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Engineering and Targeting Neutrophils for Cancer Therapy

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Neutrophils are the most abundant white blood cells in the circulation and act as the first line of defense against infections. Increasing evidence suggests that neutrophils possess heterogeneous phenotypes and functional plasticity in human health and diseases, including cancer. Neutrophils play multifaceted roles in cancer development and progression, and an N1/N2 paradigm of neutrophils in cancer is proposed, where N1 neutrophils exert anti-tumor properties while N2 neutrophils display tumor-supportive and immune-suppressive functions. Selective activation of beneficial neutrophil population and targeted inhibition or re-polarization of tumor-promoting neutrophils has shown an important potential in tumor therapy. In addition, due to the natural inflammation-responsive and physical barrier-crossing abilities, neutrophils and their derivatives (membranes and extracellular vesicles (EVs)) are regarded as advanced drug delivery carriers for enhanced tumor targeting and improved therapeutic efficacy. In this review, the recent advances in engineering neutrophils for drug delivery and targeting neutrophils for remodeling tumor microenvironment (TME) are comprehensively presented. This review will provide a broad understanding of the potential of neutrophils in cancer therapy.

1. Introduction

Neutrophils are the most abundant leukocytes in human circulation, and regarded as the primary defense against infection.[1] In response to inflammatory stimuli, neutrophils are recruited to the sites of infection, inflammation, and tissue damage, where they exert antimicrobial and inflammatory functions through phagocytosis, degranulation, release of neutrophil extracellular traps (NETs) and activation of immune response.[2] Due to their fragility and short lifespan, the biological roles of neutrophils in human diseases have long been neglected. Although the infiltration of neutrophils in tumor tissues was observed almost half a century ago, the exact roles of neutrophils in cancer have not been well understood until the last decade. The recognition of the heterogeneity and intricate nature of neutrophils in cancer, including the existence of various subsets of neutrophils, has been steadily increasing.[3]

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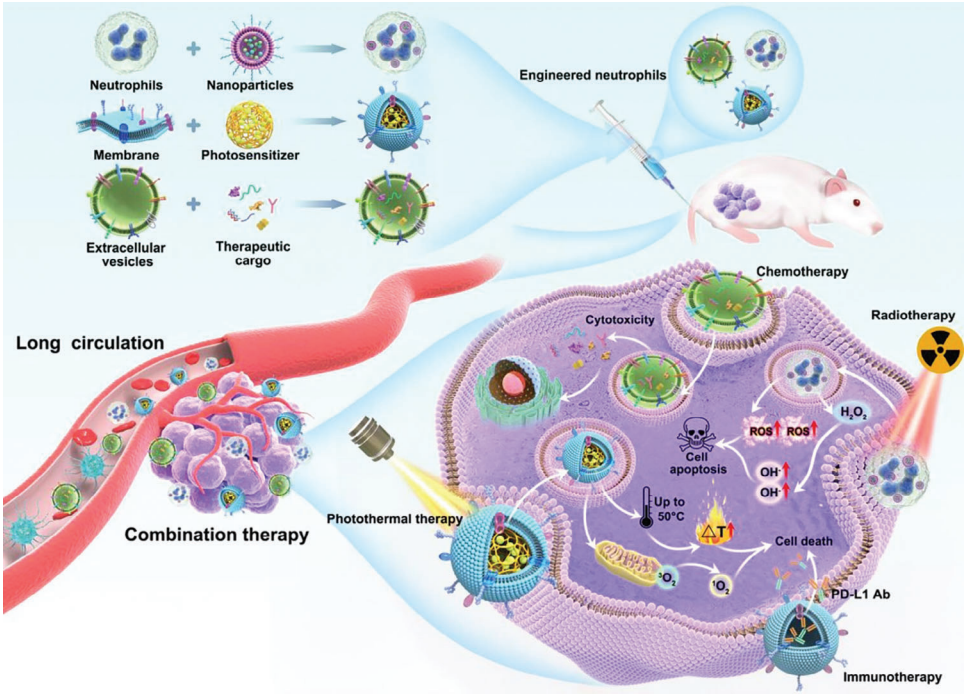

Figure 1. Engineered neutrophils and their derivates as natural carriers for drug delivery and cancer-targeted therapy. Neutrophils and their derivates (e.g., membranes and exosomes) are used to deliver drugs, nanomaterials, and various therapeutic molecules. The engineered neutrophils and their derivates have high stability in the circulation, inflammation responsiveness, blood vessel extravasation, tissue penetration, tumor-targeting and controllable drug release abilities, significantly improving the effectiveness of cancer therapy. The image was generated by using the Blender software.

Growing evidence suggests that neutrophils have diverse phenotypes and multifaceted roles in cancer. At present, a classification of tumor-associated neutrophils (TANs) into anti-tumor N1 and pro-tumor N2 neutrophils has been established, in which N1 TANs are characterized by tumor cell-killing, anti-metastatic, and immunostimulatory activities while N2 TANs possess tumor-promoting, pro-metastatic, and immunosuppressive activities.[4] N1 TANs exert anti-tumor activities through the secretion of cytotoxic substances, activation of anti-tumor immune response, and antibody-dependent cytotoxicity effect (ADCC). N2 TANs promote tumor initiation, development and progression by inducing genotoxicity and malignant transformation, enhancing tumor cell proliferation and angiogenesis, releasing NETs, accelerating EMT, remodeling extracellular matrix and establishing pre-metastatic niche, and mediating immunosuppression. The recent development of single-cell sequencing (scRNA-seq) technology further leads to improved understanding of the phenotypic heterogeneity and functional plasticity of neutrophils in cancer.

Targeted modulation of the phenotype and function of neutrophils in the tumor microenvironment (TME) represents a new frontier of cancer therapy. For instance, in advanced and metastatic tumor models, targeting cancer-related granulocytosis and the recruitment of neutrophils into cancer and depleting neutrophils by specific antibodies and inhibitors, have achieved promising anti-cancer effects.[5] Alternatively, targeting the pro-tumor factors released by neutrophils through antibody blockade, pharmacological inhibition, and gene interference has also shown encouraging therapeutic results.[6] With the understanding of molecular mechanisms that control the pro-tumor polarization of neutrophils in cancer, the strategy of re-polarizing TANs from a pro-tumor to an anti-tumor state by direct systemic injection or NP-mediate delivery of drugs and inhibitors has been proposed. Furthermore, considering that natural neutrophils have potent anti-tumor activities, neutrophil-activating therapies have been recently developed and shown to eradicate multiple tumors in mice.

Given their natural inflammation-responsive and physical barrier-crossing abilities, together with their multifaceted roles in cancer development and progression, neutrophils have been demonstrated as potential anti-cancer drug delivery vehicles for cancer therapy.[7] Utilizing neutrophils as viable cellular carriers for drug delivery offers a way to address the obstacles associated with nanomaterials, such as low-stability and biocompatibility, as well as insufficient tissue penetration and tumor-targeting abilities.[8] The main procedure of using neutrophils to deliver nanotherapeutics includes: drug-loaded nanomaterials are incubated with ex vivo isolated neutrophils and re-infused into the body or directly injected to be taken up by circulating neutrophils in vivo, and then the nanodrug-laden neutrophils escape from immune clearance, migrate toward target tissues, penetrate through physiological barriers, and subsequently release the loaded drugs to be uptaken by tumor cells.[9] The augment of inflammatory response by combined therapies (e.g., chemotherapy, radiotherapy, and phototherapy) can further improve the chemotaxis and accumulation of nanodrug-laden neutrophils in tumors, which significantly enhances the therapeutic efficacy (**Figure 1**).

Table 1. The distinction between N1 and N2 neutrophils in cancer.

Parameter	N1 (anti-tumor)	N2 (pro-tumor)
Morphology	Mature, small, more lobulated and hypersegmented nucleus	Mature, large, more circular nucleus
Density on gradient centrifugation (blood only)	High-density fraction	Low-density fraction
Identification markers	Human: $CD66^+$ $CD16b^+$ $HLA\text{-}DR^+$	Human: CD66+$CD16b^+$
	Mouse: $Ly6G^+CD11b^+$	Mouse: $Ly6G^+CD11b^+$
Other phenotypic markers	CD54, CD86, OX40L, 4-1BBL, TNFα, ICAM-1, FAS	CCL2, CCL17, VEGF, MMP9, CXCR4, Arginase, PD-L1
Functional properties	↑Cytotoxicity, ↑Migratory capacity, ↑Phagocytosis, ↑Oxidative burst,	↓Cytotoxicity, ↓Migratory capacity, ↓Phagocytosis, ↓Oxidative burst,
	T cell activation	T cell suppression

The strategies of using neutrophil membrane-mimetics and neutrophil-derived extracellular vesicles (EVs) as new therapeutics and drug delivery systems have been recently proposed. Inherited from the source cells, neutrophil membranes preserve the expression of targeting ligands and "do not eat me" signal molecules on their surface. Thus, they can be used to coat the drug-loaded nanomaterials to improve their biocompatibility and stability and endow them with higher targeting ability.[10] Neutrophils derived EVs have been previously produced to load drugs and nanoparticles (NPs) for anti-inflammation therapy.[11] Recently, neutrophils-derived EVs have been used to load anticancer drugs for cancer treatment by using their inflammatory chemotaxis function and tissue penetration ability.[12] Our group has developed a strategy to generate massive neutrophil exosome-like nanovesicles (NNVs) as a new platform for anticancer drug loading and tumor-targeting therapy, which significantly improves the effectiveness of chemotherapy drug while reducing its systemic toxicity.[13]

In this review, we summarized the recent advances in engineering neutrophils for drug delivery and cancer-targeted therapy, with an emphasis on neutrophil-based living cell delivery system, neutrophil membrane-mimetic nanoplatforms, and neutrophil-derived EVs. We also discussed about the opportunities and challenges of targeting neutrophils in the TME for cancer therapy.

2. Neutrophils in Cancer: the Anti-Tumor and Pro-Tumor Paradigm

In the past two decades, growing studies suggest that neutrophils display many phenotypes and play varying roles in the context of cancer. Neutrophils possess distinctive polarization phenotypes, namely the anti-tumor (N1) and pro-tumor (N2) phenotypes, in response to specific stimuli originating from the TME.[4] Previous studies have defined the phenotypes of N1 and N2 neutrophils based on their morphology, density, cell surface marker, cytokine or chemokine expression, and functional properties (also summarized in **Table 1**). Neutrophils play a dual role in the processes of tumorigenesis, tumor development and progression, highlighting a paradigm shift in neutrophil function in cancer (**Table 2**).[4] For example, tumor necrosis factor α (TNFα) and reactive oxygen species (ROS) can be utilized by N1 neutrophils for tumor killing and by N2 neutrophils for T cell suppression, probably depending on distinct tumor stage.

The dynamic and sometimes contradictory role of neutrophils may be attributed to their different polarization state and the existence of distinct subsets in the TME. Previous studies have shown distinct sub-types of neutrophils that have specific pro-tumor and anti-tumor activities. For instance, Engblom et al. demonstrate that lung cancer-induced osteocalcin-expressing osteoblasts promote tumor growth by remotely supplying a subset of tumor-infiltrating $SiglecF^{high}$ neutrophils.[14] We have previously identified a subset of $P2RX1^-$ neutrophils that promote pancreatic cancer liver metastasis.[15] The study from Wang et al. has discovered that a subset of PD-$L1^+$ TANs suppress T cell cytotoxicity to promote gastric cancer progression.[16]

Single-cell transcriptomics has revolutionized our understanding of neutrophil biology by unraveling the phenotypical heterogeneity and functional diversity of neutrophil subsets. Salcher et al. have provided the first high-resolution single-cell atlas that reveals the diversity and plasticity of tumor-resident neutrophils (TRN) in human NSCLC, which identifies TRN subpopulations with non-canonical functional properties.[17] Wang et al. have identified four sub-populations of TANs in human pancreatic ductal adenocarcinoma (PDAC) using scRNA-seq. Of which, a terminally differentiated pro-tumor subpopulation (TAN-1), featured with hyperactivated glycolytic activity, is associated with poor prognosis.[18] In a recent study by Gungabeesoon et al., they demonstrate that a specific subpopulation of neutrophils, characterized by a distinct $Sell^{hi}$ ($CD62L^{hi}$) phenotype with an interferon gene signature, acutely accumulates in tumors during successful immunotherapy and is associated with better treatment outcome.

2.1. Neutrophils and Their Anti-Tumor Potential

The anti-tumor potential of neutrophils is mainly attributed to their secretion of cytotoxic substances and anti-tumor immune response activation (**Figure 2**). Preliminary studies suggest that neutrophils derived from healthy donors have significant and targeted cytotoxic effects on cancer cells both in vitro and in vivo.[19] Early study also suggests that radiation therapy (RT) induces sterile inflammation with a rapid and transient infiltration of neutrophils into the tumors. RT-recruited TANs exhibit an increased production of ROS and induced apoptosis of tumor cells.[20]

Moreover, neutrophils entrapped in the metastatic niche have been found to suppress the metastatic potential of tumor cells through the generation of hydrogen peroxide (H_2O_2) and cell

Table 2. Neutrophils and tumor progression: a contrast of anti-tumor and pro-tumor potential.

Activity	Mechanism	Function	Tumor types	Refs
Anti-tumor	Generation of H_2O_2 and cell contact	Suppress the metastatic potential of tumor cells	Breast cancer	[21]
	HGF/MET-dependent nitric oxide release	Exert cancer cell killing effect	Melanoma and lung cancer	[22]
	Neutrophil elastase	Attenuate tumorigenesis	Breast cancer, melanoma, and lung cancer	[23]
	ROS production	Suppress tumor growth	Melanoma and lung cancer	[37]
	Debridement of hypoxic tumor cells	Oppose uterine epithelial carcinogenesis	PTEN-deficient uterine cancer	[24]
	Induce ferroptosis	Promote tumor cell necrosis	Glioblastoma	[25]
	Restrict the activities of bacteria	Reduce growth and invasion of cancer cells	Colorectal cancer	[26]
	Antibody-mediated trogocytosis	Destruct cancer cells	Melanoma	[28]
	ROS production via C5a/C5aR1/LTB4/XO signaling	Induce tumor cell death by oxidative damage and ADCC	Melanoma	[29]
	Display APC phenotype	Activate T cell response	Head and neck cancer	[32]
	Stimulate T cell activation and IFN-γ release	Initiate anti-tumor response	Human early-stage lung cancer	[30]
	Exhibit both neutrophils and APCs characteristics	Cross present tumor antigens and stimulate the anti-tumor T cell responses	Human stage I/II lung cancer	[31]
	Amplify the production of IL-12 by macrophages	Promote the polarization of $UTC_{\alpha\beta}$ cells	Sarcomas	[34]
Pro-tumor	Release of ROS and inflammatory factors (such as IL-1β)	Induce DNA damage and promote inflammation-associated carcinogenesis	Lung cancer, hepatocellular carcinoma, and colitis-associated cancer	[40]
	Production of neutrophil elastase, PGE2, and transferrin	Promote tumor cell proliferation	Lung cancer, breast cancer	[41–43]
	Release of neutrophil elastase and FGF2	Enhance tumor cell migration and invasion	Pancreatic cancer, colorectal cancer	[45,46]
	Release of iNOS, IL-1β, and MMPs to suppress T cell and NK cell activity	Establishment of pre-metastatic niche	Breast cancer, melanoma	[47,48]
	Release of MMP 9, VEGF, and OSM	Favor tumor angiogenesis	Prostate cancer, esophageal carcinoma, and breast cancer	[49–51]
	Production of CCL2 and CCL17, Arg-1, MMP9, and expression of PD-L1	Inhibit T cell activity	Hepatocellular carcinoma, gastric cancer	[16,53,54]
	Release of NETs (integrin $\alpha V\beta 1$ and MMP9)	Induce therapy resistance	Bladder cancer, breast cancer	[59,63]
	Formation of CTC-neutrophil clusters	Escort CTCs and promote cell cycle progression	Breast cancer	[62,65]
	NET-associated proteases (neutrophil elastase and MMP9)	Awake dormant tumor cells	Breast cancer	[66]

contact.[21] Neutrophil-derived H_2O_2 induces a Ca^{2+} influx into tumor cells to kill them effectively, which is mediated by TRPM2, a H_2O_2-sensitive Ca^{2+}-permeable channel. The HGF/MET signaling pathway appears to play a pivotal role in facilitating the release of nitric oxide (NO) from neutrophils, thereby exerting a cytotoxic effect on cancer cells.[22] A recent study indicates that neutrophil elastase (NE) functions as a selective agent in the eradication of cancer cells, thereby mitigating tumorigenesis through the precise cleavage of CD95 (also known as Fas).[23]

The results from spontaneous mouse cancer models suggest that neutrophils may serve as safeguards to eliminate cancer cells at a very early stage of tumor development and progression. For instance, hypoxia-induced inflammation in early-stage uterine tumors recruits neutrophils to slow tumor growth and progression by promoting the detachment of tumor cells from the basement membrane.[24] Furthermore, neutrophils facilitate the iron-mediated aggregation of lipid peroxides within glioblastoma cells by transference of granules laden with myeloperoxidase (MPO) into neoplastic cells, thereby fostering cellular necrosis.[25] Intriguingly, neutrophils have been reported to inhibit colorectal cancer (CRC) growth and progression by restricting the expansion of bacteria and mitigating tumor-associated inflammatory responses.[26] These findings indicate that native neutrophils have anti-neoplastic roles via a spectrum of mechanisms and suggest the potential of neutrophils for cancer therapy.

Neutrophils have been long regarded as the primary effector cells for antibody-dependent cellular cytotoxicity (ADCC). Neutrophils are necessary and sufficient for anti-tumor IgG

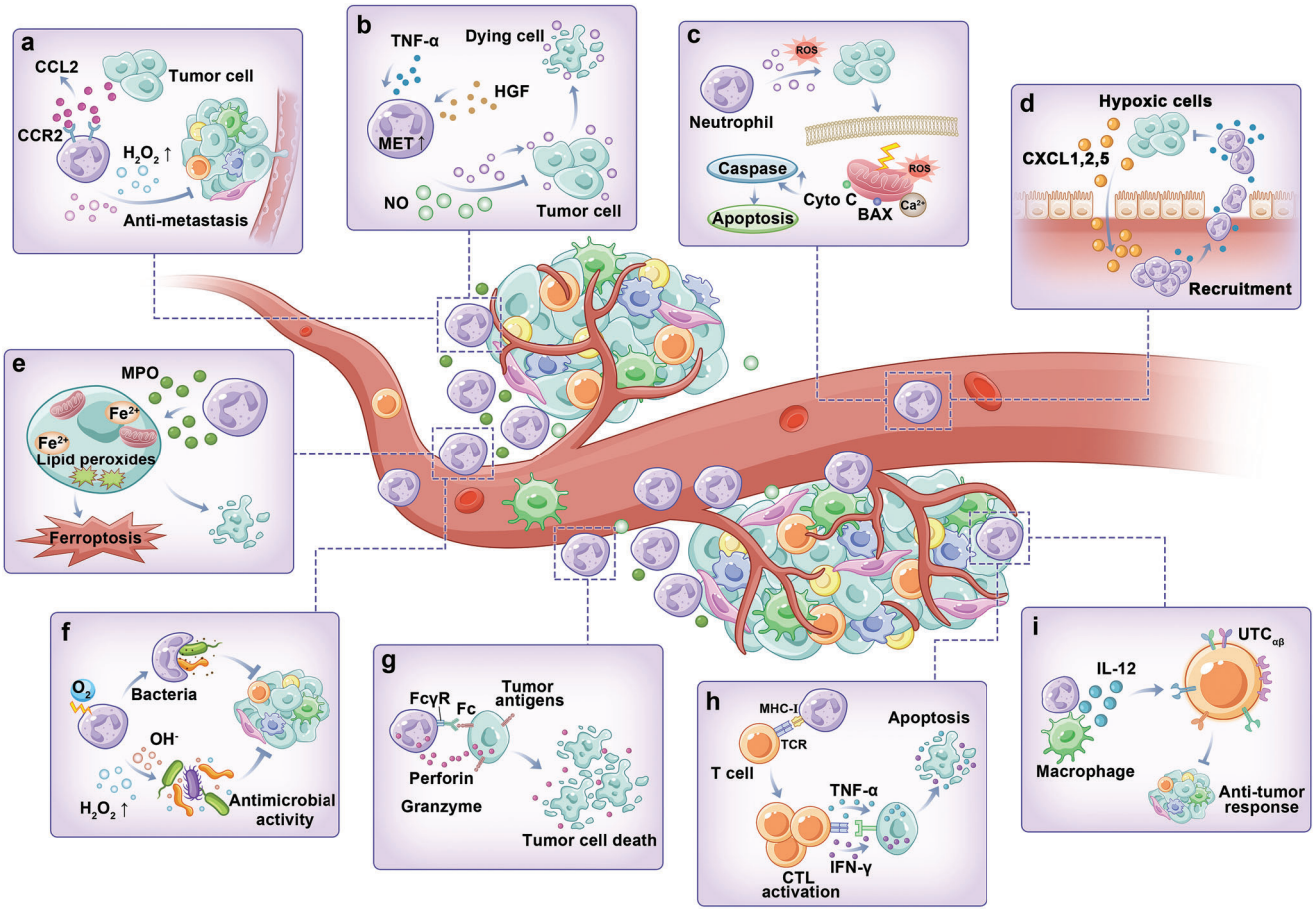

Figure 2. Anti-tumor potential of neutrophils. Neutrophils exert anti-tumor activities through various mechanisms. a) Neutrophils suppress the metastatic potential of tumor cells via generation of hydrogen peroxide (H_2O_2). b) Neutrophils kill cancer cells by releasing nitric oxide dependent on HGF/MET signaling pathway. c) Neutrophils inhibit tumor growth via reactive oxygen species (ROS) production. d) Hypoxia-induced inflammation recruits neutrophils to induce the detachment of tumor cells from basement membrane. e) Neutrophils release myeloperoxidase (MPO) into tumor cells and induce intracellular lipid peroxidation and necrosis. f) Neutrophils restrict the expansion of bacteria and relieve tumor-associated inflammation. g) Neutrophils destruct tumor cells through antibody-dependent cell-mediated cytotoxicity. h) Neutrophils stimulate T cell activation and IFN-γ release to initiate anti-tumor response. i) Neutrophils amplify the production of IL-12 by macrophages, which in turn promotes the polarization of $UTC_{\alpha\beta}$ cells. The image was generated by using the Blender software.

mAb therapy of subcutaneous syngeneic or xenograft tumors in mice through the Syk (spleen tyrosine kinase)-dependent Fcγ-R induced killing.[27] Neutrophils destroy cancer cells through antibody-mediated trogocytosis, which can be potentiated by CD47-SIRPα checkpoint blockade.[28] The recent study from Linda et al. shows that the synergistic intratumoral administration of tumor necrosis factor (TNF), anti-CD40, and anti-neoplastic antibodies facilitates a therapeutic activation of neutrophils. These therapeutically activated neutrophils eradicate multiple tumors and reduce metastatic seeding independent of T cell immunity.[29] This therapy directs neutrophils to tumors through TNF/TNFR1 signaling, initiating C5a generation. Subsequently, C5a triggers neutrophils to produce leukotriene B4, which enhances xanthine oxidase (XO) activity to catalyze the production of ROS, leading to oxidative damage and death in tumor cells. Moreover, the anti-neoplastic antibody activates neutrophils to kill tumor cells by ADCC. By using a similar strategy (TNF+anti-CD40+anti-EGFR), this therapy also activates human neutrophils to kill lung cancer cells.

The crosstalk between neutrophils and T cells in anti-tumor immunity has been widely revealed. A pioneering study from Eruslanov et al. demonstrates that TANs are able to stimulate T cell proliferation and IFN-γ release in early-stage human lung cancer.[30] The cross-talk between TANs and activated T cells facilitates a notable enhancement in the expression of costimulatory molecules on neutrophil surfaces. This interaction augments T cell responses, establishing a positive feedback loop. In addition, a subset of TANs with a hybrid phenotype of both granulocyte and antigen presenting cells (APCs) accumulate in early lung cancer tissues, which are capable of stimulating the anti-tumor T cell responses.[31] The generation of hybrid neutrophils is mediated by tumor-derived IFN-γ and granulocyte-macrophage colony-stimulating factor(GM-CSF) and negatively regulated by a neutrophil differentiation transcription factor Ikaros. In consistent, in the early phase of cancer, neutrophils migrate to tumor-draining lymph nodes, instigating an anti-cancer T cell response.[32] Intriguingly, FcγR-mediated endocytosis facilitates the transition of neutrophils into APCs, thereby inducing $CD8^+$

T cell-dependent anti-tumor immunity in murine models.[33] Furthermore, TANs enhance IL-12 secretion by macrophages in certain human tumors, consequently steering a segment of unconventional $\alpha\beta$ T cells (UTC$\alpha\beta$) toward a type 1 polarization. This subset of cells exhibits an innate-like phenotype, demonstrating significant anti-tumor potential in vivo.[34]

Recently, Gungabeesoon et al. reveal that therapy-elicited neutrophil response in patients is associated with better outcome. They suggest that during successful immunotherapy, neutrophils accumulate in tumors, show a *Sell*^{hi} state, and acquire an IFN-stimulated gene signature under the control of interferon-responsive transcription factor IRF1. This therapy-induced neutrophil population is also seen in human patients, and seems essential for successful immunotherapy.[35] More importantly, systemic neutrophil response in lung cancer patients is associated with better outcome following immunotherapy.[35] In consistent with this, Hirschhorn et al. demonstrate that neutrophils are essential for the eradication of antigenically heterogeneous tumors by T cell immunotherapies, in which T cells mediate the initial anti-tumor immune response and neutrophils mediate the destruction of tumor antigen loss variants.[36]

Intriguingly, the anti-tumor activities of neutrophils can be enhanced by the activation of cell-autonomous signaling. For instance, β-glucan-mediated trained innate immunity fosters an anti-tumor phenotype in neutrophils, inhibiting tumor growth through ROS production.[37] The recent study from Roy *et al.* has illustrated that the potentiation of IL-36 signaling in neutrophils not only enhances tumor cell cytotoxicity, but also augments the responses of other immune cells, such as T and NK cells.[38] Consequently, a deeper understanding of the anti-tumor activities of neutrophils and the underlying mechanisms could pave the way for innovative avenues in cancer therapy.

2.2. Neutrophils and the Pro-Tumor Potential

Despite their natural anti-tumor capacity, cancers co-opt neutrophils to participate in tumor initiation, development, and progression (**Figure 3**). Numerous investigations demonstrate that neutrophils play a significant role in multiple processes of tumor.[2a,6b,39] The earliest and direct evidence comes from animal studies showing that neutrophil depletion by a specific antibody suppresses inflammation-associated carcinogenesis such as lung cancer, CRC, and hepatocellular carcinoma (HCC).[40] The infiltration of a high amount of neutrophils in tissues leads to DNA damage in epithelial cells by releasing toxic substances such as ROS, which drives the malignant transformation of inflammation to cancer.[40b]

N2 TANs promote tumorigenesis, tumor growth and metastasis, angiogenesis, therapy resistance and relapse, and immunosuppression via distinct mechanisms. Neutrophils secrete many proteinases and inflammatory factors to enhance the proliferating ability of tumor cells. For instance, in mouse lung cancer models, NE, a neutrophil-specific serine proteinase, promotes the degradation of IRS (insulin receptor substrate) in lung cancer cells, which thus increases the interaction between PI3K and PDGFR (platelet-derived growth factor receptor), promoting lung cancer cell proliferation.[41] Similarly, PGE2 (prostaglandin E2) from neutrophils also enhances the proliferating ability of lung cancer cells.[42] Moreover, GM-CSF from tumor cells induces transferrin expression in neutrophils through the activation of the STAT5 pathway, which acts through TfR1 to stimulate tumor cell growth.[43]

In addition to favor tumor growth, N2 TANs contribute to tumor metastasis via distinct manners: (1) producing pro-metastatic proteins such as IL-1β and OSM; (2) inducing EMT of tumor cells; (3) escorting tumor cells to the metastatic site; (4) mediating tumor angiogenesis and remodeling extracellular matrix (ECM); (5) releasing NETs to accelerate metastatic seeding; and (6) inhibiting immune surveillance.

Neutrophils enhance the migration and invasion of tumor cells and participate in forming pre-metastatic niche. For instance, the increased neutrophil infiltration and loss of epithelial E-cadherin expression are observed in tumor tissues.[44] Neutrophils release elastase to reduce E-cadherin expression in pancreatic cancer cells, thus promoting their migration and invasion.[45] Tumor-conditioned neutrophils produce a high level of fibroblast growth factor 2 (FGF2) to support angiogenesis and the growth of hepatic metastases.[46] In breast cancer cells, the secretion of IL-1β instigates a cascade of immunological responses, initially activating $\gamma\delta$T cells to synthesize IL-17. This, in turn, facilitates the recruitment of neutrophils, a process mediated by the upregulation of granulocyte colony-stimulating factor (G-CSF) expression. Subsequently, these neutrophils discharge inducible nitric oxide synthase (iNOS). This mechanism dampens the functionality of CD8$^+$ T cells, thereby fostering the propensity for lung metastasis of breast cancer cells.[47] Moreover, neutrophils exert an inhibitory effect on NK cells, a phenomenon that augments vascular extravasation and tumor metastasis, further exacerbating the disease progression.[48]

Tumor angiogenesis provides favorable conditions for tumor growth and metastasis; Neutrophils play a crucial role in this process. Neutrophils are found to be the primary source cells of matrix metallopeptidase 9 (MMP9), and the released MMP9 is in an activated form that can promote tumor angiogenesis.[49] In addition, elastase released by neutrophils promotes esophageal cancer cells to express vascular endothelial growth factor (VEGF).[50] Cancer cells excrete GM-CSF, facilitating the augmentation of oncostatin M (OSM) synthesis by neutrophils. This process sequentially escalates the expression of VEGF by breast cancer cells, thereby fostering angiogenesis.[51] Furthermore, a positive correlation has been identified between the infiltration of neutrophils and the formation of blood vessels within human tumor tissues. Notably, experimental tumor models have demonstrated that the curtailment of neutrophil chemotaxis toward the tumor locale markedly attenuates tumor angiogenesis, concurrently diminishing the vascular extravasation of tumor cells.

Neutrophils promote the malignant progression of tumor by mediating immunosuppression through complex interactions with other immune cells in the TME. Neutrophils inhibit the activation of T cells through the generation of arginase 1 (ARG1), ROS and NO.[39] Especially, N2 TAN possesses a similar activity to myeloid-derived suppressor cells (MDSCs) and releases ARG1, which is usually stored inactively in the extracellular granules of neutrophils and is activated upon release, to inhibit T cell proliferation by reducing extracellular arginine synthesis.[52] In addition, neutrophil-secreted MMP9 activates TGF-β-mediated T-cell suppression to promote CRC progression.[53] In human liver cancer,

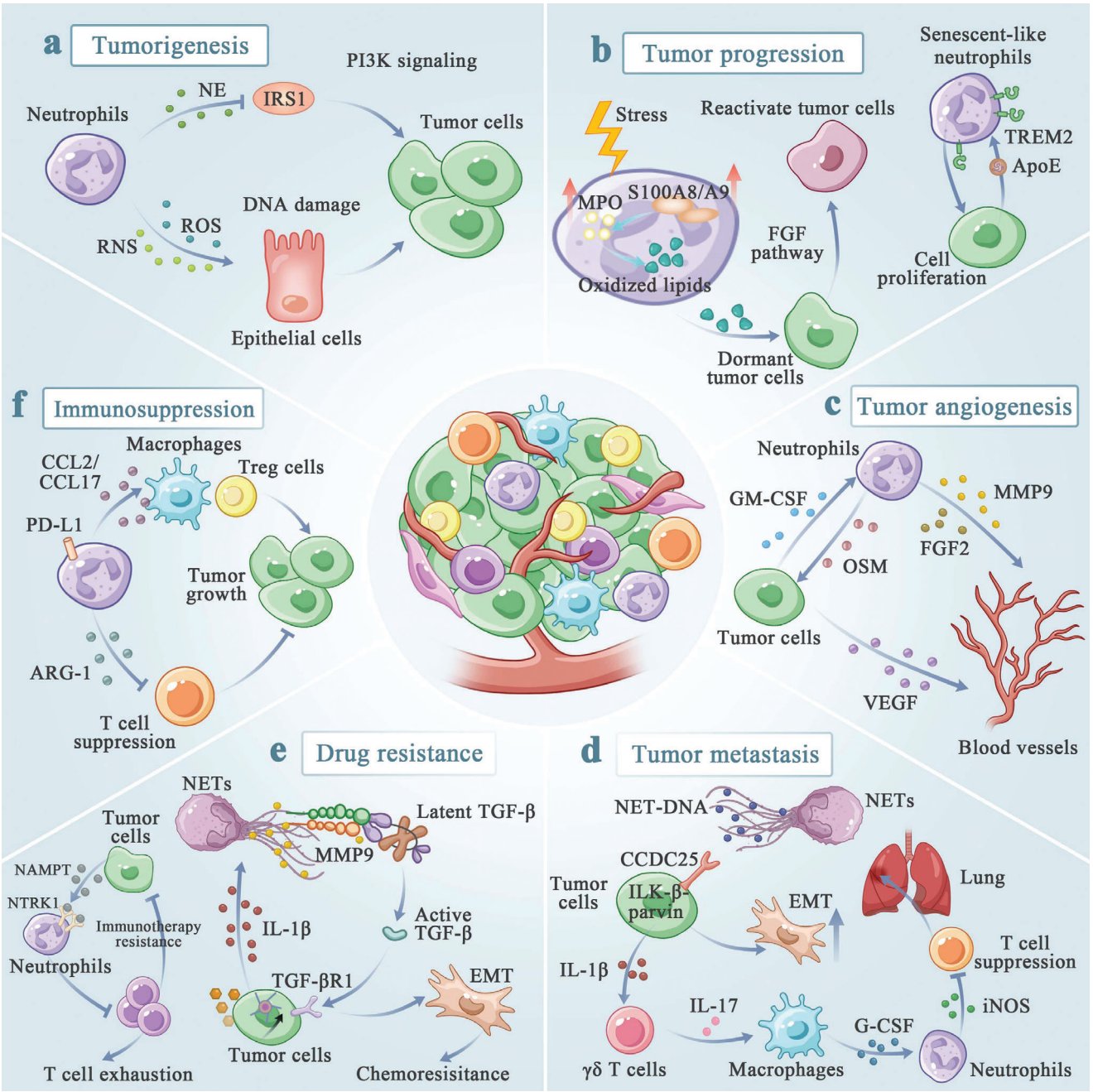

Figure 3. Pro-tumor potential of neutrophils. Neutrophils exert pro-tumor effects through several mechanisms. a) Neutrophils produce ROS to induce genotoxicity of epithelial cells and malignant transformation and support tumor cell proliferation by releasing NE. b) The pro-inflammatory S100A8/A9 proteins from neutrophils can induce activation of myeloperoxidase and release of oxidized lipids to accelerate tumor progression. Tumor cells derived ApoE induce neutrophil senescence, which in turn favors tumor cell proliferation. c) Neutrophils induce tumor angiogenesis by direct production of MMP9 and FGF2. Neutrophils can also favor tumor vessel formation by generating OSM, which activates STAT3 pathway in tumor cells and stimulates VEGF production. d) Neutrophils promote tumor metastasis via NET-DNA formation and iNOS-mediated T cell suppression. e) The neutrophil extracellular traps formed during chemotherapy are activated by TGF-β to confer therapeutic resistance. Neutrophils also induce T cell exhaustion and lead to resistance to immunotherapy. f) Neutrophils exert immunosuppressive effects by secreting arginase 1 (ARG1) to inhibit T cells or recruiting macrophages and Treg cells to the TME. The image was generated by using the Blender software.

neutrophils produce CCL2 and CCL17 to recruit macrophages and T-regulatory cells (Treg) cells to promote tumor growth and sorafenib resistance.[54] The increased infiltration of PD-L1$^+$ neutrophils in gastric cancer tissues is associated with poor patient outcomes, which may be attributed to their inhibition of T cell proliferation in a PD-L1/PD-1 axis-dependent manner.[16] Meng *et al.* have identified a specific CD10+ALPL+ neutrophil population in tumor tissue from HCC patients and confirmed that this population is closely associated with anti-PD-1 resistance. CD10+ALPL+ neutrophils exhibit immunosuppressive properties through the initiation of specific irreversible exhausted T cells in anti-PD-1 resistant patients.[55] Zhao et al. have compared tumor-infiltrating neutrophils (TINs) and circulating neutrophils in murine mammary tumor models using scRNA-seq and identified Acod1 (aconitate decarboxylase 1) as the most upregulated metabolic enzyme in mouse TINs and also validated high Acod1 expression in human TINs.[56] Acod1 produces itaconate to mediate Nrf2-dependent defense against ferroptosis and maintain the abundance of TINs, which ultimately promotes tumor metastasis by suppressing anti-tumor immunity.

The early study shows that neutrophils increase intraluminal survival of circulating tumor cells (CTCs) by inhibiting their clearance by NK cells and secret IL-1β and MMP9 to increase extravasation of CTCs. Recently, Gong et al. also demonstrate that tumor-associated inflammation reinforces the immunosuppressive activity of lung-infiltrating neutrophils toward T cells and NK cells, promoting breast cancer lung metastasis.[57] Neutrophils infiltrated in tumors significantly decrease the cytotoxicity and infiltration capability of NK cells. Neutrophils could recruit B cells to the TME and stimulate their differentiation to become functionally active, immunoglobulin-secreting plasma cells.[58]

Moreover, neutrophils have been linked to tumor therapy resistance, including chemotherapy, radiotherapy, immunotherapy, and anti-angiogenesis therapy. It has been reported that neutrophil levels correlate with outcomes in cervical cancer patients and antibody depletion of neutrophils increases radiation sensitivity in mice.[59] In addition, CRC refractory to anti-VEGF antibody therapy recruits neutrophils into tumor stroma to promote angiogenesis through the G-CSF/Bv8/Prokineticin 2 axis, leading to therapy failure.[60] In mouse pancreatic cancer, a gain-of-function mutation in p53 gene, R172H, upregulates CXCL12 to recruit neutrophils and reduces sensitivity to combined CD40 immunotherapy and chemotherapy.[61] By integrating high-resolution single-cell datasets of NSCLC, Salcher et al. demonstrate that TRN gene signature identifies patients with immunotherapy failure.[17]

NETs are network structures released by neutrophils when activated, containing DNA, MPO, histones, and granule proteins that capture and kill invading microorganisms. Accumulating studies reveal that NETs released by neutrophils are an important mechanism mediating metastatic growth and therapy resistance, and increased NETs formation in cancer patients is closely associated with reduced survival. Neutrophils release NETs to entrap tumor cells and increase their adhesion with hepatic sinusoids, thus promoting liver metastasis.[62] Chemotherapy promotes NETs formation in breast cancer lung metastasis, which activates TGF-β pathway and promotes EMT in cancer cells, leading to therapy resistance.[63] A recent study from Taifour et al. also demonstrate that breast cancer cell-derived Chi3l1 induces neutrophil recruitment and NETs release, which blocks T cell infiltration into the tumor.[64]

CTCs have been identified as a pivotal factor in the facilitation of cancer metastasis and recurrence. Neutrophils interact with CTCs within the bloodstream to drive cell cycle progression and improve metastatic potential.[65] Surprisingly, neutrophils, when stimulated by persistent inflammation, possess the capability to reactivate dormant cancer cells through NETs. This reactivation is facilitated by two NET-associated proteases: NE and MMP9, which instigate the proliferation of dormant cancer cells by modulating the extracellular matrix.[66] Furthermore, the transmembrane protein CCDC25 functions as a NET-DNA receptor on cancer cells, detecting extracellular DNA and consequently activating the ILK-β-parvin pathway, thereby augmenting cell motility.[67]

A more recent study demonstrates that a subset of neutrophils in the TME display a senescent phenotype, which is mechanistically associated with apolipoprotein E secreted by tumor cells and TREM2 (triggering receptor expressed on myeloid cells) on neutrophils. Senescent-like neutrophils are more immunosuppressive and tumor-promoting than their canonical counterparts.[68] In summary, the important role of neutrophils in tumors suggests that targeting neutrophils may have potential therapeutic value.

3. Neutrophil-Based Drug Delivery Systems

Using host cells as Trojan horses to deliver nanodrugs to tumors is a promising approach in cancer therapy. The potential of neutrophils and their derivates as drug-delivery vehicles for cancer therapy has recently gained considerable attention.[69] Neutrophils can release the payloads in response to inflammation, making them an ideal drug carrier for enhancing the delivery of therapeutic cargos in inflammatory diseases.[70] In this section, three main strategies that utilize neutrophils as drug-delivery vehicles are discussed: 1) neutrophils as living cell drug delivery systems; 2) neutrophil membrane-coated NPs as drug-delivery vehicles; and 3) neutrophils-derived EVs as drug delivery platforms (**Figure 4**).

As the most abundant innate immune cells in human circulation, neutrophils have many advantages compared to other immune cells, such as large quantity, convenient extraction procedure, rapid response to inflammation, and versatile biological activities.[71] Taking use of neutrophils and their derivates as drug delivery vehicles represent a main filed of the application of neutrophils in nanomedicine-based tumor therapy. The use of circulating neutrophils (a hitchhiking strategy) for targeted drug delivery has been widely proposed as they can penetrate through biological barriers and accumulate in large numbers at inflammation sites and tumors. Neutrophil-based delivery system transports drug-loaded liposomes/NPs) (either entrapped in neutrophils or attached to the surface of neutrophils) to tumors following an inflammatory chemokine gradient, which enhances the specificity, efficacy, and safety of chemotherapy, photodynamic/photothermal therapy, and immunotherapy as well as achieves combination therapy and theranostics.

Inspired by biomimetic technology, neutrophil membranes (or hybrid membrane) are produced to camouflage drug-loaded NPs and endow them with new activities such as prolonged blood circulation, targeted tumor delivery and preferential accumulation,

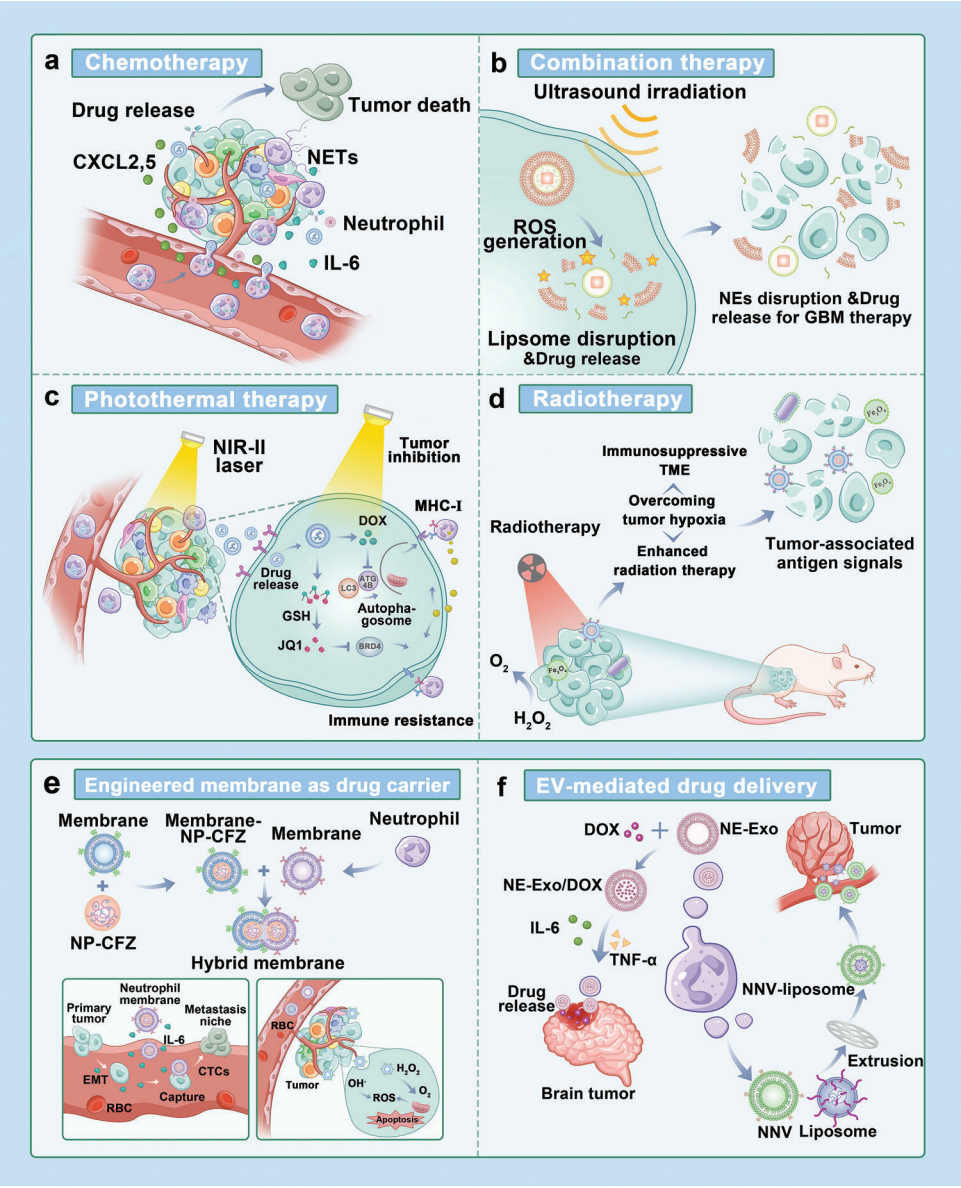

Figure 4. Neutrophil-based drug delivery systems. a) Chemotherapy: Drug-loaded neutrophils migrate toward local tumor sites and exert higher tumor inhibition effects. b) Sonodynamic therapy: neutrophil-loaded acoustic sensitizers overcome elimination from blood circulation and enhance their sonodynamic therapy effect on deep tumors. c) Photothermal therapy: neutrophil-delivered photosensitizers in tumor site generate hyperthermia upon NIR laser irradiation, leading to anti-tumor immune response. d) Radiotherapy: after injection of nanoparticle-loaded neutrophils, radiation induces the immunogenic death of tumor cells and releases a large number of tumor-related antigens. e) Illustration of neutrophil membrane-coated nanomaterials as drug carriers for cancer therapy. Coating with neutrophil membranes or hybrid membranes efficiently enhances the penetration of nanomaterials across microvascular endothelium and elicits long-term therapeutic efficacy in cancer. f) EVs derived from neutrophils could exert a direct anti-tumor effect and deliver chemotherapeutic drugs (such as DOX) into tumor. The image was generated by using the Blender software.

excellent cellular internalization, thus achieving enhanced tumor therapy effect. More recently, neutrophils derived EVs have been utilized as a unique drug delivery platform for tumor therapy.

3.1. Neutrophils as Living Cell Drug Delivery Systems

Many types of cells, such as red blood cells (RBCs), cancer cells and macrophages have been utilized as potential drug delivery systems. RBCs can significantly improve nanomaterials' biocompatibility and half-life in vivo but do not have active tumor-targeting ability. Macrophages mainly depend on antigen homing affinity and immunocompatibility, whereas cancer cell-mediated drug delivery targets cancer cells through homolytic binding but has a certain tumorigenic risk. A neutrophil-based drug delivery system is more versatile than these drug carriers. They circulate in the blood stream like RBCs and macrophages and specifically target tumor sites through surface adhesion molecules. More

importantly, neutrophils have strong inflammatory responsiveness, which could be used to achieve tumor-targeting delivery by intrinsic or induced tumor-associated inflammation. The strategies of using both endogenous and exogenous neutrophils to deliver drugs to tumors have been widely tested.

3.1.1. Neutrophils as Chemotherapy Drug Delivery Vesicles

Neutrophil-based delivery system can transport drug-loaded nanomaterials to target inflamed tissue following an inflammatory chemokine gradient.[72] Previous studies suggest that neutrophils loaded with photocatalytic NPs (Fe_3O_4@TiO_2) could reduce bacterial infection by releasing ROS and activating the immune system.[73] Neutrophils have also been powered with urease catalysis micromotor as a nanodrug delivery system to promote thrombolysis and suppress thrombosis.[74] Naumenko et al. demonstrate that neutrophil-mediated transport is crucial for delivering short-circulating magnetic NPs to tumors.[69a] The accumulation of NPs in tumors dramatically reduces when neutrophils are depleted by anti-Ly6G antibody, which further confirms neutrophils' role as biocarriers for tumor targeting. The work from the same group also shows that extravasating neutrophils opens the vascular barrier and improve liposome delivery to tumors.[75] Due to their tumor tropism, this nanoimmunotraining strategy suggests the possibility of using neutrophils as living cell drug delivery platforms for anti-cancer treatment.

Inspired by the enhanced therapeutic specificity and efficacy of cell-mediated drug-delivery systems, Xue et al. have used neutrophils to deliver liposomes containing paclitaxel (PTX). They demonstrate that neutrophils carrying liposomes/PTX efficiently suppress the recurrence of glioma in mice.[76] After surgical tumor resection, the high levels of inflammatory factors in the inflamed brain trigger the release of liposomal PTX from neutrophils and their entry into the residual tumor cells, leading to efficient impeded relapse and improved survival.

The use of circulating neutrophils (a hitchhiking strategy) for targeted drug delivery has been widely proposed as they can penetrate through biological barriers and accumulate in large numbers at the site of inflammation (and tumors).[77] For example, Ding *et al.* created sialic acid (SA)-stearic acid compounds to alter the surface of liposomal epirubicin (EPI-SL), enhancing uptake by circulating neutrophils and monocytes (N/Ms). In response to inflammatory cytokines secreted by TME, EPI-SL-containing N/Ms specifically target tumor and mediate tumor accumulation of liposomal epirubicin, which impedes even eradicates tumor growth in mice, suggesting that N/Ms-mediated delivery improves tumor-targeting efficiency and therapeutic efficacy of EPI.[78] In addition, Luo *et al.* have synthesized poly (sialic acid)-octadecylamine conjugate (PSA-ODA) and used it to decorate the surface of liposomal pixantrone (Pix-PSL). The Pix-PSL is taken-up by circulating neutrophils and then delivered to tumor sites guided by inflammatory microenvironment, showing a higher anti-tumor effect and lower systemic toxicity than liposomal pixantrone alone.[79] Similarly, neutrophil-mediated delivery of SA-modified liposomal DOX has also been proved effective for tumor therapy.[80]

Luo *et al.* have used neutrophils as drug delivery carriers for bone disease treatment, facilitating the crossing of bone marrow-blood barrier.[81] These neutrophils deliver drug-infused PLGA NPs, enhancing drug levels in the bone marrow. This method demonstrates notable tumor growth suppression in a bone metastasis cancer model, offering a promising avenue for targeted bone marrow drug delivery and efficient bone disorder treatment. Furthermore, Su *et al.* have designed paclitaxel nanocrystals (PTX NC) coated with anti-CD11b antibody (Ab) (Ab/PTX NC) to target activated neutrophils and transport Ab/PTX NC across tumor vasculature.[82] The neutrophil-targeted NPs delivery system can migrate to the TME under a photo-induced inflammatory response and display a stronger tumor inhibition compared to the control group (**Figure 5**).

High-intensity focused ultrasound (HIFU) is a new therapeutic tool for solid tumors, but its clinical benefit is hindered by local recurrence. To solve this problem, Shen et al. have used neutrophils as the carriers for PEGylated liposome doxorubicin (PLD@NEs) to achieve targeted therapy for residual tumors after HIFU ablation. In mouse hepatoma models, PLD@NEs efficiently migrate toward the residual tumor site as a result of HIFU-elicited inflammatory response and strongly suppress tumor regeneration that is observed in HIFU alone group, suggesting that the combination of HIFU with neutrophil-mediated nanodrug delivery may further improve their efficacy.[83]

Prior research indicates that Salmonella preferentially inhabits hypoxic tumor areas, demonstrating anti-tumor properties. Nevertheless, the presence of host neutrophils in the tumor hinders its effectiveness. Mi et al. developed a method involving sialic acid-coated silver nanoparticles (AgNPs) targeting neutrophils, migrating to tumors colonized by Salmonella through neutrophil infiltration. This approach enhances the anti-tumor potential of Salmonella by eliminating neutrophils, directly attacking tumor cells, and removing remaining Salmonella post full tumor elimination, thereby realizing a synergistic treatment outcome with increased biosafety.[84]

3.1.2. Neutrophils as Photodynamic/Photothermal Therapy Delivery Platforms

Photodynamic therapy (PDT) and photothermal therapy (PTT) utilize externally generated ROS from photosensitizers to eradicate tumor cells and foster anti-tumor immunity through the initiation of immunogenic cell death, which releases tumor-associated antigens. A promising avenue in cancer treatment is tumor-specific monoclonal antibody-based immunotherapy. Earlier research indicated that the TA99 monoclonal antibody, which targets the gp75 antigen in melanoma, facilitates anti-tumor responses by drawing neutrophils to the tumor site. Leveraging this characteristic, Chu and colleagues devised a method where neutrophils transport albumin NPs to tumors following TA99 antibody administration. In melanoma mouse models, they illustrated that the combined systemic delivery of pyropheophorbide a-loaded albumin NPs and TA99 notably augments NP tumor accumulation and amplifies PDT efficacy, significantly restraining tumor progression and extending the lifespan of the mice, compared to singular treatments with NPs or TA99.[85]

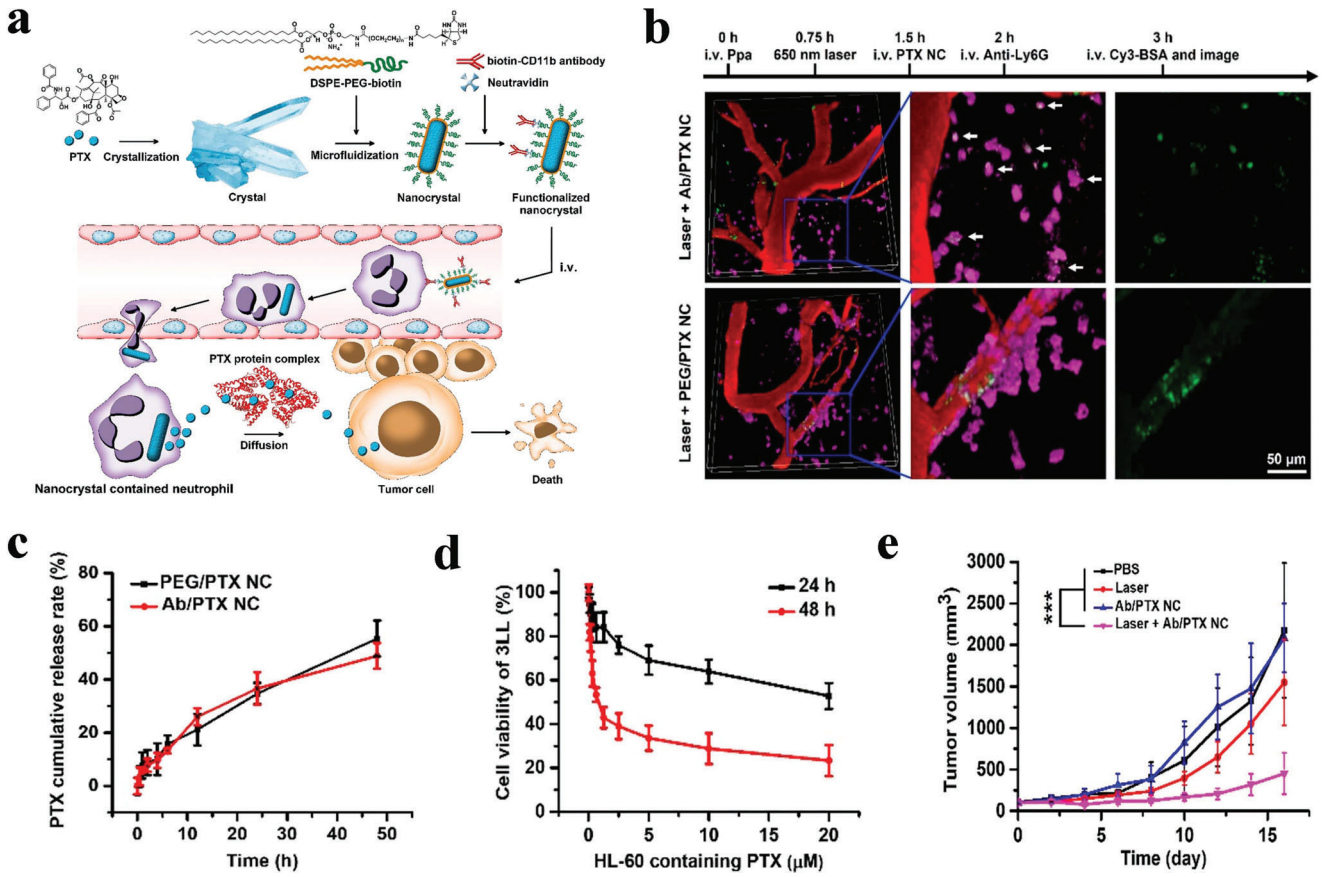

Figure 5. Neutrophil-mediated delivery of PTX nanocrystals for tumor therapy. a) Design of PTX nanocrystals (NC) for targeting activated neutrophils to enhance cancer therapies. b) Intravital images of neutrophils transport Ab/PTX NC. c) Drug release of Ab/PTX NC in PBS. d) Cell viability of 3LL cells treated with PTX NC. e) The tumor growth in a 3LL tumor mouse model (n = 6 mice/group). $^{*}P < 0.05$, $^{***}P < 0.01$ and $^{***}P < 0.001$ (One-way analysis of variance for multiple groups). Data are expressed as mean±SD. Abbreviations: PTX, paclitaxel; NC, nanocrystals; Ab, anti-CD11b antibody; PEG, poly(ethylene glycol). a-e) Reproduced with permission.[82] Copyright 2023, American Chemistry Society.

Remodeling TME by photosensitization activates neutrophil infiltration and enhances the delivery of NPs to tumor tissue. In another study, Chu et al. have prepared gold nanorods NPs decorated with anti-CD11b Abs (NPs-CD11b) and shown that neutrophils efficiently deliver NPs-CD11b to tumor sites, where tumor photosensitization and PDT of NPs-CD11b result in significant inhibition of tumor growth and increase of mouse survival, indicating that NPs loaded with antibodies can be delivered to tumor site via neutrophil infiltration to enhance cancer therapy.[86] Dong et al. have proposed another strategy to improve neutrophil tumor tropism by altering TME.[87] This strategy includes the construction of vaccine-like nano-CpG adjuvant and pre-immunization on mice, which mimics pathogen stimulation to achieve enhanced tumor-targeting of neutrophils, thus providing a simple and feasible approach for the delivery of nanomedicines.

To improve tumor accumulation of NPs, Ye et al. have designed a multistage neutrophil-based NP delivery system in which albumin-modified Au nanorods are conjugated with RGD (AuNRBR) followed by uptake by neutrophils (AuNRBR/N).[88] AuNRBR/N shows significantly stronger tumor-targeting ability than free AuNRBR in a mouse lung cancer model due to their recruitment by inflammatory signals in TME. The release of AuNRBR from neutrophils improves deep tissue penetration, which results in enhanced PDT and tumor growth inhibition.

To overcome the lack of ability to target subcellular locus (organelle) and improve the anti-cancer efficacy of cell-based drug delivery system, Xu et al. have generated "photoactive neutrophil" (PAN) by loading living neutrophils with multifunctional RA/Ce6 nanocomplex (RGD-apoptotic peptide conjugate decorated liposomal photosensitizer Ce6) which exhibits strong inflammation-amplified tumor-targeting ability for enhanced mitochondria-specific photo-chemotherapy.[89] In response to PDT-induced inflammation, PAN is actively recruited to tumor sites and releases RA/Ce6 into cancer cells, where they accumulate in mitochondria to trigger combined PDT and induce mitochondrial membrane disruption, resulting in enhanced and synergistic therapeutic effects. Therefore, PAN represents a neutrophil-based multistage targeted and mitochondria-specific combination therapy. Using a similar approach, Li *et al.* have engineered neutrophils to deliver the photosensitizer Ce6 and infused them into mouse breast cancer models, leading to more Ce6 accumulation in tumors than Ce6 nanoformulation. Upon illumination, the embedded Ce6 is activated to induce ROS generation and NET formation, leading to intensified cytolytic effect and significant tumor growth inhibition.[90]

3.1.3. Neutrophils as Delivery Vehicles for Combination Therapy

Neutrophil-based drug delivery systems can efficiently deliver therapeutic cargos to primary and metastatic tumors and achieve a combination therapy effect. PTT causes tumor ablation but is accompanied by an inflammatory effect, which recruits neutrophils to the tumor site. Given this property, Zhang et al. have explored PEGylated gold nanorods (PEG-GNRs) as the photothermal agent and paclitaxel-loaded neutrophils as the chemotherapeutic agent.[91] The combination of PTT and chemotherapy (with inflammation-mediated active targeting ability) significantly enhances anti-tumor efficacy and reduces systemic toxicity, which offers an encouraging synergistic approach for cancer-targeted treatment.

To improve the efficacy of standard chemo-radiotherapy and decrease their side effects, Ju et al. have developed a novel therapeutic strategy that combines cytopharmaceutical-based neoadjuvant chemotherapy with radiotherapy for effective cancer treatment, in which human peripheral blood neutrophils are designed to deliver Abraxane, the commercial albumin-bound paclitaxel NPs. As expected, the application of radiotherapy exerts tumor disruption. It induces the release of inflammatory factors that direct the chemotaxis of neutrophils to the tumor sites, where these factors activate Abraxane/NEs to form NETs and release Abraxane concomitantly to induce a superior inhibitory effect on tumor growth.[92] The Abraxane/human neutrophils cytopharmaceuticals-based neoadjuvant therapy can identify heightened signals generated by radiotherapy inflammation, selectively concentrate at the tumor location, and administer the nanodrug directly to the cancer cells, thereby facilitating targeted chemotherapy triggered by radiotherapy.

The mononuclear phagocyte system can hinder conventional nanovector-facilitated medication transport and obstructed by physiological barriers like vascular and interstitial barriers. To mitigate this issue, Li *et al*. suggested a method involving the utilization of nano-pathogenoids (NPNs) that mimic pathogens, leveraging circulating neutrophils to amplify the precision and effectiveness of drug delivery to tumor sites.[93] The NPN system is constructed using PEG-PLGA NPs to encapsulate photothermal transducer and cisplatin followed by coating with bacteria outer membrane vesicles (OMVs). Thus, NPNs can be effectively recognized and internalized by circulating neutrophils due to the inheriting pathogen-associated molecular patterns on OMVs. During PTT, neutrophils travel to the inflamed tumor location and swiftly discharge NPNs. These are then absorbed by tumor cells, facilitating anti-tumor actions. Remarkably, the combination of cisplatin-loaded NPNs with PTT nearly obliterated tumors in all the experimented mice, showcasing a potent nanoplatform for improved tumor-targeted delivery and collaborative anti-tumor impact through the utilization of circulating neutrophils.

Yu et al. developed a photothermal-induced tumor immunotherapy strategy using neutrophil-camouflaged stealth nanovehicles. The anti-CD11b- and IR820 (new indocyanine green)-conjugated albumin NPs are loaded with decitabine and injected in vivo systemically to achieve efficient tumor-targeting delivery by neutrophil hitchhiking. In a triple-negative breast cancer animal model, they demonstrate that the photothermal-controlled release of decitabine upregulates GSDME (gasdermin-E), and the laser irradiation activates caspase-3, which exerts pyroptosis to improve the host adaptive immune response and reduce in situ tumor recurrence after resection. In addition, this therapeutic strategy induces a strong and long-term immune memory to prevent lung metastasis.[94]

Using a similar strategy, Qiu et al. have employed PDT/PTT to enhance tumor infiltration of ibrutinib (IBR) NPs-delivered neutrophils for cancer immunotherapy. The injected DiR-loading liposomes initiate acute inflammation via PDT/PTT, and SA derivative-coated IRB-loading NPs are internalized by the activated circulating neutrophils and delivered into the tumor.[95] DiR-mediated PDT/PTT and IBR-mediated immunotherapy enhances anti-tumor T-cell immune responses and efficiently reduces tumor growth in a mouse orthotopic breast cancer model, indicating a synergistic anti-tumor effect for breast cancer therapy.

Recently, Hao et al. have prepared a new neutrophil cytopharmaceutical by conjugating liposomal STING (stimulator of interferon genes) agonists on the surface of neutrophils via click chemistry. By taking use of the tumor vascular extravasation and tissue penetration activities of neutrophils, the loaded liposomal STING agonists are released in response to hyaluronidase in the TME to be uptaken by tumor cells and infiltrating immune cells. In triple-negative breast cancer (TNBC) mouse models, the treatment effectively activates the STING pathway and potentiates antitumor immunity and thus sensitizes tumors to ICIs (immune checkpoint inhibitors), indicating that neutrophils are a versatlile vehicle for delivering STING agonists and neutrophil cytopharmaceutical may boost the therapeutic potential of ICIs (**Figure 6**).[96]

3.1.4. Chimeric Antigen Receptor-Modified Neutrophils as Drug Delivery Vehicles for Cancer Therapy

Owing to their short half-life and resistance to genetic alteration, neutrophils have not yet been manipulated with chimeric antigen receptors (CARs) like other immune cells to augment their immunotherapeutic potential. Interestingly, Chang et al. have successfully modified human pluripotent stem cells using synthetic CARs and distinguished them into efficient neutrophils through the application of a chemically distinct platform.[97] The resultant CAR neutrophils (CAR-Neu) demonstrate enhanced and targeted cytotoxicity against tumor cells, as observed in vitro and in vivo. Thus, massive production of CAR neutrophils may provide a new cancer treatment approach. Most recently, the same group has used the genetically engineered CAR-Neu to deliver hypoxia-targeting tirapazamine (TPZ)-loaded silica NPs (SiO_2 NPs). The systemically administered CAR-neutrophil@R-SiO_2-TPZ NPs initially target external normoxic tumor cells, establishing immunological synapses and initiating phagocytosis to destroy the tumor cells. Following apoptosis, CAR-Neu releases R-SiO_2-TPZ NPs, which are subsequently absorbed by tumor cells, reacting to the hypoxic TME to effectively eliminate them. This combined chemo-immunotherapy approach demonstrates enhanced and targeted anti-cancer efficacy in a GBM mouse model, suggesting that the biomimetic CAR-neutrophil drug delivery system serves as a secure, robust and adaptable platform for cancer therapy.[98]

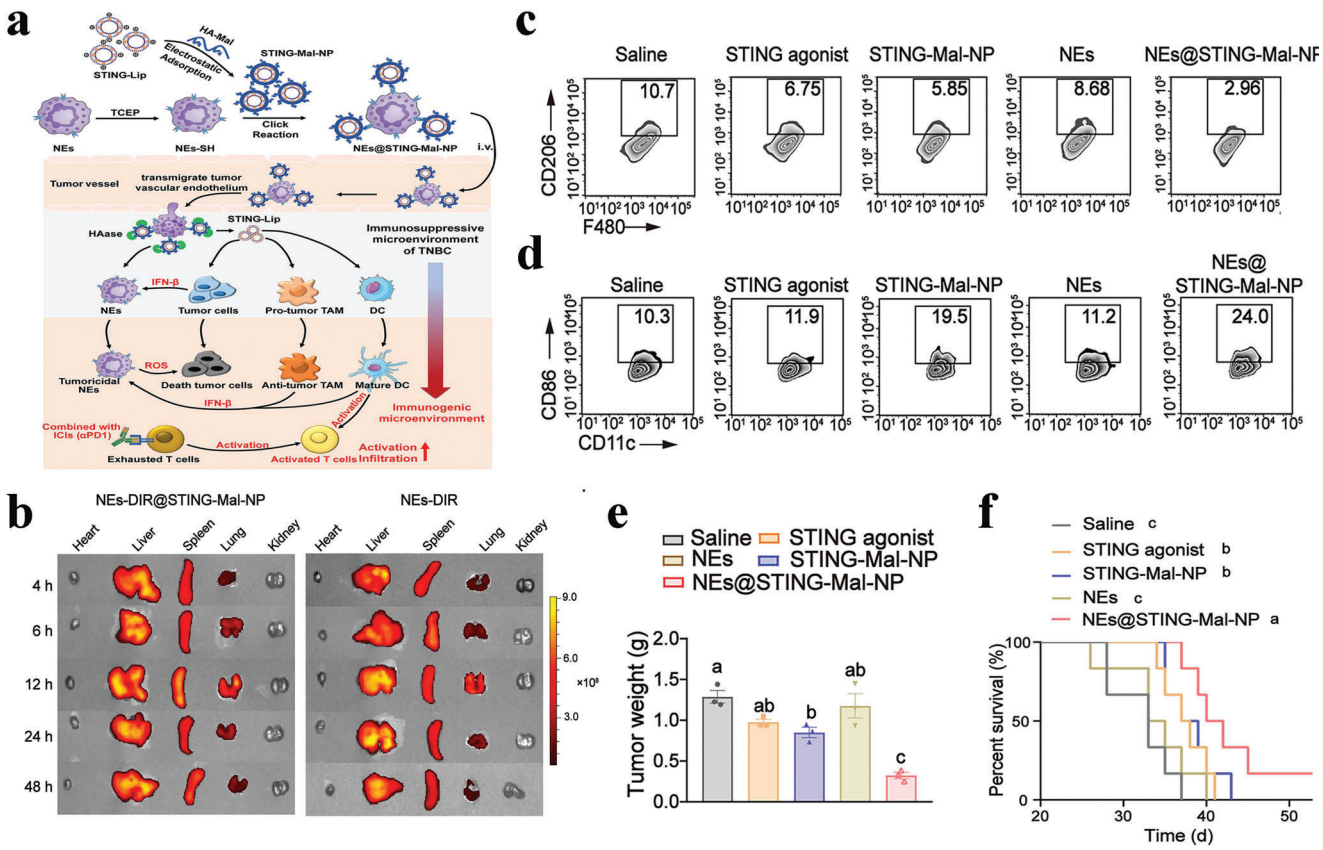

Figure 6. Tumor-penetrating NEs@STING-Mal-NP for immunotherapy. a) Schematic diagram of tumor-penetrating neutrophil cytopharmaceuticals (NEs@STING-Mal-NP). b) The biodistribution of NEs-DIR@STING-Mal-NP in 4T1-bearing mice. (n = 5 mice per group). c,d) Flow cytometry analysis of CD206 expression in TAMs and CD86 expression of DCs from orthotopic 4T1-bearing mice. (n = 3 mice per group). e) Tumor weights of mice receiving different treatments. (n = 3 mice/group). f) Survival curves of mice in each group. (n = 6 mice/group). Data were analyzed by one-way ANOVA with Turkey's correction (e) and a long-rank (Mantel-Cox) test (f). Data presented as means±error bars denote SEM. n.s denotes no significant difference. Statistically significant differences were indicated by "abcd", and there are no significant differences between groups marked with the same letter. Abbreviations: NEs, Neutrophils; STING, stimulator of interferon genes; Mal, maleimide; NP, Nanoparticle. a–f) Reproduced with permission.[96] Copyright 2023, American Chemistry Society.

3.1.5. Neutrophils as Cancer Theranostic Systems

The combination of disease diagnosis and monitoring with treatment by theranostic platforms is a new biomedical nanotechnology. To achieve cancer imaging and therapy simultaneously, Wu et al. have engineered neutrophils with doxorubicin (DOX)-loaded magnetic macroporous silica NPs (ND-MMSNs) for magnetic resonance imaging tracking and brain tumor-targeting drug delivery.[99] They demonstrate that after surgical resection of primary tumor, ND-MMSNs actively target inflamed brain, remarkably improve intratumoral drug concentration, and delay the relapse of surgically treated glioma. In addition, Wang et al. have fabricated indocyanine green (ICG)-loaded magnetic silica NIR-responsive NPs and loaded them on the endogenous neutrophils to form NP-neutrophil complex, which could achieve MRI tracking and dual tumor-targeting, significantly enhancing the killing effect of PTT without recurrence in tumor-bearing mouse models.[100] These studies suggest that the engineered neutrophils offer a new approach to targeted cancer theranostics using living cells as NP carriers.

Using neutrophils' ability to cross physical barriers and target tumor tissue, Li et al. have developed a neutrophil drug delivery system for ultrasound augmented chemo-immunotherapy in GBM. They have designed and synthesized novel NPs that are composed of a ZGO nanosensitizer core covered with hollow TiO_2 for persistent luminescence imaging, anti-PD-1 antibody for immunotherapy, paclitaxel-loaded and ROS-responsive liposome as outermost layer of the NPs for chemotherapy and antibody encapsulation. The acquired NPs are internalized by neutrophils for blood-brain barrier (BBB) targeted delivery.[101] (**Figure 7**). Intravenously injected NE-NPs are attracted by the inflammatory GBM microenvironment to penetrate the BBB. Then, ultrasound irradiation at primary tumor sites induces ROS generation to break up liposome coverage for PTX and anti-PD-1 antibody release to kill tumor and further recruits more NE-NPs to tumor sites by tempting local inflammation, greatly enhancing GBM therapy and suppressing tumor recurrence.

To produce multifunctional living cells for visual tumor diagnosis and therapy, Sun et al. have engineered neutrophils with customized liposomes to generate acoustic functional oxygen-carrying sonosensitizer cells (termed as Acouscyte/O_2).[102] They

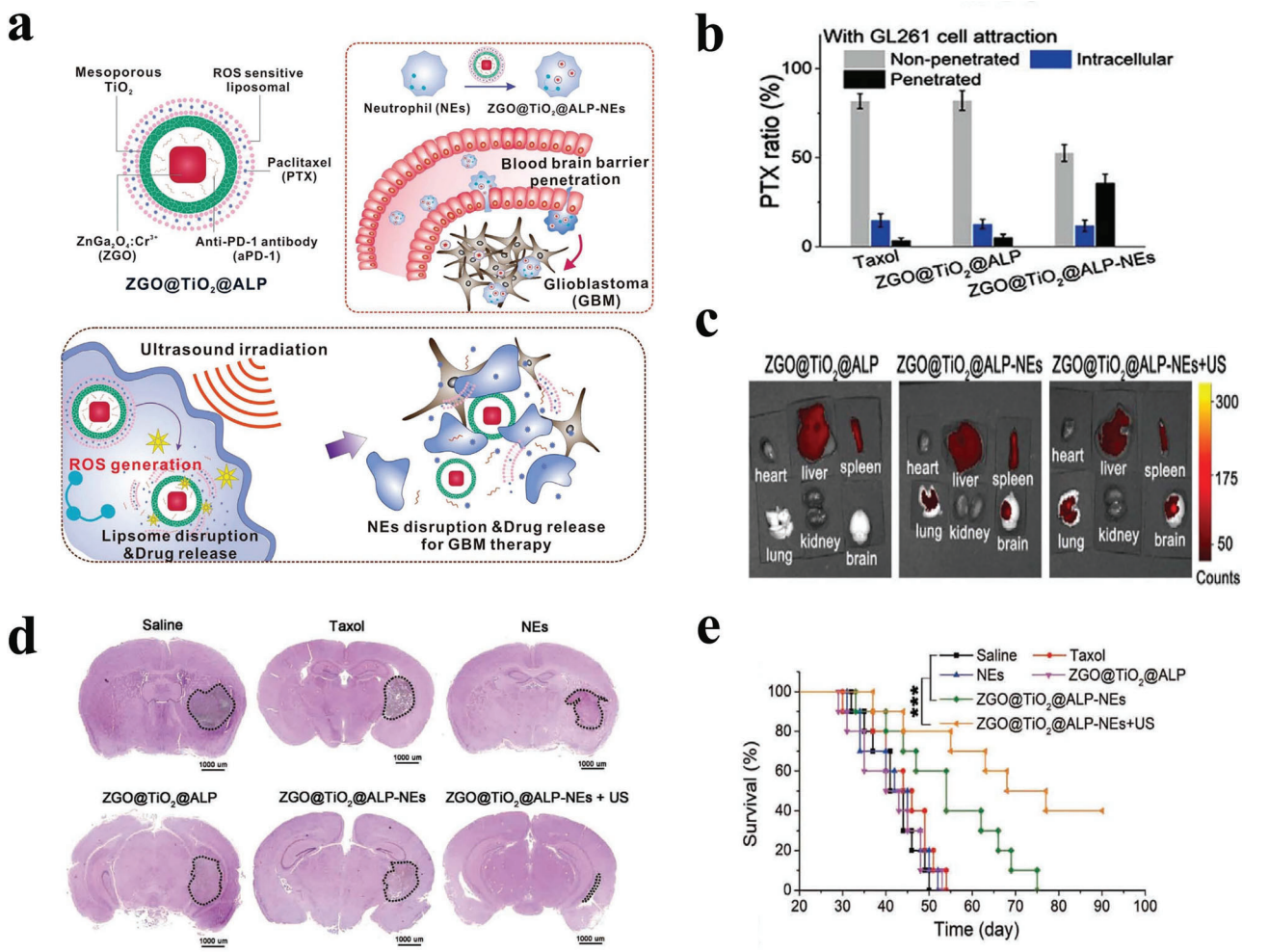

Figure 7. Neutrophil targetedly delivers nanosensitizer for ultrasound- augmented chemotherapy/immunotherapy of glioblastoma. a) Schematic illustration of nanosensitizer and their amplified chemo/immuno GBM therapy. b) PTX distribution in the transwell chamber after incubation with GL261 cells. (n = 4 independent experiments). One-way analysis of variance (ANOVA) for multiple groups. Data are given as mean±SD. c) Ex vivo luminescence images of major organs and brain of different groups at 24 h post i.v. injection. d) Histological analyses of brain tissues. e) Survival curves of mice with different treatments.Treatment group (n = 4) and control mice (n = 10). ***$P < 0.001$, **$P < 0.01$. Data are given as mean±SD. Abbreviations: GBM, Glioblastoma; ZGO, $ZnGa_2O_4:Cr^{3+}$; TiO_2, Titania; NEs, neutrophils; ALP, Anti-PD-1 antibody; US, Ultrasound. a–e) Reproduced with permission.[100] Copyright 2021, Wiley-VCH John Wiley & Sons.

have encapsulated oxygen-carried perfluorocarbon and temoporfin into cRGD peptide-modified multilayer liposomes and then loaded them into neutrophils. Acouscyte/O_2 selectively targets tumor to increase oxygen levels and trigger sonodynamic therapy in response to ultrasound stimulation, which results in complete tumor clearance and prolonged mouse survival time. In addition, the tumors can be real-time monitored by fluorescence and ultrasound imaging by perfluorocarbon and temoporfin. Therefore, acouscyte/O_2 represents a new engineered neutrophil-based theranostic platform with multiple advantages such as long circulation time, inflammation recruitment and tumor-targeting ability, high oxygen loading and controlled drug release, and simultaneous tumor imaging and therapy (**Figure 8**).

Yang and colleagues suggested a unified approach for realizing cancer theranostics by utilizing circulating neutrophils. Their research employed peptidoglycan multilayer networks of bacteria to transport AgAuSe quantum dots (QDs) by leveraging circulating neutrophils for targeting tumors. These constructed nanomaterials demonstrate notable stability, facilitating superior drug delivery and precise targeting, thereby enhancing drug imaging and augmenting therapeutic outcomes under NIR-II laser radiation.[103] Combined with sonodynamic therapy, this drug delivery system eliminates the established solid tumor without recurrence, indicating potential for circulating neutrophils as drug delivery vehicles for NIR-II fluorescent QDs and other theranostic nanomaterials.

3.2. Neutrophil Membrane-Mimetics as Drug Delivery Vehicles for Cancer Therapy

Cell membrane-layered functional NPs provide a biomimetic approach for targeted drug-delivery and have emerged as multifunctional nanocarriers for biomedical applications.[104] Cell

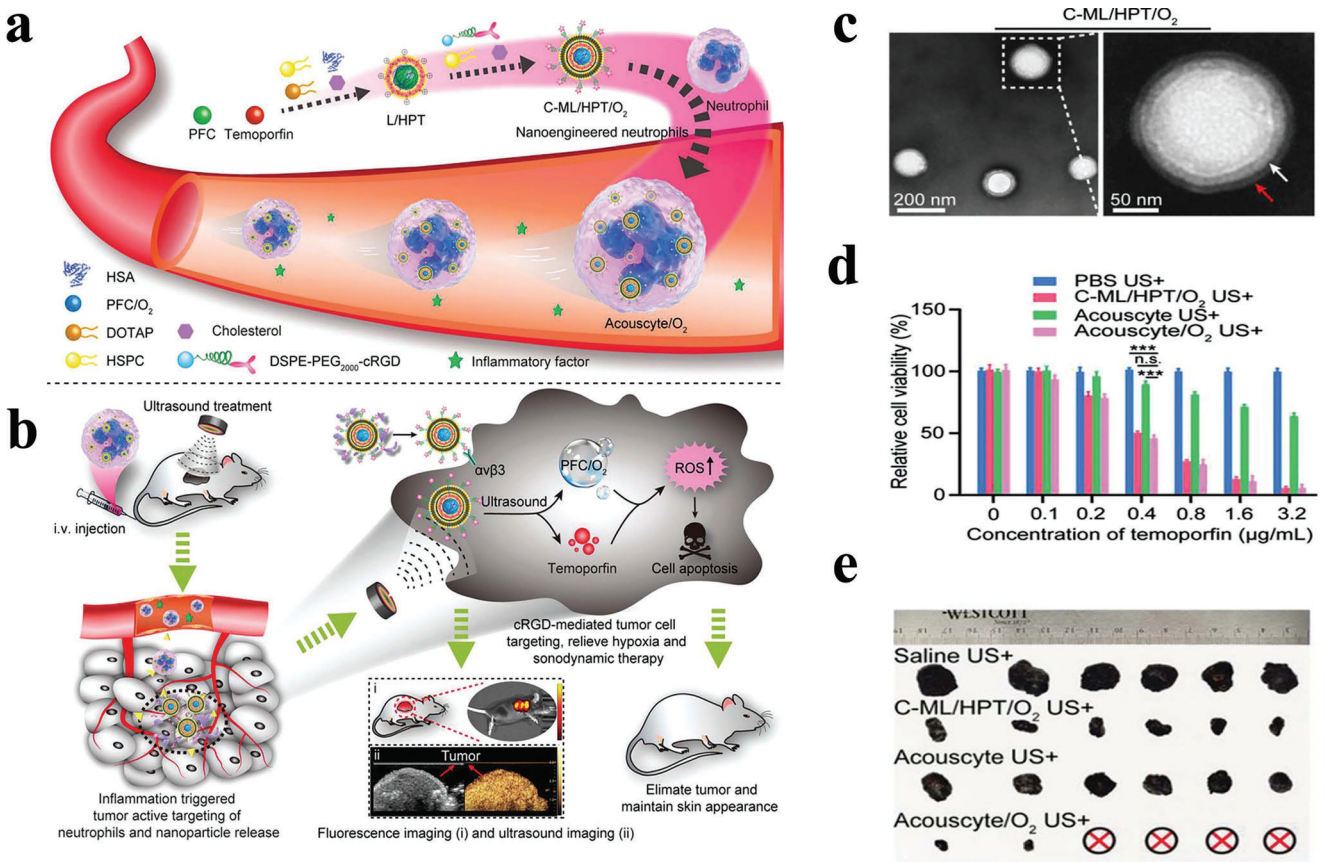

Figure 8. Nanoengineered neutrophils as cellular sonosensitizer for visual SDT of malignant tumors. a) Schematic illustration of oxygen-carrying and acoustical neutrophils (Acouscyte/O_2). b) Acouscyte/O_2 selectively accumulates in tumor tissues and efficiently transports oxygen and sonosensitizers to cancer cells. c) TEM images of C-ML/HPT/O_2. d) Cell viability of B16F10 cells with different treatments. (n = 6 independent experiments). n.s.: no significance; $^{**}P < 0.01$, $^{***}P < 0.001$ (over two groups of data were analyzed by one-way ANOVA analysis with Tukey's post-hoc test). Data were shown as mean±SD. e) Representative images of tumors after 21 d of different treatments (n = 6 mice per group). Abbreviations: SDT, sonodynamic therapy; Acouscyte/O_2, Oxygen-carrying and acoustical neutrophils; C-ML, cRGD modified multilayer liposomal; HPT, HSA-encapsulated perfluorocarbon and sonosensitizer temoporfin; US, Ultrasound. a–e) Reproduced with permission.[102] Copyright 2022, Wiley-VCH John Wiley & Sons.

membranes from different types of cells, such as cancer cells, platelets, RBCs, stem cells, and immune cells, are comparable both structurally and functionally to their parent cells and express those specific makers of host cells. For instance, cancer cell membranes stably express specific adhesion proteins, allowing homing to homologous tumor sites.[105] Cell membranes from RBCs and platelets highly express CD47 (an integral membrane protein), which helps evade immune clearance from the circulation. Inspired by biomimetic technology, neutrophil membrane-camouflaged nanomaterials inherit the advantages of neutrophils and NPs, which help prolong the blood circulation time and tumor-targeting ability of drug-laden NPs (**Table 3**).

A previous study by Zhang et al. has used human peripheral blood and mouse whole blood neutrophils to test the effect of neutrophil membrane-coated NPs on inhibiting synovial inflammation and alleviating joint damage in inflammatory arthritis. They reported that ≈125 million human neutrophils or 200 million mouse neutrophils were able to yield 1 mg membrane material (protein weight).[106] Recently, Yang et al. compared the yield of neutrophil membrane vesicles derived from mouse peripheral blood by using three different approaches (homogenization, hypotonic lysis, and repeated freeze-thaw). They found that the neutrophil membrane vesicles obtained by the homogenization method had the highest protein content and the largest number of cell membrane vesicles (≈2–3 folds higher than those produced by other two methods), probably as homogenization may disrupt the cells more completely.[107]

3.2.1. Neutrophil Membrane-Camouflaged NPs for Drug Delivery

Recently, immune cell membranes have been designed to endow new activities to synthetic NPs, including prolonged blood circulation, enhanced tissue targeting, better cellular interactions, controlled drug release, and reduced toxicity.[117] Neutrophil membrane-coated NPs have shown significant therapeutic efficacy in several inflammatory diseases such as sepsis, stroke, pneumonia, pancreatitis, and arthritis, and ischemia-reperfusion injury.[106,118] Based on the innate interaction between neutrophils and inflamed brain microvascular endothelial cells, Feng et al. have coated mesoporous Prussian blue nanozyme with neutrophil membrane to improve its delivery to

Table 3. Neutrophil membrane-coating strategy for cancer therapy.

Core-shell structure	Nanoparticle	Therapeutic payload	Tumor model	Outcome	Refs
Nm@MSNs-DOX/SM	MSNs	DOX/SM	Lymphoma	Targeted chemotherapy and anti-inflammation therapy	[108]
NNPs/CLT	PEG-PLGA	CLT	Melanoma	Improve anti-tumor efficacy	[109]
NNPs/CLT	PEG-PLGA	CLT	Pancreatic cancer	Enhance tumor inhibition effect	[110]
TNM-PN	PLGA	PTX	Ovarian cancer	Amplified anti-tumor therapy	[111]
NM-HB NPs	PLGA	Hypocrellin B	Hepatocellular carcinoma	Suppress tumor growth by PDT	[112]
NM-NP-CFZ	PLGA	CFZ	Breast cancer	Target CTCs and inhibit the formation of a metastatic niche	[113]
pCSs	PLGA	PD-1 Ab	Breast cancer and melanoma	Disrupt myeloid expansion and enhance cancer immunotherapy	[114]
PNMAuDIs	AuNC	DOX/ICG	Breast cancer	Ablate the growth of primary tumor and inhibit cancer metastasis	[115]
Super neutrophils	ZIF-8 NPs	GOx/CPO	Breast cancer	Excellent inflammation-targeting and tumor and pathogen eradication	[116]

the damaged brain for ischemic stroke therapy.[119] The combination of nanomedicine and cell derivate significantly improves the efficacy and safety of drugs.[120] Gao et al. have generated cell membrane-derived nanovesicles using nitrogen cavitation to disrupt activated neutrophils quickly.[121] This nanovesicle-based drug delivery system possesses intact expression of integrin $\beta 2$ to bind to intercellular adhesion molecule 1 (ICAM-1) on vascular inflammation endothelium and significantly alleviates acute lung inflammation through the loaded NF-κB inhibitor TPCA-1, providing a functionalized neutrophil nanovesicle-based drug delivery system for disease treatment. Similarly, Meng et al. have recently generated cellular membrane nanovesicles of neutrophils and modified them with cholesterols to deliver dexamethasone for enhanced treatment of COVID-19, which achieves better therapy effects and biosafety than the drug alone.[122]

The use of neutrophil membranes to coat NPs for anti-cancer drug delivery has been tested in several cancer models. Previously, Zhou et al. have produced celastrol (CLT)-loaded and neutrophil membrane-cloaked PEG-PLGA NPs (NNPs/CLT) to treat acute pancreatitis (AP). In a rat model of AP, NNPs efficiently cross the blood-pancreas barrier and specifically accumulate in the pancreas, significantly downregulating the levels of serum amylase and pancreatic MPO.[123] Thus, a neutrophil membrane-camouflaged delivery vehicle improves the targeting ability of NPs and the therapeutic efficacy of drugs. At the same time, it reduces systemic toxicity, which represents a highly promising delivery vehicle for targeted therapy. The same group further demonstrates that celastrol-loaded PEG-PLGA NPs coated with neutrophil membranes could achieve targeted delivery of chemotherapeutics to malignant melanoma.[109] The celastrol-loaded PEG-PLGA NPs coated with neutrophil membranes show remarkably prolonged blood circulation and more selective accumulation at the tumor site, which significantly improves the anti-tumor efficacy and prolongs the survival time of mice. Consistent with these studies, Cao et al. have obtained NNPs/CLT and confirmed that NNPs/CLT shows pancreas-specific drug delivery and selective accumulation at the tumor site after systemic administration compared to NPs alone. NNPs/CLT greatly enhances tumor inhibition effect and prolongs the survival of tumor-bearing mice in multiple pancreatic cancer models.[110]

Mesoporous silica NPs (MSNs) coated with neutrophil membranes have been used to enhance tumor-targeted chemotherapy drug delivery following systemic administration. For instance, Zhao *et al.* have designed a novel anti-tumor NP complex by using MSNs loaded with DOX and shanzhiside methylester (SM) as the core and neutrophil membrane (Nm@MSNs-DOX/SM) as the shell.[108] This Nm@MSNs-DOX/SM drug delivery system shows good biocompatibility and active tumor-targeting, which enhances the anti-tumor effect by targeted chemotherapy and anti-inflammatory therapy (**Figure 9**).

In another study, Wang et al. have fabricated PTX-loaded neutrophil membrane-camouflaged NPs modified with tumor necrosis factor-related apoptosis-inducing ligand (TNM-PN) for amplified anti-tumor therapy.[111] As a result of TRAIL modification and the adhesive interactions between neutrophils and inflamed tumor vascular endothelial cells, TNM-PN show prolonged blood circulation, targeted tumor delivery and preferential accumulation, excellent cellular internalization, thus achieving enhanced tumor inhibition and mouse survival. Moreover, Zhang et al. have constructed neutrophil membrane-coated hypocrellin B-loading PLGA NPs (NM-HB NPs) for simultaneous NIR imaging and therapy.[112] In a mouse model of HCC, the NM-HB NPs target and accumulate at tumor site and significantly suppress tumor growth by PDT.

In the early stage of metastasis formation, CTCs disseminate to, seed, and colonize at the distant metastatic site, which provides a key target for anti-metastasis therapy. Previous studies suggest that neutrophils possess both CTCs and inflammatory niche-targeting properties through the cell adhesion molecules on their surface. Inspired by this mechanism, Kang et al. have designed a neutrophil-mimicking drug delivery system (NM-NP) by coating PLGA NPs with neutrophil membrane.[113] They demonstrate that NM-NPs display enhanced association with tumor cells under shear flow in vitro and higher CTC capture efficiency in vivo. Moreover, NM-NPs loaded with proteasome inhibitor carfilzomib (NM-NP-CFZ) selectively deplete CTCs in the circulation and inhibit the formation of metastatic niche, which offers an effective approach for preventing cancer metastasis by targeting and neutralizing CTCs. Using the similar strategy, Wu et al. have proposed that surface functionalization of immunomagnetic NPs (IMNs) with neutrophil membranes could enhance the interaction with CTCs and improve the isolation of CTCs.[124] The neutrophil membrane-coated IMNs (Neu-IMNs) exhibit excellent separation efficiency and much improved purity, indicating that neutrophil membrane modification may be helpful in both noninvasive cancer diagnosis and targeted cancer therapy.

Myeloid-derived suppressor cells (MDSCs) promote tumor progression through distinct mechanisms and suppressing

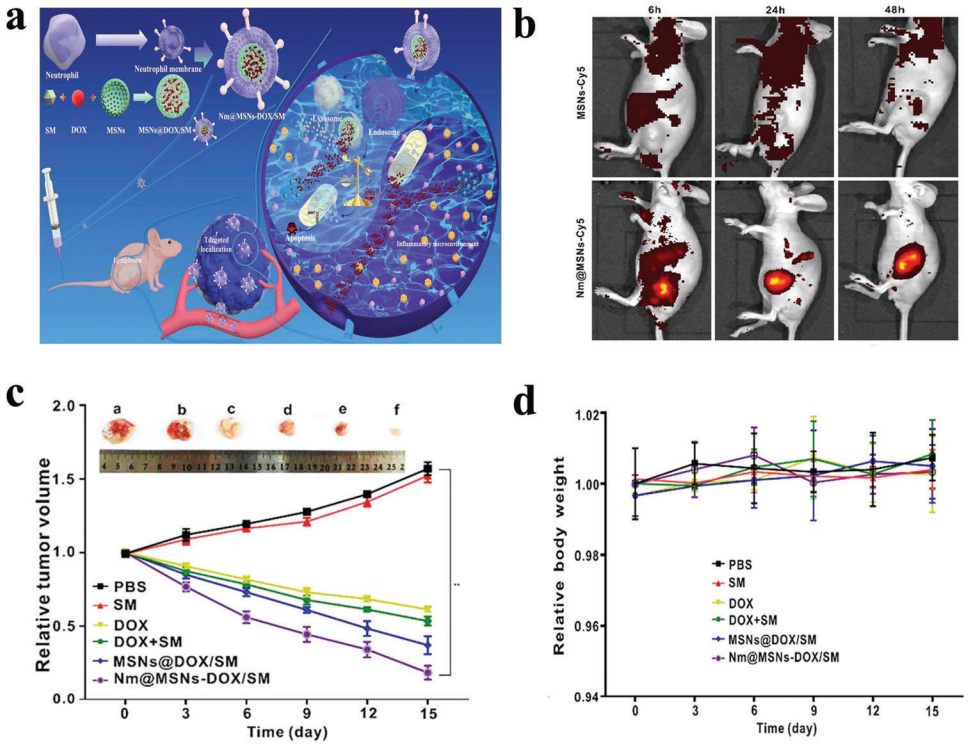

Figure 9. Neutrophil membrane-based core-shell structured nanocomplexes for targeted therapy of lymphoma. a) Schematic diagram of Nm@MSNs-DOX/SM construction and its targeted therapeutic mechanisms in lymphoma. b) In vivo fluorescence images of SU-HDL-2 xenograft model after intravenous injection of Cy5-labeled Nm@MSNs (n = 3 mice per group). c) Tumor growth curves of mice with various treatments (n = 3 mice per group). $^{*}P < 0.05$ and $^{**}P < 0.01$ (over two groups of data were analyzed by one-way ANOVA analysis with Tukey's post-hoc test). Data were shown as mean±SD. d) Body weight of mice with various treatments. Abbreviations: SM, Shanzhiside methylester; DOX, Doxorubicin; MSNs, Mesoporous silica nanoparticles; Nm, Neutrophil membrane. a–d) Reproduced with permission.[108] Copyright 2021, BMC SpringerNature.

MDSC expansion and tumor accumulation represents a new strategy for cancer treatment. Li et al. have developed nano-sized pseudo-neutrophil cytokine sponges (pCSs) by coating the neutrophil membrane vesicles onto the PLGA polymeric NPs.[114] The prepared pCSs inherit membrane receptors from the parental cells, enabling them to act as decoys to absorb and neutralize growth factors and chemokines that mediate MDSCs expansion and tumor-trafficking. pCSs injection reduces the accumulation of MDSCs in tumors and enrichment in peripheral lymphoid organs and avoids the compensatory influx of alternative myeloid subsets. Importantly, pCSs treatment increases the number and restores the anti-tumor activity of T cells, resulting in significant inhibition of breast cancer and melanoma progression. More importantly, combining pCSs with the anti-PD-1 immune checkpoint blockade synergistically suppresses melanoma tumor growth and prolongs tumor-bearing mouse survival. These findings indicate that neutrophil membrane-based pseudocell nanoplatform provides a new approach to effective cancer immunotherapy. In another study, Cui et al. have manufactured a neutrophil mimicking metal-porphyrin-based nanodevice loaded with porcine pancreatic elastase for cancer therapy.[125] The neutrophil membrane camouflaged nanodevice can not only suppress primary tumor growth under laser irradiation, but also stimulate T-cell response-mediated abscopal effect to suppress distal tumors (**Figure 10**).

3.2.2. Hybrid Cellular Membrane as Drug Delivery Vehicles

The concept of using hybrid cellular membrane-camouflaging for targeted drug delivery has emerged. For instance, Rao et al. have proposed a nontoxic and effective cancer immunotherapy approach that uses hybrid cellular membrane nanovesicles (hNVs) as a drug delivery system.[126] The fabricated hNVs consist of NVs from platelets (P-NVs), M1 macrophages (M1-NVs), and cancer cells overexpressing high-affinity SIRPα variants (SαV-C-NVs). Inherited from parental cells, hNVs efficiently accumulate in surgical wound sites, interact with CTCs in the blood, repolarize tumor-associated macrophages (TAMs) toward M1 phenotype, and block the CD47-SIRPα interaction, thus enhancing macrophage phagocytosis of cancer cells, as well as potentiating anti-tumor T cell immunity. In malignant melanoma models, the systemic administration of hNVs significantly inhibits local recurrence and distant metastasis after surgery. Moreover, hNVs enhance the cytosolic delivery of a stimulator of interferon genes (STING) agonist, which reprograms the tumors from "cold" toward "hot" states, thus improving its therapeutic efficacy in a poorly immunogenic triple-negative breast cancer model.

Neutrophil membrane has been previously used as a component of hybrid membrane for liver disease therapy. Xie et al. have designed membrane-coated gelatin NPs for the treatment of nonalcoholic steatohepatitis (NASH), in which gelatin NPs are loaded with pioglitazone and vitamin E (G-PV) and then

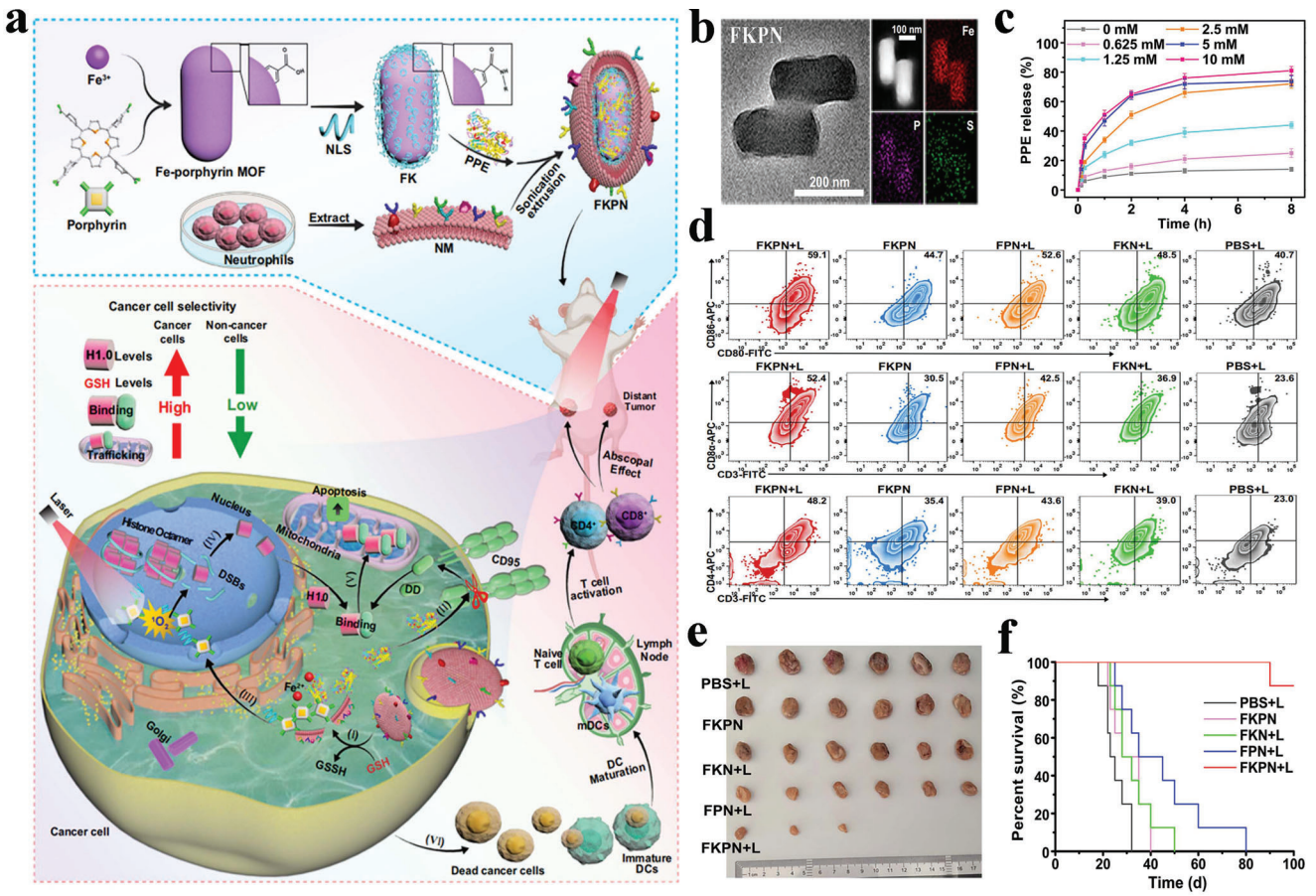

Figure 10. A neutrophil mimicking nanodevice for cancer therapy. a) Schematic illustration of biomimetic nanodevice FKPN. b) TEM image of FKPN. c) GSH-responsive release curve of PPE from FKPN. (n = 3 independent experiments). ***p<0.001 (P values were assessed using two-tailed Student's t-test). Data were presented as mean±SD. d) Flow cytometry analysis of dendritic cells, $CD8^+$ T cells and $CD4^+$ T cells after various treatments. e) Representative photographs of the tumors. (n = 6 mice). f) The survival percentages of treated mice. (n = 8 mice). Data were presented as mean±SD. Abbreviations: PPE, Porcine pancreatic elastase; GSH, glutathione; FKPN, a biomimetic nanodevice by integrating PPE, nuclear $^1O_2$ generator porphyrin-NLS, metal node Fe^{3+}, and neutrophil membrane (NM). a–f) Reproduced with permission.[125] Copyright 2023, SpringerNature.

encapsulated with the platelet-neutrophil hybrid membranes (PNM).[127] The PNM-G-PV show immune evading and inflammatory enrichment capabilities. At the NASH site, the elevated presence of MMP9 facilitates the intelligent response of gelatin NPs to degradation, subsequently releasing vitamin E and pioglitazone for medicinal intervention. In a NASH rat model, PNM-G-PV demonstrates superior therapeutic effectiveness compared to either G-PV or PV utilized independently. The biomedical use of PNM-G drug delivery system in liver cancer deserves further investigation.

Inspired by the hybrid cellular membrane approach, Ye and colleagues utilized a platelet-neutrophil hybrid membrane to envelop the exterior of a gold nanocage (AuNC), creating nanokillers (NSKs). These structures are capable of concurrently seizing and eradicating CTCs and tumor-derived exosomes through the use of high-affinity membrane adhesion ligands.[115] The biomimetic PNM-coated NSKs are then loaded with DOX and ICG for combined chemotherapy and PTT (**Figure 11**). NSKs demonstrate enhanced cellular uptake, superior tumor infiltration, and increased cytotoxicity on tumor cells when compared to non-coated AuNCs or single membrane-coated AuNCs. In mouse xenograft and orthotopic breast cancer models, NSKs not only completely ablate primary tumor growth but also efficiently inhibit cancer metastasis.

3.2.3. Membrane-Mimicking Artificial Neutrophils

Inspired by the natural property of neutrophils, Wu et al. have designed a core shell supramolecular hybrid nanogel to deliver chloroperoxidase (CPO) and superoxide dismutase (SOD), which simulates neutrophil lysosomes to responsively convert ROS in TME. The cascade enzymatic reactions of SOD and CPO within the bioinspired nanogel represent an enzyme dynamic therapy that is able to induce tumor cell apoptosis and inhibit cell proliferation by controllable producing singlet oxygen species, thus achieving promising therapeutic effects in primary cancers.[128]

Given the versatile functions of neutrophils against tumors and infections, Zhang et al. created synthetic "super neutrophils" that excel in pinpointing inflammation sites and generating hypochlorous acid (HClO), enhancing the ability to target and destroy malignant tumor cells and pathogens.[116] These "super

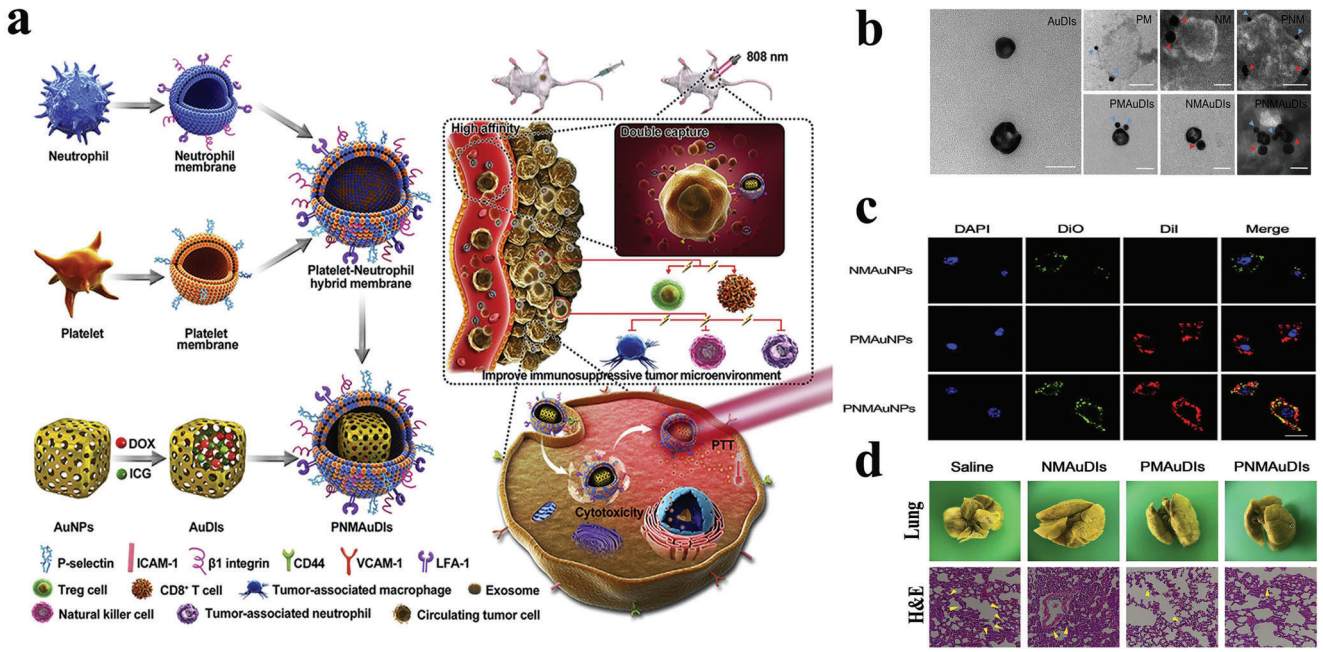

Figure 11. Neutrophil-platelet hybrid membrane nanovesicles for breast cancer metastasis inhibition. a) Schematic illustration of PNMAuDIs and their synergistic effects against breast cancer metastasis. b) TEM images of the PNMAuDIs samples. c) The adhesion of the PNMAuNCs to 4T1 cells. d) Lung tissues and H&E staining with indicated treatments. (n = 3 mice per group). Yellow arrows demonstrate the lung metastases. Abbreviations: NM, neutrophil membrane; PM, platelet membrane; PNM, platelet and neutrophil hybrid cell membrane; AuNC, gold nanocage; AuDIs, AuDs and AuIs with DOX or ICG; DOX, doxorubicin; ICG, indocyanine green. a–d) Reproduced with permission.[115] Copyright 2020, Elsevier B.V.

neutrophils" are constructed by incorporating glucose oxidase (GOx) and chloroperoxidase (CPO) into a zeolitic imidazolate framework-8 (ZIF-8), facilitating HClO production through enzymatic cascades, followed by a coating of neutrophil membrane to aid in inflammation targeting. Remarkably, these engineered "super neutrophils" can produce HClO at a rate seven times higher than their natural counterparts, offering a promising and efficient approach in tumor nanomedicine.

3.3. Neutrophil-Derived EVs as New Drug Delivery Platforms

As natural nanosized vesicles secreted by nearly all types of cells, EVs mediate signal transduction and play essential roles in intercellular communication. As a result of their unique physiochemical characteristics, EVs are considered as potential therapeutic agents and promising drug delivery vehicles.[129] Compared with synthetic nanomaterials, EVs are intrinsically biocompatible, biodegradable, low toxic, and non-immunogenic, making them more ideal for drug delivery than synthetic NPs. EVs have the potential to escape from clearance by the host immune system and to pass through physiological barriers due to specific surface protein profiles. Moreover, EVs inherit targeting properties from their producing cells, which is beneficial for the accumulation of therapeutic agents at tumor sites after systemic administration.

To generate EVs for drug delivery, most studies have used neutrophils from human peripheral blood and mouse bone marrow. Some studies have used neutrophil-like cell lines (such as HL-60). For instance, Meng et al. have isolated neutrophils from mouse/rhesus bone marrow and obtained neutrophil-nanovesicles (N-NVs) through a serial sonication and extrusion method to deliver dexamethasone for the treatment of COVID-19 cytokine storm.[122] Zhang et al. have collected neutrophils from bone marrow of mice (LPS-activated) and isolated neutrophil-derived exosomes from the harvested supernatant to deliver nanoenzyme for the treatment of advanced rheumatoid arthritis.[106] Another study from Wang et al. has isolated neutrophils from mouse bone marrow and used neutrophil-derived exosomes to deliver doxorubicin (DOX) in tumor therapy.[12] In our recent work, we used neutrophils from the peripheral blood of healthy donors and isolated their derived nanovesicles to serve as drug carrier for targeted and combined tumor therapy.[13]

One of the features of neutrophil-derived EVs is their intrinsic inflammatory chemotaxis. Neutrophil-derived EVs can actively migrate toward the site of tissue injury or infection guided by a concentration gradient of chemokines, enabling them to cross vascular barrier into inflammation site and injured tissue. Compared with neutrophil-derived EVs, macrophage-derived EVs can also accumulate in the tumor tissues directed by inflammation and release cytokines to further establish a local inflammatory microenvironment, while NK-derived EVs mainly depend on the natural cytotoxicity receptor to target tumor cells rather than responding to inflammatory signals.[130] Similar to NK-derived EVs, neutrophil-derived EVs can carry cytotoxic proteins such as granzyme A, granzyme B, perforin and FasL to directly kill tumor cells.[131]

Previous studies have shown that neutrophils derived microvesicles can be harnessed as a unique therapeutic strategy for inflammatory diseases such as ischemic stroke, arthritis, and

gout.[132] Dong et al. demonstrate that neutrophil membrane-derived NVs loaded with Resolvin D2 (RvD2) could specifically bind to inflamed brain endothelium to enhance the resolution of neuroinflammation, thus protecting brain damage after reperfusion therapy of ischemic stroke.[11] Gao *et al*. have reported the generation of scalable and drug-loaded neutrophil-derived EVs by nitrogen cavitation (NC-EVs) for anti-inflammation therapy. NC-EVs are similar to naturally secreted EVs (NS-EVs) with a 16-fold higher yield and enrichment of targeting ligand integrin β2. NC-EVs show great potential to be used as a drug delivery platform for the anti-inflammation drug piceatannol, an NF-κB pathway inhibitor. Piceatannol-loaded NC-EVs dramatically attenuate acute lung inflammation and LPS-induced sepsis, thus alleviating acute lung injury and increasing mouse survival.[133]

In addition to targeted delivery of drugs, neutrophil-derived exosomes can also deliver nano-enzymes to the site of inflammation. For instance, Zhang et al. have developed ultrasmall prussian blue NPs functionalized neutrophil nanovesicles (uPB-Exo) through click chemistry, which inherit the unique tissue homing ability of neutrophils and have high anti-infection effect.[134] The uPB-Exo selectively accumulate in inflammatory synovitis and induce a cascade of anti-inflammatory responses, leading to precise treatment of rheumatoid arthritis in vivo. Therefore, neutrophil NV-mediated drug delivery has good targeting ability and therapy effect, thus can be used as an alternative approach for cell therapy.

Encouraged by the intrinsic inflammatory chemotaxis and excellent BBB-crossing capability of neutrophils, Wang *et al*. have proposed a bioinspired neutrophil-exosomes (NEs-Exos) system to deliver DOX for glioma treatment.[12] NEs-Exos show excellent responsiveness to inflammatory brain TME and abilities to cross and penetrate the BBB. The systemic administration of DOX-loaded NEs-Exos efficiently suppresses tumor growth and prolongs survival time in a glioma mouse model, suggesting that NEs-Exos based drug delivery system represents a new platform for improving the efficacy of chemotherapy.

To enhance EVs' targeting ability and drug loading efficiency, previous studies have come up with a variety of EVs' targeting ability and drug loading efficiency and effective strategies for EVs engineering.[135] Membrane modification of EVs is a common and valuable functionalization strategy, which enables them to efficiently accumulate in tumors.[136] In addition, fusing liposomes with EVs to construct hybrid EVs or coating NPs with EV membrane to fabricate nanovesicles is a relatively novel method to produce bio-mimetic EVs. Although some shortcomings of engineered or bio-mimetic EVs remain, such as scale-up production and reproducibility, they are promising tools for efficient drug delivery and targeted therapy. Our recent study showed that exosomes from neutrophils (N-Ex) encourage tumor cell apoptosis by delivering cytotoxic proteins and activating the caspase signaling pathway. Additionally, we have created a targeted drug delivery system by engineering N-Ex with superparamagnetic iron oxide NPs (SPION) to achieve higher tumor-targeting ability. We have further fabricated exosome-like nanovesicles from neutrophils (NNVs) and embedded DOX into NNVs after modification with SPION (SPION-NNV-DOX) to enhance tumor accumulation. In contrast to liposome-loaded DOX and natural NNVs, SPION-NNV-DOX demonstrates a preferential concentration at tumor locations when subjected to an external magnetic field. This facilitates potent tumor growth inhibition and significantly extends the lifespan of mouse tumor models.[13] These findings indicate that NNVs may provide an alternative platform for neutrophil-based drug delivery and cancer-targeted therapy.

4. Targeting Neutrophils for Cancer Therapy

Recent advances in understanding neutrophil biology, function, and heterogeneity have led to a reasonable idea that targeting the pro-tumor roles of neutrophils and restoring the anti-tumor functions of neutrophils may have a potential therapeutic effect in cancer. Therefore, several strategies, such as targeting the recruitment of neutrophils to tumors, inhibiting the regulators and mediators of the pro-tumor roles of neutrophils, re-polarizing TANs from a pro-tumor to anti-tumor state, and reprogramming of neutrophils into non-canonical APCs, have been proposed and tested in many pre-clinical studies (**Figure 12** and **Table 4**).

4.1. Inhibiting the Recruitment of Neutrophils into Tumor and Depleting Tumor-Associated Neutrophils

Considering the essential roles of neutrophils in supporting cancer growth and metastasis, targeting TANs may represent a new therapeutic approach. CXCR2 is a prominent chemokine receptor that directs neutrophil recruitment. Blocking CXCLs/CXCR2 signaling has been explored as a potent strategy in neutrophil-targeted cancer therapies. Previous studies on mice have shown that Ly6G$^+$ neutrophils are the dominant source of CXCR2 in blood, and CXCR2 deficiency attenuates neutrophil recruitment. Systemic depletion of Ly6G$^+$ cells suppress established skin tumor growth and colitis-associated tumorigenesis and reduces Apc$^{Min/+}$ adenoma formation.[137] Raccosta et al. demonstrate that the oxysterol/CXCR2 axis plays an important role in recruiting pro-tumor TANs. Interfering with the oxysterol/CXCR2 axis delays tumor growth and prolongs the overall survival of tumor-bearing mice.[138]

CXCR2 inhibition also enhances T-cell activity and confers sensitivity to chemotherapy, radiotherapy, and immunotherapy. The blockade of CXCR2 enhances the effect of chemotherapy via regulation of neutrophil infiltration. SB225002, a selective inhibitor of CXCR2, significantly reduces infiltration of neutrophils and enhances anti-tumor T cell activity via promoting CD8$^+$ T cell activation, significantly inhibiting the progression of lung cancer and promoting the therapeutic effect of cisplatin.[139] In PDAC mouse models, utilizing anti-Ly6G antibodies to diminish neutrophil levels or obstructing CXCR2 pathways leads to decreased tumor expansion, halted metastasis, and heightened presence of cytotoxic T cells, enhancing the efficacy of checkpoint inhibition therapy.[140] Co-depletion of CXCR2$^+$ TAN overcomes the compensatory response of neutrophil mobilization by depletion of CCR2$^+$ TAM, which augments anti-tumor immunity and improves chemotherapy efficacy in PDAC.[141] Neutrophil depletion also enhances the therapeutic effect of PD-1 antibody on glioma.[142] In mouse xenograft tumor models, combined anti-PD-1 and neutrophil depletion therapy significantly inhibits tumor growth and promotes survival. Genetic and pharmacological approaches to deplete neutrophils have been tested in mouse soft

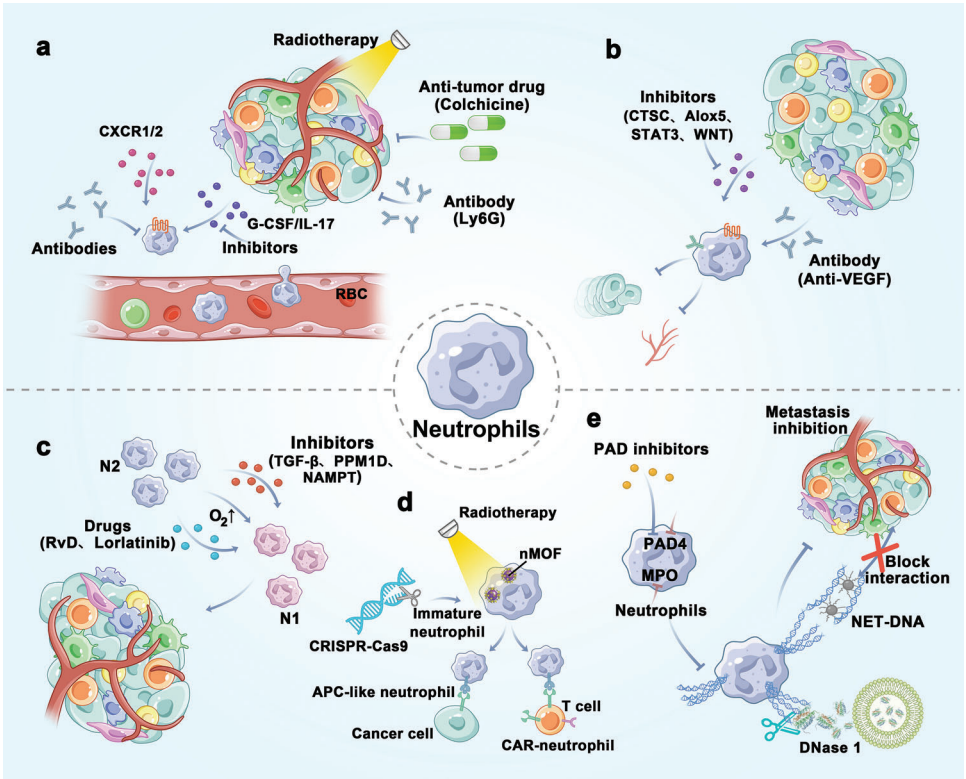

Figure 12. The strategies of targeting neutrophils for cancer therapy. a) Antagonists and inhibitors for chemokines and cytokines (as well as their receptors), such as CXCR2, G-CSF, and IL-17, could suppress the expansion and recruitment of neutrophils into tumor. Chemotherapy drugs (colchicine) and antibodies (anti-Ly6G) are used to deplete TANs. b) Inhibitors for Alox5, STAT3 and Wnt signaling could suppress the tumor-promoting roles of TANs. c) Drugs and inhibitors reprogram TANs toward the anti-tumor N1-like phenotype. d) Nanomaterials (nMOF) and CRISPR-Cas9 technology could reprogram neutrophils into an APC-like hybrid neutrophil phenotype and present superior cytotoxicity against tumor cells. e) DNAse I or PAD4 inhibitors prevent the formation of NETs and eliminate the effect of NETs on tumor metastasis. The image was generated by using the Blender software.

tissue sarcoma models.[59a] Neutrophil depletion prior to image-guided focal radiation improves tumor response to radiotherapy and single-cell RNA sequencing reveals decreased MAPK activation with neutrophil depletion and radiotherapy.

Recently, Wang et al. demonstrate that CEMIP (cell migration-inducing protein), interacts with the TGFβR1/2 to activate the TGFβ signaling pathway in CRC cells, stimulating CXCL1 and CXCL3 production and driving immunosuppressive neutrophil infiltration, leading to impaired $CD8^+$ T cell anti-tumor immunity and low response to PD-1 blockade.[143] Thereby, pharmacologic inhibition of CEMIP by pirfenidone reduces the recruitment of neutrophils, restores $CD8^+$ T cell infiltration and anti-tumor activity, impedes tumor progression, and enhances the therapeutic efficacy of PD-1 blockade in inhibiting liver metastasis.

Previously, Coffelt et al. have shown that IL-1β-activated $\gamma\delta$T cells produce IL-17 to elicit a GSF-dependent expansion and polarization of neutrophils to suppress $CD8^+$ cytotoxic T lymphocytes and promote breast cancer metastasis. Neutralization of IL-17 or G-CSF prevents neutrophil accumulation and downregulates the T-cell-suppressive phenotype of neutrophils.[47] Moreover, depleting neutrophils profoundly reduces pulmonary and lymph node metastases. In addition, Zhang et al. demonstrate that EZH2 (enhancer of zeste homolog 2) acts as a transcription factor to increase c-Jun expression in brain metastatic cells when phosphorylated at tyrosine-696 (pY696) by Src tyrosine kinase, which up-regulates G-CSF to recruit $Arg1^+$ and $PD\text{-}L1^+$ immunosuppressive neutrophils into the brain to drive metastatic outgrowth.[144] G-CSF-blocking antibodies or immune checkpoint blockade therapies combined with Src inhibitors impede brain metastasis in multiple mouse models.

Colchicine compounds have been known as potent anti-inflammatory drugs that could strongly inhibit neutrophil chemotaxis to the inflammatory site. Hence, Chen et al. have synthesized low-toxic colchicine derivative (BCS) nanocomposite and modified them with sialic acid and cholesterol derivatives (SA-CH) for improving neutrophil targeting.[145] They demonstrate that neutrophils effectively absorb SA-CH-modified BCS preparations, reduce infiltration of neutrophils into tumor, enhance T cell function, and effectively inhibit tumor growth and metastasis in a triple-negative breast cancer model. The value of nanomaterial-mediated delivery of specific antibodies or inhibitors for neutrophil expansion and recruitment in cancer therapy deserves further investigation in future studies.

4.2. Suppressing the Pro-Tumor Roles of Neutrophils

Neutrophils release various proteinases and inflammatory factors to exacerbate tumor-related inflammation, accelerate tumor

Table 4. The strategies for targeting neutrophils in cancer therapy.

Strategy	Agent	Target/function	Therapeutic effect	Refs
Inhibiting TAN expansion and recruitment	Blockade of CXCR2	CXCR2	Inhibit tumor growth, enhancing therapeutic effect	[139]
	Pirfenidone	CEMIP	Inhibit tumor progression and liver metastasis	[143]
	Antibodies of IL17A or G-CSF	Neutralization of IL-17 or G-CSF	Inhibit breast cancer metastasis	[47]
	Anti-G-CSF, inhibitor	Scr, G-CSF, PD-1 and CTLA-4	Deter pY696-EZH2 driven brain metastases	[144]
	SA-CH-modified BCS	Inhibit neutrophil chemotaxis to the inflammatory site	Inhibit tumor growth and the metastasis in a TNBC model	[145]
Suppressing the regulation of tumor-promotingTANs	AZD7986	CTSC	Inhibit breast cancer lung metastasis in mice	[147]
	SIP-11	SPIB-SPI1 interaction	Inhibit aerobic glycolysis and cancer progression	[149]
	SH-4-54	STAT3 activation	Suppress lung cancer brain metastasis	[150]
	Warfarin	Gas6/AXL axis	Inhibit metastatic relapse after gemcitabine treatment	[152]
	Lipofermata	FATP2	Abrogate the activity of PMN-MDSCs and delay tumor progression	[154]
	Zileuton	Alox5	Abrogate the pro-tumor activity of neutrophils and reduce metastasis	[155]
	HZ-5 NPs	Sustained release of Zileuton	Inhibit tumor growth and lung metastasis	[156]
	Hyperoxia	Relief of tumor hypoxia	Improve the anti-tumor activity of recruited neutrophils	[172]
Targeting NETs	AuPB@mPDA carriers	Precise and controlled release of DNase I	Eliminate NETs in both orthotopic CRC and liver	[159]
	poly (aspartic acid) based-cationic materials	Interfere with NET-DNA/CCDC25 interaction	Compete with NET-DNA for CDC25binding and suppress cancer metastases	[160]
	CCDC25- DNase I hybrid liposome	Targeting ablation of neutrophil extracellular traps	Eliminates NETs and inhibits CRC liver metastases	[161]
Repolarizing TANs to an anti-tumor state	RvD1	Promoting resolution of inflammation	Reprogram TANs into an anti-cancer phenotype	[162]
	Cisplatin	Inducing tumor cell ferroptosis and activating neutrophils	Promote the efficacy of immune checkpoint inhibitor therapy	[167]
	GSK2830371	Inhibition of PPM1D/Wip1	Enhance anti-tumor responses	[169]
	FK866	NAMPT	Restrain tumor angiogenesis and growth	[170]
	Lorlatinib	Tyrosine kinases	Attenuate liver metastasis of PDAC	[168]
	dMSN-SB	TGF-β signaling	Induce long-term anti-tumor memory and increase mouse survival	[174]
	SIS3	Smad3	Promote N1 phenotype and reduce tumor growth.	[164]
	Melatonin	Increase CXCL2 secretion from tumor cells	Induce TANs infiltration and activation	[163]
Reprogramming of neutrophils to non-canonical APCs	nMOFs	Activated by RT-RDT	Facilitate immune-mediated tumor regression	[175]

cell proliferation, degrade extracellular matrix, induce EMT, and help to establish pre-metastatic niche, generate pro-angiogenic factors to fuel tumor vascularity, as well as suppress the activity of anti-tumor immunity.[146] Targeting the specific factors and key signaling pathways that regulate and mediate the pro-tumor roles of neutrophils have achieved encouraging therapeutic results.

Cathepsin C (CTSC) from breast cancer cells promotes lung metastasis by both recruiting and activating neutrophils through the CTSC/PR3/IL-1β/NF-κB signaling pathway. Targeting CTSC with AZD7986 inhibits breast cancer lung metastasis in mice.[147] Uhl et al. demonstrate that uPA-PAI-1 heteromerization promotes breast cancer progression by attracting neutrophils. Blockade of uPA-PAI-1 heteromerization by a novel small molecule inhibitor WX-340 effectively prevents tumor progression.[148] Wang et al. demonstrate that SPI1 (Salmonella pathogenicity island 1) physically interacts with SPIB to promote aerobic

glycolysis in colon cancer cells, which induces pro-tumor polarization of neutrophils and in turn their delivery of SPI1 mRNA into cancer cells, constituting a positive feedback loop to favor cancer progression.[149] Therapeutic targeting of SPIB-SPI1 interaction with an inhibitory peptide of 11 amino acids (termed as SIP-11) inhibits aerobic glycolysis and cancer progression. Tyagi et al. show that chronic nicotine exposure induces N2-neutrophils via STAT3 activation, which promotes the stemness and metabolic switching in lung cancer cells and induces brain metastasis. Blocking STAT3 activation with a small-molecule inhibitor, SH-4-54, selectively inhibits nicotine-induced neutrophil N2 polarization and suppresses brain metastasis.[150]

Wellenstein et al. demonstrate that p53 deficiency in cancer cells induces the release of Wnt ligands, which stimulate the production of IL-1β by TAMs, subsequently driving neutrophilic inflammation. In p53-null cancer cells, the inhibition of Wnt secretion through pharmacological and genetic means diminishes IL-1β synthesis and inflammation by macrophages, thereby mitigating metastasis.[151]

Curtailing neutrophil-mediated angiogenesis nullifies the resistance encountered in CRC genetic models when treated with anti-VEGF antibodies. Concurrent administration of antibodies targeting G-CSF or Bv8/PROK2 with anti-VEGF hampers tumor advancement and myeloid cell infiltration in models of anti-VEGF-resistant CRC liver metastasis.

Suppressing neutrophil-dependent angiogenesis abrogates resistance to anti-VEGF antibody in a genetic model of CRC. Antibodies blocking G-CSF or Bv8/PROK2, suppress tumor progression and myeloid cell infiltration when combined with anti-VEGF in anti-VEGF-resistant CRC liver metastasis models.[60] Bellomo et al. demonstrate that gemcitabine treatment triggers the recruitment of neutrophils to promote the proliferation of hepatic metastatic pancreatic cancer cells via Gas6/AXL signaling axis. Disruption of neutrophil infiltration by anti-Ly6G antibody or Gas6/AXL signaling inhibition by warfarin inhibits metastatic relapse after gemcitabine treatment.[152]

Stress hormones induce rapid release of proinflammatory S100A8/A9 proteins by neutrophils, which triggers activation of MPO and results in accumulation of oxidized lipids in them. Once released, these lipids up-regulate the fibroblast growth factor (FGF) pathway in tumor cells, mediating tumor cells to exit from the dormancy and formation of new tumor lesions. Targeting the FGF pathway with BGJ398, a selective pan-FGFR antagonist, abrogates stress-induced reactivation of dormant tumor cells by neutrophils.[153] Veglia et al. demonstrate that the upregulated expression of fatty acid transport protein 2 (FATP2), under the control of GM-CSF/STAT5 pathway, modulates the immunosuppressive activity of human neutrophils exclusively through the synthesis of PGE2. Targeted inhibition of FATP2 by selective pharmacological inhibitor lipofermata abrogates the activity of neutrophils, substantially delays tumor progression, and improves the efficiency of immune checkpoint inhibitor (anti-CTLA4) in mice.[154] Bancaro et al. show that the HDAC inhibitor romidepsin kills senescent immunosuppressive neutrophils in a TREM2-dependent manner and, when administered in combination with a CXCR2 inhibitor, further inhibits prostate cancer progression by enhancing the efficacy of ENZA, a standard-of-care for prostate cancer.[68]

Neutrophils support lung colonization of metastasis-initiating breast cancer cells through leukotrienes. Inhibition of the leukotriene-generating enzyme arachidonate 5-lipoxygenase (Alox5) by zileuton abrogates the pro-metastatic activity of neutrophils and consequently reduces metastasis.[155] To improve cancer theranostic effect, Tang et al. have constructed functionalized NPs with MPO-targeting properties, in which the ligands with two 5-hydroxytryptamine ends can oligomerize and crosslink with surrounding biological substrates catalyzed by MPO in inflamed tissues. Then, the NPs are conjugated with PLGA-PEG for self-assembly and loaded with photosensitizers HPPH and zileuton. Under PDT-induced inflammation, neutrophil-mediated delivery of engineered HZ-5 NPs shows enhanced accumulation and retention in the tumor in a mouse breast cancer model.[156] This strategy significantly inhibits tumor growth and lung metastasis through the sustained release of Zileuton, which provides a new avenue for cancer theranostic nanomedicine (**Figure 13**).

4.3. Targeting Neutrophil Extracellular Traps (NETs)

NETs are net-like structures released by neutrophils through a specific process called NETosis and have been described as a fundamental mechanism for innate immune defense against pathogens. Despite the key antimicrobial activity of NETs, the excessive formation of NETs may cause tissue injury and inflammatory diseases. NETs have recently been linked to cancer progression, metastasis, and recurrence.[157] NETs have been reported to help capture CTCs in the circulation and awaken the residual dormant cancer cells in cancer niche, promoting cancer metastasis and recurrence.[66,158] Hence, the clearance of NETs or inhibition of NETosis has emerged as a promising cancer therapy approach. Previous studies have used DNase I and PAD4 (protein-arginine deaminase 4) inhibitors to disrupt NETs and achieved effective results in experimental cancer models. For instance, treatment with NET-digesting, DNase I-coated NPs markedly reduces breast cancer lung metastases in mice.[158a] Moreover, the blocking antibody that targets NET-remodeled laminin reduces dormancy of cancer cells awakened by inflammation in mice.[66]

Although DNase I has excellent potential to disrupt NETs, it is of great challenge to systemically administrate DNase I for cancer treatment as DNase I has a short circulating half-life and systematic inhibition of NETs may impair host defense against bacterial infection. Therefore, it is of great need to achieve tumor-specific delivery and controlled release of DNase I in the metastatic niche for localized degradation of NETs. In a recent study, Chen et al. have constructed a core-shell nanoplatform that consists of a photoactive plasmonic gold blackbody (AuPB) as the core and mesoporous polydopamine (mPDA) as the shell for efficient loading and localized, light-triggered release of DNase I under NIR-II radiation.[159] The precise and controlled release of DNase I from systemically delivered AuPB@mPDA carriers eliminates the extracellular NETs in both orthotopic CRC and liver, thus sensitizing immune checkpoint therapy of CRC by increasing the contact of immune cytotoxic cells with tumor cells and reducing liver metastasis by abolishing NET-mediated capture of CTCs and metastatic seeding, indicating that the AuPB@mPDA

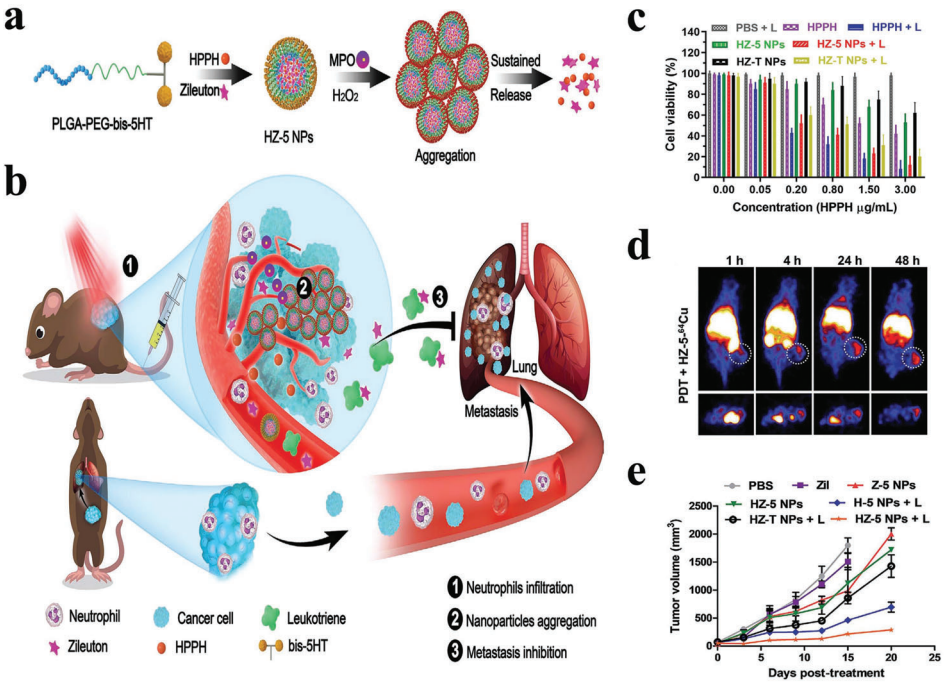

Figure 13. Photoresponsive HZ-5 NPs for targeted PDT therapy. a) Schematic illustration of HZ-5 NPs design and drug release through MPO-catalyzed aggregation. b) PDT induces the accumulation of MPO targeting NPs in tumor and inhibits lung metastasis by releasing Zileuton. c) Cytotoxic effects of HZ-5 NPs on 4T1 cells. (n = 3 independent experiments). One-way analysis of variance (ANOVA) for multiple groups. Values are mean±SD. d) Representative PET images of mice after injection with ^{64}Cu-labeled HZ-5 NPs. (n = 3 mice per group). e) Tumor growth curves of different groups. (n = 5 mice per group). One-way analysis of variance (ANOVA) for multiple groups. All statistical data are represented as mean±SD. Abbreviations: L, Laser; HPPH, 2-(1-hexyloxyethyl)−2-devinyl pyropheophorbide; 5-HT, 5-hydroxytryptamine; HZ-5, 5-hydroxytryptamine (5-HT) is equipped onto nanoparticles (NPs) loaded with photosensitizers and Zileuton; NPs, nanoparticles; PDT, photodynamic therapy; PET, positron emission tomography. a-e) Reproduced with permission.[156] Copyright 2020, Wiley-VCH John Wiley & Sons.

represents an effective NET-targeting delivery system for immune-mediated tumor regression and metastasis inhibition.

The interaction between NET-DNA and CCDC25 is critical for the induction of cancer cell chemotaxis and migration. Based on this, Liang et al. have proposed a new strategy for controlling cancer metastasis by constricting the poly (aspartic acid) based-cationic materials to interfere with NET-DNA/CCDC25 interaction. They demonstrated that the cationic materials have a strong ability to compete with NET-DNA for binding to CCDC2. The cationic materials efficiently reduce the level of hepatic NET-DNA infiltration, remarkably suppress cancer metastases in mouse and human cancer cell metastatic models and exhibit excellent treatment safety.[160] Recently, Wang et al. have fabricated biomimetic CCDC25-overexpressing cell membrane hybrid liposomes to target NETs for treating CRC liver metastases.[161] They have generated cells stably expressing CCDC25 by genetic engineering and used their derived membranes to fuse with DNase I-encapsulated liposomes. The hybrid liposomes exhibit enhanced affinity for NETs and successfully inhibit CRC liver metastases, providing another therapeutic approach for treating NET-associated cancer metastasis.

4.4. Re-Polarization of Neutrophils to an Anti-tumor State

Previous studies have shown that some traditional therapies could re-activate the anti-tumor functions of neutrophils. For instance, Resolvin D1 (RvD1) is a lipid autacoid that promotes the resolution of inflammation. Mattoscio et al. demonstrate that RvD1 stimulates the re-polarization of neutrophils into an anti-tumor phenotype, which reduces cancer growth by recruiting anti-tumor monocytes through increased production of monocyte chemoattractant protein-1 (MCP-1).[162] Chan *et al.* suggest that melatonin treatment skews neutrophils to an anti-tumor phenotype and enhances anti-tumor immunity in PDAC, which may be associated with the induction of CXCL2 expression in tumor cells and the recruitment and activation of neutrophils.[163]

TGF-β/Smad signaling is critical for neutrophil N2 polarization. The blockade with SM16, a TGF-β receptor kinase inhibitor, results in the recruitment and activation of TANs with an anti-tumor phenotype.[4a] In addition, Chung et al. demonstrate that Smad3-knockout mice exhibit increased neutrophil infiltration and a switch to a predominant N1 antitumor state in a lung cancer model.[164] Smad3 activation in TANs is associated with a predominant N2 state of polarization and a poor outcome in NSCLC patients. Pharmaceutical inhibition of Smad3 with its inhibitor SIS3 enhances the antitumor capacity of neutrophils against NSCLC via promoting their N1 re-polarization.[164]

On the contrary, type I IFN signaling has been shown to regulate the anti-tumor phenotype of neutrophils both in human and mice. Interferon therapy in mice induces re-polarization toward anti-tumor N1 TANs and melanoma patients who receive type I IFN therapy also show similar changes in neutrophil activation.[165] In addition, IFN signaling has been shown to be

essential for the effect of β-glucan-induced trained immunity, associated with neutrophil reprogramming toward the immunostimulatory phenotype.[37]

The study by Leslie et al. shows that tumor infiltration of CXCR2$^+$ neutrophils is associated with resistance to anti-PD1 therapy in non-alcoholic steatohepatitis (NASH)-associated HCC. The combination with CXCR2 inhibitor AZD5069 resensitizes NASH-HCC to anti-PD1 immunotherapy. AZD5069/anti-PD1 combination therapy reprograms the phenotype of TANs, which switch from a pro-tumor to anti-tumor phenotype.[166]

Zhou et al. demonstrate that cisplatin induces ferroptosis of tumor cells, followed by N1 neutrophil polarization in the TME, which in turn remodels the "cold" tumor to a "hot" one through enhancing T-cell infiltration and Th1 differentiation. Cisplatin-induced ferroptosis promotes the efficacy of immune checkpoint inhibitor therapy, suggesting a synergistic anti-tumor efficacy of chemotherapy and immunotherapy.[167] Lorlatinib is a new tyrosine kinase inhibitor (TKI) for NSCLC patients with anaplastic lymphoma kinase gene rearrangement. Nielson et al. have identified an effect of lorlatinib on modulating TANs for PDAC therapy. They demonstrate that lorlatinib suppresses the growth of PDAC at both primary tumor and metastatic site by affecting neutrophils in three manners: (1) by modulating the development of neutrophils in the bone marrow, (2) by reducing their accumulation in the TME, and (3) by suppressing their ability to stimulate PDAC cell proliferation. Moreover, the combined treatment with lorlatinib improves the response of anti-PD-1 therapy, resulting in more activated CD8$^+$ T cells in PDAC tumors.[168]

The key transcription factors that regulate the pro-tumor phenotype and function of neutrophils have been revealed. Uyanik et al. suggest that chemical inhibition of PPM1D/Wip1 in human and mouse neutrophils increases their anti-tumor phenotypes, p53-dependent expression of co-stimulatory ligands, and proliferation of cocultured cytotoxic T cells, which potentiates anti-tumor therapy effect.[169] Pylaeva et al. demonstrate that nicotinamide phosphoribosyltransferase (NAMPT) regulates the pro-tumor function of TANs through SIRT1 signaling. Inhibition of NAMPT by FK866 reprograms neutrophils into anti-tumor effector cells that efficiently repress tumor angiogenesis and growth.[170] Interleukin-1 receptor-associated kinase M (IRAK-M) has been identified as a key transcription factor that controls the immune suppressive function of neutrophils. IRAK-M deficiency reprograms neutrophils to express reduced levels of immune suppressive molecules (such as PD-L1) while enhanced level of stimulatory molecules (such as CD80 and CD40), which is mediated by enhanced STAT5 activation and reduced STAT1/3 activation. IRAK-M deficient neutrophils demonstrate improved ability to promote the proliferation and activation of effector T cells. The transfusion of IRAK-M deficient neutrophils potently renders an enhanced anti-tumor immune response in mouse CRC model.[171] Hypoxia potently regulates the phenotype of TANs and promotes the interactions between TANs and tumor cells. Mahiddine et al. demonstrate that the relief of tumor hypoxia improves neutrophil-dependent tumor control, leading to a massive reduction in tumor burden, mediated via their production of NADPH oxidase-derived ROS and MMP9.[172]

HCC has a "cold" immune state and responds poorly to immunotherapy. The angiotensin-converting enzyme inhibitor captopril has been shown to repress tumor growth through anti-tumor polarization of neutrophils. Based on this, Wang et al. have explored the possibility of converting HCC immune state from "cold" into "hot" and remodeling TANs to potentiate anti-cancer immune response and enhance immunotherapy efficacy by using an acidic/photo-sensitive dendritic cell (DCs)-based neoantigen nano-vaccine, which consists of $SiPCCl_2$-hybridized and Fe (III)-captopril coordinated MSNs coated with membranes of HCC neoantigen-stimulated, maturated DCs.[173] They demonstrate that the nano-vaccines can not only actively target HCC tumor tissues to induce immunological cell death and tumor-associated antigen release through PDT and in situ tumor vaccination but achieve the lymph-homing ability to directly induce the activation and proliferation of CD8$^+$ T cells, strengthening the immune responses against the primary and distant tumor growth. In addition, the release of captopril from the nano-vaccines triggered by acidic TME could polarize TANs from pro-tumor N2 phenotype to anti-tumor N1 phenotype, thus improving the anti-tumor immune effects to achieve complete tumor regression in mouse models and prolong their survival time, which offers a novel immunotherapy strategy for HCC.

Irreversible electroporation (IRE), which delivers high-voltage electric pulses intratumorally to permanently disrupt cell membrane and induce cell death, is a novel ablative technique for PDAC treatment. Combining IRE with immunotherapy (such as anti-PD-1) has shown a synergistic effect on PDAC. However, tumor recurrence remains common after IRE-based immunotherapies, which may be associated with substantial infiltration of neutrophils into the tumors and subsequent TGF-β-induced N2 polarization. To further improve the therapeutic outcome, Peng *et al.* have proposed to disrupt TGF-β signaling and re-polarize neutrophils into the anti-tumor N1 phenotype by glutathione-responsive degradable MSN-mediated delivery of SB525334 (dMSN-SB), an inhibitor of TGF-β1 receptor, at the same time of electrode placement for IRE in mouse PDAC models.[174] The triple therapy of IRE, dMSN-SB, and anti-PD-1 shifts the tumor immune microenvironment from a suppressive state to an activated one, significantly increasing survival of tumor-bearing mice and tempting long-term anti-tumor memory, signifying that TAN variation is a capable and safe approach to enhance pancreatic cancer response to IRE-based immunotherapy.

4.5. Reprogramming of Neutrophils to Non-Canonical APCs

Compromised antigen cross-presentation in advanced tumors fails to generate strong anti-tumor immune responses, as most APCs in TME are usually immunosuppressive or dysfunctional. Previous studies suggest that a subset of TANs exhibit the characteristics of both neutrophils and APCs in human early-stage lung cancer. Eruslanov et al. demonstrate that TANs isolated from early-stage lung cancer patients can increase IFN-γ production and activation of T cell, and dramatically amplify T cell proliferation.[30] In 2016, the same group has identified a subset of TANs from stage I/II lung cancer patients with a granulocyte and APC hybrid phenotype (defined as CD11b$^+$CD66b$^+$CD15^{hi}HLA-DR$^+$CD14$^+$). These APC-like hybrid TANs are superior to canonical TANs in their ability to induce and stimulate anti-tumor T cell responses. Further study by

the authors reveals that GM-CSF and IFN-γ are requisite factors in the tumor for the development of hybrid neutrophils by down-regulating Ikaros.[31]

These APC-like "hybrid neutrophils" can cross-present antigens and trigger anti-tumor T cell responses. Reprogramming neutrophils can be achieved by nanomaterials or gene editing technology, enabling them to cross-present tumor antigens effectively or enhance their anti-tumor cytotoxicity. To induce effective anti-tumor immunity, Guo et al. have used nanoscale metal-organic frameworks (nMOFs), which could be activated by radiotherapy-radiodynamic therapy (RT-RDT), to reprogram neutrophils into an APC-like hybrid neutrophil phenotype. They demonstrate that systemic or local injection of nMOFs recruit peripheral neutrophils into the tumors and the activation of nMOFs by low-dose X-ray expands the population of hybrid neutrophils with non-canonical APC function for effective cross-presentation of tumor antigens, suggesting that nMOFs enable RT-RDT to reshape an advantageous TME for anti-tumor immune responses by reprogramming neutrophils.[175]

4.6. Targeting Neutrophils for Tumor Therapy in Clinical Trials

Several neutrophil-modulating tumor therapies have now entered clinical evaluation. For instance, CXCR4 inhibitor plerixafor (AMD3100) has used to treat malignant tumors by increasing circulating neutrophil counts. A phase III randomized crossover trial (NCT02231879) for treatment of WHIM syndrome indicates that plerixafor exhibits outstanding performance in drug preference, life quality and drug failure incidence of patients.[176]

Currently, a number of attempts have been made to inhibit neutrophil recruitment by blocking CXCL8, CXCR1, and CXCR2 for tumor therapy. HuMax-IL8 (BMS986253) has entered a phase I clinical trial (NCT02536469) in patients with metastatic or advanced solid tumors, which has shown high safety and improved effectiveness. The ongoing studies are evaluating the efficacy of BMS-986253 in combination with nivolumab (NCT03400332).[177]

CXCR2 inhibitors are undergoing clinical evaluation in different cancer patients, such as AZD5069 with enzalutamide in early breast cancer (NCT01861054), SX-682 with pembrolizumab in NSCLC and CRC (NCT03473925) and in metastatic melanoma (NCT03161431).[178] Reparixin combined with paclitaxel has been tested in a phase I trial and exhibits good tolerance in triple-negative breast cancer patients (NCT02370238).[6b] These analyses indicate that CXCL8 and its receptor antagonists have great potential as single agent or in combination with chemotherapy in the clinic.

In addition, anti-CD40 antibody (CP-870893) and CD47-SIRPα inhibitors (Hu5F9-G4, IBI188) are found to be safe and efficient in clinical trials via promoting neutrophil-mediated tumor cell apoptosis in cancer patients (NCT00607048, NCT02216409, and NCT03717103). Another therapeutic strategy is related to neutrophil phenotype switching in the TME. A phase Ib study (NCT02734160) of TGF-β receptor inhibitors (galunisertib) coupled with PD-L1 antibody (durvalumab) in metastatic pancreatic cancer suggests that this combined strategy is safe and efficient and might be a more suitable approach for patients in an earlier line of treatment.[179]

Moreover, other strategies such as STAT3 inhibitors (napabucasin, in metastatic CRC, NCT02753127) and therapeutic C/EBPα small activating RNA (MTL-CEBPA, in hepatocellular carcinoma, NCT02716012) have exhibited good safety and efficacy indications.[180]

5. Conclusions and Future Perspectives

This review highlights the growing evidence of engineering neutrophils for drug delivery and cancer-targeted therapy. According to the existing studies, two strategies have been proposed and widely tested for neutrophil-based cancer therapy: 1) Taking use of neutrophils and their cell derivates or mimetics as therapeutic agents and drug delivery vehicles; and 2) antagonizing the pro-tumor roles while harnessing the anti-tumor functions of neutrophils. Further understanding of the roles of neutrophils in cancer and developing more effective neutrophil-based therapeutic approaches would benefit the clinical management of cancer patients in the future.

Cell-based delivery presents a promising avenue to address the challenges associated with nanomaterials in drug delivery, including low biocompatibility, limited systemic circulation, and immunogenic reactions. As the most abundant leukocytes in human circulation, neutrophils have been regarded as an ideal cell-based drug delivery system as they can be rapidly mobilized and recruited into tumors. Previous studies have activated host circulating neutrophils to uptake exogenously injected nanomaterials (loaded with or without drug) in vivo or used nanomaterials to load drugs into neutrophils in vitro, followed by systemic infusion of neutrophils.[7a] In response to inflammatory signals from tumors under the internal or external stimulus, these drug-loaded neutrophils function as Trojan horses to achieve targeted delivery and enhanced accumulation at tumor sites, microenvironment-responsive release of drugs, and efficient internalization by tumor cells. The former method is convenient but challenged by the clearance of nanomaterials by the mononuclear phagocyte system. In contrast, the latter approach is more efficient and biocompatible but needs in vitro preparation of neutrophil-nanomaterial complexes. Both methods require a rational design of nanomaterials with high binding affinity and specificity for neutrophils. Most current studies have achieved promising results in animal models, but whether the system is effective and safe in clinical applications has not been tested. A comprehensive analysis of the safety and tolerance of neutrophil-based living cell drug delivery system is required before it can be used for human tumor therapy. Thus, high-quality and reliable clinical trials should be developed to evaluate the therapeutic potential of neutrophil-based living cell drug delivery systems in cancer patients. Moreover, the long-term efficacy and safety of infusing a large amount of drug-loaded neutrophils in vivo and attracting the circulating drug-internalized neutrophils to tumors require careful evaluation. The use of gene editing and synthetic biology technologies may significantly enhance their tumor-targeting ability, therapy efficacy, and biosafety.

Cell membrane-camouflaged NPs retain their membrane structures and inherent biological functionalities of the source cells, which help them to escape from immune clearance,

prolong circulation time, and migrate to the target tissue under the direction of membrane surface proteins.[7b,181] The neutrophil membrane preserves the inflammatory tendency and promotes the accumulation of NPs in the tumor site after subsequent systemic administration. A hybrid cell membrane method, including a neutrophil membrane, has also been proposed to endow biomimetic NPs with multiple functionalities. Up to now, the membranes are mainly isolated from the peripheral blood and bone marrow neutrophils of healthy individuals and neutrophil-like cell line HL-60, the former has the limitations of short lifespan and heterogeneity while the latter is a leukemia cell line. Therefore, a stable and reproducible source of neutrophils is critical to promote their further application in tumor therapy. Previous studies have reported massive preparation of neutrophil membranes via serial centrifugation and extrusion methods. Up to now, there is no uniform route for neutrophil membrane preparation, which may limit its clinical use. The yield, integrity, and heterogeneity of the prepared neutrophil membrane (or hybrid membrane) need to be considered. Neutrophil-derived EVs may be more valuable than their membranes as they can be produced on a large-scale for clinical use following the standard of operation. The use of EVs to load drugs or therapeutic molecules for cancer treatment has been tested in several clinical trials and achieved encouraging results. Further study on the effectiveness and safety of neutrophil-derived EVs in cancer therapy may provide new clues. The combination with light, sound, electricity, magnetic and other responsive nanomaterials is also a promising strategy for establishing a multi-modal drug delivery and treatment system.

The multifaceted roles of neutrophils in cancer highlight the potential of targeting neutrophils for cancer therapy.[182] Further study on the mechanisms for both anti-tumor and pro-tumor activities of neutrophils will be helpful for the discovery of new targets of tumor therapy. The combination of currently available treatments with neutrophil-targeted therapy may also contribute to more effective tumor therapy approaches. Targeted blockade of the known neutrophil subsets has been proposed as a potential cell therapy approach. The previous studies show that depletion of neutrophils or interference with their chemotaxis results in significant inhibition of tumor progression in mouse models, these strategies are not feasible or not yet successful in human cancer. Considering that neutrophils are numerous and can amplify their own activation and recruitment, strategies to harness their potential to function as anti-tumor effector cells are of potential interest. A deeper understanding of the regulatory mechanisms responsible for acquiring distinct neutrophil states is needed to allow selective manipulation of neutrophil subpopulations. An alternative therapeutic approach may be to manage the functions of neutrophils in vivo or the adoptive transfer of anti-tumor neutrophils to suppress tumor growth. As clinical trials targeting neutrophils have not entered the clinic thus far, therapeutic strategies aimed at repolarizing neutrophils or interfering with their pro-tumor functions may be more practicable. Taking use of advanced technologies like scRNA-seq to identify critical neutrophil subsets may provide new targets. How to achieve precise targeting of the pro-tumor neutrophil subset still needs more study as there is a lack of specific identification markers on them (most are functional markers). Further identification of key molecules that regulate or mediate the pro-tumor functions of neutrophils may provide new therapeutic targets, which can be utilized as a novel mode of cancer immunotherapy. In addition, the reliability of human data remains unclear since most of the previous studies on neutrophils and cancer have been performed in mice, and the tumors in humans are more heterogeneous than those in mouse models.

Furthermore, more effective strategies that take full advantage of the anti-tumor effect of neutrophils need to be developed. Activating the anti-tumor activities by certain approaches, such as combined antibodies, holds great promise in tumor therapy. Future work needs to figure out the most suitable antibody panel for distinct tumor types and completely evaluate their efficacy and safety. Despite promising findings, neutrophil-targeting therapies may be hampered by the high heterogeneity of complex subpopulations. Therefore, deeply profiling the diversity of neutrophil differentiation in different tumor settings at the single-cell level and further defining the unique identification markers and functions of different neutrophil subsets are essential for targeted neutrophil re-polarization as well as more precise neutrophil-targeted therapies. The therapy timing and selection of appropriate regimens may have important impacts on the therapeutic effect as neutrophils play dynamic and dual roles in cancer progression. The state of neutrophils in the TME and their heterogeneity need to be evaluated before targeting them for a successful therapy. In addition, in-depth analysis of the correlation between neutrophil subset characteristics, neutrophil functions and patient prognosis and treatment response may aid in the personalized therapy.

Overall, neutrophils have emerged as a new frontier of cancer therapy. Combining the natural properties of neutrophils with the advantages of nanomaterials has brought new methods for cancer therapy. Accumulating evidence from basic medical studies suggests neutrophils have dual roles in cancer. Therefore, strategies that specifically disrupt the pro-tumor roles but reinstate the anti-tumor functions of neutrophils should be developed. Despite the success of these therapeutic approaches in many mouse tumor models, the precise functions and subpopulations of neutrophils as well as the regulation of neutrophil polarization in different tumors are still unclear, which requires further investigation to provide more pre-clinical data for developing these approaches as a new therapeutic regimen. More efforts are still required to optimize the neutrophil-based therapeutic approaches to pave the way for clinical translation. Once the above-mentioned challenges are solved, neutrophil-based engineering and targeting would provide new strategies for cancer therapy.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

drug delivery, extracellular vesicles, membrane, neutrophils, targeted therapy

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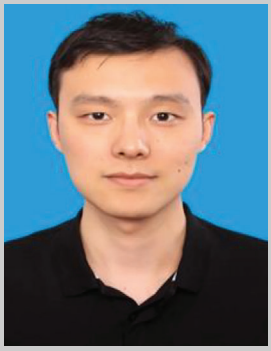

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