

Ehsan Y Sabry
Department of Chemistry,
Shahjalal University of Science and Technology,
Bangladesh
Tel: +8801716073270
E-mail: subhan-che@sust.edu