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Exosomes shape inflammatory tumor microenvironment

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ABSTRACT

The pervasive inflammatory response orchestrates every stage of tumor initiation and progression, not only serving as a catalyst for tumorigenesis but also as a nurturing environment for malignant growth. Within this intricate microenvironment teeming with cancer cells, immune cells, and stromal cells, a continuous exchange of inflammatory signals mediated by exosomes, small membrane-bound vesicles guide the development of the proinflammatory tumor microenvironment (TME). In this review, we delve into the intricate dialogue mechanisms among tumor cells, resident immune cells and stromal cells, scrutinizing the roles of exosomes derived from both tumor cells and other resident cells in shaping the inflammatory milieu. Anti-tumor therapies harnessing the diverse compositions and effects of exosomes have unveiled novel strategies for combating tumor malignancy.

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1. Introduction

Neoplasms remain a leading cause of mortality worldwide and increasing evidence suggests that tumor progression is not merely determined by genetic alterations within tumor cells, but also profoundly influenced by intricate interplays between tumor cells and their surrounding microenvironment [1–3]. Renowned as a critical mediator of tumor development, the tumor microenvironment (TME) comprises a diverse array of components, including immune cells, stromal cells, extracellular matrix, cytokines, chemokines and signal molecules, intricately shaping the behaviors and properties of tumor cells and other cells [4–6]. The inflammatory response has undergone a remarkable transformation in its perceived role, initially recognized as the body's defense against infections, and now understood to be a pivotal driving force within the TME. This central orchestrator within the TME exerts a profound impact, influencing not only the initial formation of tumors but also exerting regulatory control over their subsequent growth, invasion, and metastasis [7,8]. This understanding has unveiled the multifaced roles of inflammation in tumor development, exposing an intricate relationship between the tumor inflammatory response and tumor progression such as tumor growth, metastasis, and treatment resistance.

The establishment of the inflammatory TME is a complex process involving dynamic interplays of multiple factors, with exosomes emerging as critical signaling mediators [9–11]. These ubiquitously secreted membrane vesicles are produced by virtually all cell types, and have garnered significant attention as pivotal players in the intricate landscape of cell-to-cell communications [12–14]. Exosome biogenesis is regulated by multiple molecules, and studies have demonstrated the profound impact of inflammatory factors on their secretion [15,16]. Reciprocally, exosomes induced by inflammation have been shown to effectively induce inflammatory responses in recipient cells [17,18]. Within the inflammatory TME, the molecules released by exosomes presumably play crucial regulatory roles in both tumor development and inflammatory processes [19,20]. Notably, the microRNA (miRNA) cargoes within exosomes can target and modulate the expression of inflammatory factors, thereby influencing the nature and magnitude of the inflammatory response [21]. Moreover, proteins and cytokines within exosomes play vital roles in mediating tumor cell communication and regulating the TME [22,23]. This intricate molecular regulatory network underscores the fundamental biological roles of exosomes in shaping the inflammatory TME.

In this review, we delve into the intricate interplays between tumor resident cells and their exosomes in shaping the inflammatory TME and the consequent therapeutic implications. By unrav-

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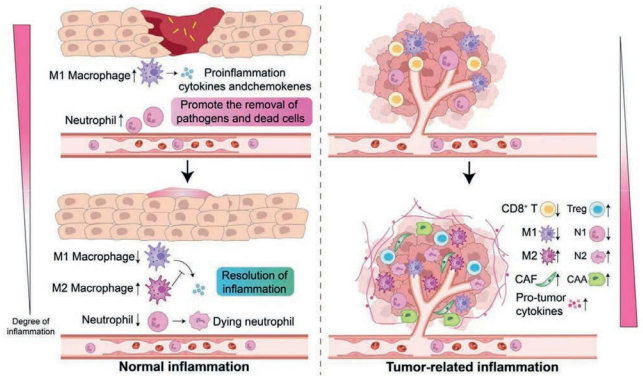


Fig. 1. The inflammatory responses in normal and tumor tissues. In the early stages of inflammation, macrophages engulf pathogens or dead cells, intensifying inflammatory signals through the secretion of pro-inflammatory factors and chemokines. As inflammation progresses, M1 macrophages undergo polarization into M2 cells, leading to the suppression of pro-inflammatory factors. Additionally, the secretion of neutrophils and the late apoptosis of neutrophils collaboratively contribute to the resolution of inflammation. While in the early stages of cancer, tumor cells are under the surveillance of immune cells. However, as the tumor evolves, resident cells in the TME undergo reeducation by tumor cells, promoting tumor growth. This is manifested by the proliferation of immunosuppressive cells such as M2, Tregs, N2, and pro-cancer stromal cells. This disrupts the balance of the cytokine network between tumor cells and immune cells, leading to the secretion of many inflammatory factors (pro-cancer factors), thus creating chronic inflammatory TME.

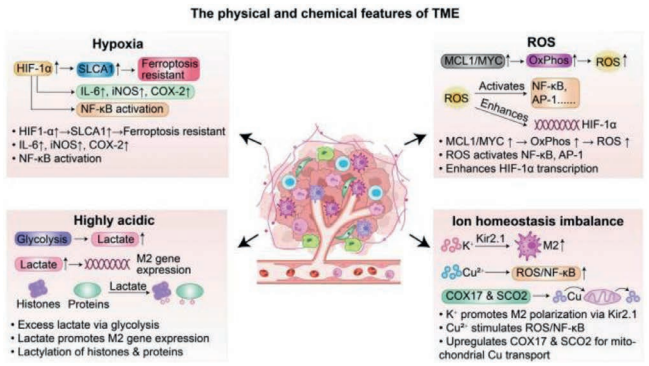


Fig. 2. The physical and chemical features of the TME that promote chronic inflammation. Multiple physicochemical factors within the TME contribute to the establishment of a chronic inflammatory state that supports tumor progression and immune evasion. (1) Hypoxia: Rapid tumor cell proliferation leads to oxygen deprivation, and upregulates HIF-1α, which consequently activates SLC1A1 and pro-inflammatory mediators such as IL-6, iNOS, and COX-2, and promotes NF-κB activation and resistance to ferroptosis. (2) ROS: High ROS levels arise from mitochondrial oxidative phosphorylation (OxPhos), particularly under the regulation of MCL1 and MYC. ROS enhances transcription of HIF-1α and activates pro-inflammatory transcription factors such as NF-κB and AP-1. (3) Acidic environment: Increased glycolysis generates excess lactic acid, which induces histone/protein lactylation and upregulates M2 macrophage gene expression, contributing to an immunosuppressive and chronic inflammatory TME. (4) Ion imbalance: Elevated extracellular potassium (K^+) and copper ions (Cu^{2+}) influence immune cell polarization. K^+ promotes M2 macrophage polarization *via* Kir2.1, while Cu^{2+} triggers ROS/NF-κB signaling and upregulates mitochondrial copper transporters (COX17 and SCO2), further enhancing inflammation. Together, these interrelated factors establish a supportive niche for tumor survival, immune escape, and chronic inflammation.

eling the multifaced mechanisms through which exosomes contribute to the establishment of the inflammatory TME, our aim is to provide novel insights that can inspire the development of innovative therapeutic strategies. The exploration of the roles of exosome-driven inflammatory TME holds the potential to elucidate a more profound understanding of the microscopic mechanisms underlying tumor procession, thus paving the way for the identification of novel targets and strategies to advance tumor treatment.

2. The features of inflammatory TME

2.1. Understanding the inflammatory microenvironment: Normal versus *tumor*

Inflammation is a host defense mechanism that restores tissue homeostasis in response to infection or injury (Fig. 1) [24,25]. In normal tissues, immune cells such as macrophages and neutrophils coordinate the production of cytokines and chemokines to regulate immune responses and repair, with macrophages transitioning from a pro-inflammatory (M1) to an anti-inflammatory (M2) phenotype during resolution [26–28]. This tightly regulated process is self-limiting and promotes wound healing. In tumors, however, this balance is disrupted. Tumor-associated inflammation is persistent, driven by sustained immune activation and abnormal communication among TME-resident cells [29–31]. Pro-inflammatory cytokines such as interleukins (ILs), tumor necrosis factor-α (TNF-α), and transforming growth factor-β (TGF-β) maintain pathological crosstalk [32,33], leading to prolonged immune cell activation and stromal cell reprogramming [34,35]. As a result, the TME maintains a pro-inflammatory milieu in which normal mechanisms of resolution are impaired, promoting tumor growth, proliferation, and metastasis.

2.2. Physicochemical factors promoting chronic inflammation in TME

Chronic inflammation in the TME is sustained not only by impaired resolution mechanisms but also by distinct physicochemical conditions, including hypoxia, elevated reactive oxygen species (ROS), acidic pH, and ion homeostasis disruption. These factors promote the polarization and activation of pro-inflammatory cells, reinforcing tumor-promoting inflammation (Fig. 2).

2.2.1. Hypoxia

Hypoxia is a hallmark of solid tumors and a potent driver of inflammation [36,37]. Hypoxia-inducible factor 1-alpha (HIF-1α) enhances lactate production, regulates ferroptosis resistance, and promotes therapeutic resistance [38,39]. Importantly, HIF-1α promotes inflammatory responses by inducing IL-6, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) expression, and its activity is strongly synergistic with nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling [40]. This bidirectional interaction forms a positive feedback loop: Hypoxia-driven pro-inflammatory mediators enhance NF-κB activation, which in turn elevates HIF-1α transcription [41–44]. Consequently, hypoxia acts as both a trigger and amplifier of tumor-associated inflammation.

2.2.2. ROS

In normal tissues, elevated ROS can activate M1 macrophages to produce inflammatory mediators. In tumors, however, ROS often support cancer cell self-renewal and drug resistance [45]. For example, in triple-negative breast cancer, myeloid cell leukemia-1 (MCL1) and MYC proto-oncogene, bHLH transcription factor (MYC) overexpression promotes mitochondrial oxidative phosphorylation in resistant tumor stem cells, leading to ROS accumulation, HIF-1α stabilization, and enhanced survival [46]. Similarly, platinum drugs in ovarian cancer selectively expand tumor stem cells dependent on mitochondrial oxidative phosphorylation, generating high ROS levels [47]. Elevated ROS also activate transcription factors such as NF-κB and activator protein-1 (AP-1), reinforcing inflammatory signaling [48,49]. Thus, ROS are indispensable in maintaining the inflammatory TME.

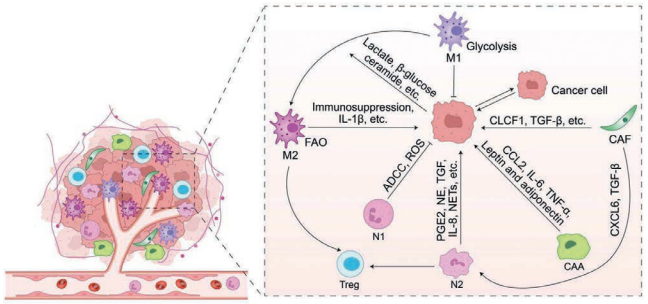


Fig. 3. TME-resident cells are re-educated by tumor cells to support tumor progression. Tumor cells, as central regulators of the TME, secrete various inflammatory mediators (*e.g.*, cardiotrophin-like cytokine factor 1 (CLCF1), TGF-β) that educate surrounding immune and stromal cells, fostering an immunosuppressive and pro-tumorigenic niche. Macrophages are polarized from M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotypes under the influence of lactate, β-glucose, ceramides, and other metabolites. M2 macrophages rely on FAO for energy supplement and secrete IL-1β and other immunosuppressive factors, promoting immune escape and tumor progression. Neutrophils are similarly reprogrammed into an N2 phenotype, which releases prostaglandin E2 (PGE2), neutrophil elastase (NE), TGF-β, IL-8, and neutrophil extracellular traps (NETs), promoting chronic inflammation and supporting tumor progression. In contrast, anti-tumor N1 neutrophils are suppressed by antibody-dependent cell-mediated cytotoxicity (ADCC) and ROS pathways. Stromal cells such as CAFs and CAAs are also key contributors to the inflammatory TME. CAFs secrete CXCL6 and TGF-β, supporting immune modulation and neutrophil recruitment. CAAs release CCL2, IL-6, TNF-α, leptin, and adiponectin, which support tumor proliferation, metabolic reprogramming, and immune suppression. Collectively, this network of multiple interactions establishes a chronic inflammatory loop within the TME that facilitates tumor growth, metastasis, and therapeutic resistance.

2.2.3. Acidic environment

The vigorous glycolysis of tumor cells often leads to the production of excess lactic acid, resulting in formation of an acidic TME [50,51]. Lactate directly modulates immune responses; for instance, it can induce hypoxia- and inflammation-related pathways in macrophages, increasing their lactate production in a feed-forward manner [52]. It also promotes M2 macrophage polarization and immunosuppressive phenotypes [53]. Increased lactylation modification caused by excessive lactate is also an important driving factor inducing tumor progression and the formation of the inflammatory TME [54,55].

2.2.4. Ion homeostasis disruption

Altered ion concentrations are another characteristic of tumors. Elevated K^+ levels can drive M2 polarization of tumor-associated macrophages (TAMs) *via* Kir2.1, impairing their anti-tumor activity [56]. In breast cancer, serum Cu^{2+} levels are elevated compared to healthy individuals [57], with increased expression of copper chaperones COX17 and SCO2 in mitochondria, indicating higher copper demand [58]. Copper ions can activate the ROS/NF-κB pathway, as seen in Parkinson's disease [59], and modulate macrophage inflammatory factor production [60]. Although direct evidence in tumors is limited, ion imbalance is likely an important contributor to chronic inflammatory TME.

2.3. TME-resident cells are educated by chronic inflammatory microenvironment

Tumor cells act as central orchestrators in the TME, continuously releasing pro-inflammatory mediators that reprogram immune and stromal cells [61]. This reciprocal "education" establishes a chronic inflammatory and immunosuppressive milieu, driving tumor progression and immune evasion (Fig. 3) [62].

2.3.1. Macrophages

TAMs can comprise up to half of TME-infiltrating leukocytes [63,64] and display remarkable plasticity in response to tumor-derived IL-4, IL-13, and other factors [65–67]. While macrophages initially exhibit anti-tumor M1 functions, they are progressively polarized toward an M2 phenotype, marked by reduced antigen presentation, increased immune checkpoint expression (programmed death-ligand 1 (PD-L1), T-cell immunoglobulin and mucin domain-containing protein 3 (TIM3)), and secretion of immunosuppressive cytokines [68–70]. The accumulation of M2 TAMs leads to the formation of an immunosuppressive microenvironment that promotes the establishment of a chronic inflammatory TME, which is associated with a dismal prognosis [71–73]. This polarization is tightly linked to metabolic reprogramming, particularly enhanced fatty acid oxidation (FAO) and oxidative phosphorylation, driven by CD36-mediated lipid uptake [74–78]. FAO-induced ROS promotes NLRP3 inflammasome activation and IL-1β release, further fueling tumor-promoting inflammation. Inhibiting FAO or blocking IL-1β has been shown to impair TAM-mediated tumor support in models of hepatocellular and pancreatic cancer (PC) [79,80].

2.3.2. Neutrophils

Neutrophils, traditionally viewed as anti-tumor effectors [81,82], are reprogrammed in the TME into tumor-associated neutrophils (TANs) [83]. Under granulocyte-macrophage colony-stimulating factor (GM-CSF), TGF-β, and IL-6 influence [84–86], TANs shift from N1 to N2 phenotypes, producing TGF-β, C-X-C motif chemokine ligand 8 (CXCL8)/IL-8, and matrix metalloproteinases to promote malignancy [74,87]. N2 TANs suppress natural killer (NK) cell functions and recruit M2 macrophages and regulatory T cells (Tregs) [83,88]. They also release ROS, miRNA-containing microparticles, and DNA-damaging factors, enhancing genomic instability and inflammatory cytokine production [31,89,90], as well as prostaglandin E2, neutrophil elastase, and neutrophil extracellular traps to facilitate tumor growth [89,91].

2.3.3. Stromal cells

Stromal cells, including cancer-associated fibroblasts (CAFs), cancer-associated adipocytes (CAAs), endothelial cells, pericytes, and mesenchymal stem cells, promote angiogenesis, immune evasion, metabolic adaptation, and therapy resistance [92,93]. Among them, CAFs are particularly influential, secreting TGF-β, vascular endothelial growth factor (VEGF), IL-6, CXCL12, and TNF-α to recruit and polarize immune cells, such as driving neutrophil transformation into N2 phenotypes [94–97]. They also activate IL6-Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) signaling to enhance proliferation and reduce chimeric Antigen Receptor T-cell (CAR-T) therapy sensitivity *via* TGF-β-mediated suppression [98]. Notably, targeting CAF-specific pathways has been shown to reverse their tumor-promoting phenotype and improve therapeutic response [94]. CAAs similarly secrete chemokine (C–C motif) ligand 2 (CCL2), IL-6, TNF-α, and adipokines such as leptin and adiponectin [99–101]. Leptin activates STAT3 and promotes fatty acid β-oxidation in T cells, impairing anti-tumor activity [102], while adiponectin suppresses NF-κB signaling and macrophage phagocytosis [103–105]. In addition to signaling roles, CAAs provide lipids, ketones, and amino acids that fuel tumor metabolism and reprogram immune cell function [106,107].

Collectively, the inflammatory TME is shaped by reciprocal interactions between tumor cells and resident immune and stromal cells. Tumor-derived signals reprogram macrophages, neutrophils, CAFs, and CAAs to reinforce inflammation, immune suppression, and metabolic adaptation. These interactions form a self-sustaining circuit that drives tumor progression and therapy resistance. Targeting this network may offer effective strategies for TME remodeling.

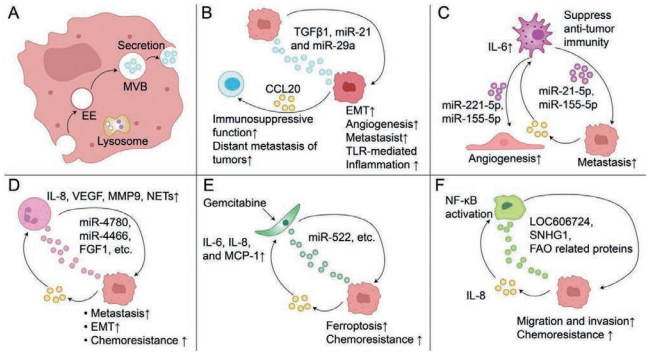


Fig. 4. Roles of exosomes in TME. (A) Schematic representation of exosomes biogenesis. (B) Exosomes derived from tumor cells can promote their own EMT by carrying TGFβ1, miR-21 and miR-29a, thereby enhancing their malignancy and creating an inflammatory environment. They can also amplify the production of immunosuppressive exosomes to enhance the function of Treg cells through delivering CCL20. (C) In addition to creating a tumor immunosuppressive microenvironment, M2 macrophage-derived exosomes can promote the metastasis of tumor cells by delivering miR-21–5p and miR-155–5p, and enhance the proliferation of vascular endothelial cells through miR-221–5p and miR-155–5p (D) N2-type neutrophil-derived exosomes can promote tumor cell metastasis, EMT and chemotherapy resistance by delivering miR-4780, miR-4466, fibroblast growth factor 1 (FGF1), piRNA-17,560, *etc.* In turn, TEX can promote the secretion of IL-8, VEGF and other cytokines. (E) Gemcitabine enhances the secretion of exosomes from CAFs cells, and these exosomes can protect tumor cells from ferroptosis and improve resistance to chemotherapy by delivering miR-522, *etc.* In turn, TEX can promote the secretion of its inflammatory cytokines. (F) Tumor-associated adipocytes can promote tumor cell metastasis and chemotherapy resistance by secreting proteins carrying LOC606724 or SNHG1 and FAO related proteins, in turn, TEX can promote the activation of the NF-κB pathway in adipocytes and promote their lipolysis.

3. Exosomes secreted in inflammatory TME promote tumor growth

Exosomes are small, membrane-bound vesicles that serve as efficient carriers for diverse bioactive molecules [108]. Their biogenesis (Fig. 4A) originates within multivesicular bodies (MVBs) and is primarily regulated by the endosomal sorting complex required for transport (ESCRT), a multi-component protein machinery [109,110]. The ESCRT pathway facilitates the formation of intraluminal vesicles (ILVs) within MVBs. ESCRT-0 initially recognizes ubiquitinated proteins and directs them to the endosomal membrane [110–112]. The coordinated action of ESCRT-I and ESCRT-II drives inward membrane budding, leading to ILV formation and maturation of MVBs into late endosomes (LE) [113]. Most MVBs subsequently fuse with lysosomes, resulting in cargo degradation [114]. However, a subset of MVBs instead fuses with the plasma membrane, releasing ILV-derived exosomes into the extracellular space *via* exocytosis [115]. These vesicles encapsulate nucleic acids (*e.g.*, miRNAs, mRNAs), proteins, and lipids, and circulate through body fluids such as blood, lymph, urine, and saliva to mediate intercellular communications among cells [116]. Within the inflammatory TME, specifically, the secretion and molecular composition of exosomes are tightly regulated. Consequently, exosomes derived from tumor cells and TME-resident cells actively shape the inflammatory landscape through multiple interrelated mechanisms [117]. Therefore, understanding the biosynthesis of TME-related exosomes and revealing the mechanisms by which they promote tumor growth will help us understand the regulatory network of tumor progression in depth.

3.1. Exosome secretion is regulated by physicochemical properties in the inflammatory TME

TME is physicochemically featured with hypoxia, high oxidative stress and high acidity. These special physicochemical properties are also the main factor leading to the changes of exosome biosynthesis and exosomal cargos in TME, as summarized in Table S1 (Supporting information) and further discussed below.

3.1.1. Hypoxia

A large number of studies have shown that oxygen deficiency helps enhance the synthesis and secretion of cellular exosomes [118,119]. In the study on gastric cancer (GC), it was found that hypoxia can promote the secretion of exosomes from GC cells in an HIF-1α-dependent manner, and GC-exo is rich in miR-301a, which can inhibit HIF-1α degradation by targeting prolyl hydroxylase 3 (PHD3), forming a positive cycle of enhanced exosome secretion and promoting tumor progression [120]. In the study on PC, it was found that hypoxia-induced upregulation of HIF-1α can promote the transcription of circular RNA pyruvate dehydrogenase kinase 1 (circPDK1) in PC cells, thereby upregulating the level of circPDK1 in exosomes, activating the bromodomain PHD finger transcription factor (BPTF)/c-Myc axis, and promoting the proliferation and aerobic glycolysis of PC cells [121]. Compared with normoxic glioma-derived exosomes, hypoxic glioma-derived exosomes highly expressed IL-6 and miR-155–3p, which can promote glioma progression by inducing M2-like macrophage polarization through an IL-6-pSTAT3-miR-155–3p-autophagy-pSTAT3 positive feedback loop [122]. Interestingly, PC cells secrete more exosomes under hypoxia with high levels of lactate, which may be related to the use of exosomes as a metabolic waste removal mechanism to promote their survival under chronic hypoxia [123]. Although there is a lot of evidence that hypoxia promotes the secretion of extracellular exosomes and causes tumor malignancy, its molecular mechanism has not been well understood yet.

3.1.2. ROS

Studies have reported that ROS levels in tumor cells are significantly higher than in normal cells, which is determined by the high metabolic activity of tumors [124,125]. The homeostasis of ROS levels is closely related to tumor cell proliferation and drug resistance. Studies have found that intracellular ROS can inhibit the lysosomal degradation of MVBs and synergistically enhance the release of exosomes [126]. Additionally, increased oxidative stress levels can induce endoplasmic reticulum stress, and thus promote the biogenesis of exosomes [127]. Supportively, the use of nanomaterials such as platinum, palladium, and graphene oxide to induce cellular oxidative stress can also lead to endoplasmic reticulum stress response and promote the production of cellular exosomes [128–130]. However, it is also pointed out that excessive ROS can also promote the degradation of MVBs by promoting autophagy, thus inhibiting the exosome secretion. Autophagy inhibitors can restore the exosome secretion [131]. This also indicates that ROS plays a complex role in regulating the secretion of exosomes.

3.1.3. Acidic environment

The acidic TME has a significant impact on the production and function of exosomes. The study found that when cell culture conditions were adjusted from pH 7.4 to the typical pH 6.5 in the TME, exosome release from tumor cells increased [132]. Using exosomes collected in an acidic microenvironment to treat normal tumor cells can significantly promote their ability to invade and migrate [133]. The uptake experiment of exosomes secreted under different pH conditions found that the exosomes secreted under low pH were most efficiently taken up by parental cells, which is related to the glycerolipid self-aggregation-based mechanism of the exosomes produced under this condition [134,135]. Lactic acid, as an important acidic component in the TME, can also regulate the secretion of exosomes by lactylating key proteins. Studies have found that after macrophages take up lactate, they can recruit acetylase p300/CBP to the nucleus through Hippo/Yes-associated pro-

tein (YAP) and β-arrestin2 to stimulate HMGB1 acetylation, and lactated/acetylated HMGB1 is released from cells through exosome secretion and has the ability to regulate endothelial permeability [136]. Therefore, normalization of TME pH may inhibit tumor progression by normalizing exosome secretion.

3.2. TME-related exosomes reshape the inflammatory TME and promote the tumor progression

3.2.1. Tumor-derived exosomes (TEXs) help shape the inflammatory TME

As mentioned previously, the inflammatory TME promotes the secretion of tumor-associated exosomes, and consequently exosomes originating from tumor cells help shape the inflammatory TME (Fig. 4B). Current research underscores the indispensable contribution of Toll-like receptor (TLR) signaling in this process [137]. Exosomal RNA, particularly enriched in small nuclear RNA (snRNA), derived from primary tumors, is shown to activate TLR3 signaling pathway in lung epithelial cells, leading to chemokine secretion, neutrophil recruitment, and the establishment of premetastatic tumor niches [138]. Similarly, exosomes released by lung cancer cells contain miR-21 and miR-29a, and interact with human TLR8 and murine TLR7. This interaction triggers TLR-mediated NF-κB pathway activation, thereby driving tumor growth and metastasis [139]. Likewise, exosomes derived from lung cancer cells engender a pro-inflammatory phenotype in mesenchymal stem cells, resulting in increased secretion of IL-6, IL-8, and monocyte chemotactic protein-1 (MCP-1), and supporting lung tumor growth *via* TLR2-dependent NF-κB activation [140,141]. TEXs incite immune cells to release TLR2- and TLR4-dependent pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β [142,143]. *Vice versa*, TLR4 activation amplifies immunosuppressive molecules in TEXs, further supporting tumor cell survival and progression [144]. In addition to the contribution to TLR-mediated pathway activation to the formation of the inflammatory microenvironment, TEXs are also involved in its formation through other mechanisms. Lung cancer or colon cancer cells have been shown to secret IL-8-rich TEXs to activate the NF-κB pathway and stimulate lipolysis in adipocytes [145]. Exosomes derived from nasopharyngeal carcinoma cells can promote the secretion of IL-6 by activating the macrophage STAT3 pathway [146]. TEXs derived from liver cancer cells have also been reported to educate hepatic stellate cells and promote their resistance to SN38 through activating the IL6/STAT3 pathway [147]. TEXs have also been reported to promote the formation of tumor-associated neutrophil extracellular traps and promote the progression of colorectal cancer by inducing the expression of IL-8 [148]. All of these reports have pointed out the key role of TEXs in the formation of inflammatory TME.

3.2.2. Exosomes derived from TAMs promote the tumor progression

TAMs constitute a prominent immunosuppressive cell population within the TME, helping shape the inflammatory microenvironment [149]. Studies have revealed that exosomes derived from TAMs (TAMDEs) downregulate major histocompatibility complex class I (MHC-I) in tumor cells by delivering apolipoprotein E (ApoE, a key regulatory component of lipid metabolism), imparting resilience to T cell-mediated killing [150]. Interestingly, TAMs are considered to be involved in the establishment of an immunosuppressive microenvironment, while TAMDEs exhibit significant pro-inflammatory activity and can enhance the synthesis of inflammation-related lipids (*e.g.*, prostaglandins, leukotrienes, and thromboxanes) in tumor cells [151]. Beyond immune regulation, TAMDEs also directly promote tumor progression. For instance, TAMDEs transfer miR-21–5p and miR-155–5p to colorectal cancer cells, downregulating the expression of brahma-related gene1 (BRG1) by binding to its coding sequence, thereby promoting colorectal cancer metastasis [152]. In addition, some studies have demonstrated a positive correlation between TAMs and the microvessel density in pancreatic ductal adenocarcinoma (PDAC) tissues. TAMDEs are observed to promote tumor growth by increasing the blood vessel density in subcutaneous tumor tissues, a phenomenon associated with the transfer of high levels of miR-155–5p and miR-221–5p from TAMDEs to mouse aortic endothelial cells (Fig. 4C) [153].

3.2.3. Exosomes derived from TANs promote the tumor progression

Exosomes derived from TANs also exert potent pro-tumor survival effects (Fig. 4D). For instance, N2-neutrophil-derived exosomes (N2-NEXs) have rich miR-4780, which regulates the expression of the target gene SRY-box transcription factor 11 (SOX11) through delivery to colorectal cancer cells, promoting tumor growth and angiogenesis [154]. Moreover, miR-4466-rich N2-NEXs induce the stemness and metabolic switching of tumor cells by regulating the Ski oncogene (SKI)/SRY-box transcription factor 2 (SOX2)/carnitine palmitoyltransferase 1A (CPT1A) axis, thereby supporting their brain metastasis [155]. N2-NEXs also harbor multiple components that promote angiogenesis, tumor invasion and metastasis, including fibroblast growth factor-1, matrix metalloproteinases (MMPs), CD66c, and lipoprotein receptor-related protein 2 [156]. Additionally, research on senescent neutrophils indicates that exosomes derived from these cells play a role in promoting chemoresistance and epithelial-mesenchymal transition (EMT) in breast cancer tissues. This effect is enhanced through the delivery of piRNA-17,560, thereby facilitating fat mass and obesity-associated protein (FTO)-mediated m6A demethylation [157].

3.2.4. Exosomes derived from CAFs promote the tumor progression

CAFs play an important role in supporting tumor progression and drug resistance by secreting a plethora of bioactive substances (Fig. 4E). IL-33 is a member of the IL-1 family and plays a remarkable role in both inflammatory diseases and tumor progression [158]. Studies have shown that exosomes derived from CAFs can promote the EMT of ovarian cancerous cells by delivering IL-33, while increasing the polarization to M2 TAMs [159]. In lung cancer research, it has been found that under hypoxic conditions, exosomes derived from bone marrow mesenchymal stromal cells transfer miRNAs (miR-193a-3p, miR-210–3p and miR-5100) to tumor epithelial cells and promote lung cancer cell invasion by activating the STAT3 signaling pathway and increasing the expression of mesenchymal-related molecules in tumor cells [160]. In GC, CAFs secrete exosomes carrying miR-522, which suppresses ferroptosis in tumor cells through targeting arachidonate 15-lipoxygenase (ALOX15) and alleviating the accumulation of lipid-ROS [161]. PDAC-related CAFs enhance the secretion of exosomes under the stress of gemcitabine chemotherapy. These exosomes promote the resistance of tumor cells to chemotherapeutic drugs by upregulating the expression of Snail in recipient epithelial cells, which can be overcome using exosome inhibitor GW4869 [162].

3.2.5. Exosomes derived from CAAs promote the tumor progression

The definitive impact of CAAs-derived exosomes (ADEs) on the inflammatory TME remains to be fully elucidated, but their supportive role in tumor progression seems to be clear due to recent reports. For instance, CAAs associated with multiple myeloma (MM) have been shown to protect MM cells from chemotherapy-induced apoptosis by delivering LOC606724 or small nucleolar RNA host gene 1 (SNHG1), thereby enhancing METTL7A activity through enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2)-mediated protein methylation [163]. In the context of melanoma progression, ADEs harbor proteins linked to FAO, a

distinctive feature of CAA exosomes, thereby promoting the migration and invasion of melanoma. Inhibition of this metabolic pathway completely abolished the exosome-mediated rise in migration [164]. ADEs also exhibit potential pro-inflammatory effects since recent studies have revealed that CAA-secreted exosomal miRNA-34a represses M2 macrophage polarization, thereby fueling obesity-induced adipose inflammation [165]. Furthermore, circ0075932 in ADEs induces inflammation and apoptosis in human dermal keratinocytes by directly binding with Pumilio RNA binding family member 2 (PUM2) and promoting PUM2-mediated activation of the AuroraA/NF-κB pathway [166]. In studies on colitis, visceral adipose tissue is found to promote the differentiation of M1 macrophages through exosome transfer of pro-inflammatory miRNA such as miR-155 and aggravate the progression of colitis [167]. Collectively, these studies implicate the potential contribution of ADEs to inflammatory TME formation (Fig. 4F).

4. Strategies for exosome inhibition and elimination

4.1. Existing strategies for exosome inhibition or clearance

Converging evidence suggests that TEXs exert a crucial influence on tumor progression through autocrine and paracrine mechanisms, regulating critical components in the TME. Targeting TEXs for therapeutic intervention holds immense potential to improve treatment outcomes of cancer patients, as summarized in Table S2 (Supporting information). Aiming at the mechanism of exosome generation, a variety of compounds have been developed to inhibit the biosynthesis of cellular exosomes, such as tipifarnib, neticonazole, nexinhib20 and nexinhib4 targeting RAB27A [168–171], and GW4869, manumycin A and spiroepoxide targeting sphingomyelinase [172–175]. However, owing to the ubiquitous nature of exosome biogenesis and secretion mechanisms, direct interventions such as genetic engineering or drug modulation of exosomes could lead to undesirable side effects in clinical settings. Instead, targeting specific molecules that are uniquely upgraded in tumor cells for exosome production could provide a more selective approach, minimizing the impact on normal cells. A notable example is the study of MM where co-culturing myeloma cells with stromal cells augmented exosome production, which was positively correlated with enhanced expression of histone deacetylase 3 (HDAC3). Suppressing the HDAC3 level significantly reduced exosome generation in the co-culture system without affecting the release of exosomes from stromal cells [176]. This study demonstrates the feasibility of addressing tumor growth driven by TEXs through targeting exosome biogenesis pathways specifically in tumor cells.

Additionally, physicochemical strategies can be employed to eliminate circulating TEXs from the bloodstream. Dialysis, a common treatment for uremia, was combined with silica microspheres and blood filtration devices to selectively capture and remove circulating tumor cells and TEXs, offering a potential option for tumor management [177,178]. In addition, studies have reported that EGFR aptamers immobilized on mesoporous silica nanoparticles can bind to circulating lung cancer cell exosomes, allowing them to be excreted into the small intestine through the Oddi's sphincter and cleared up [179].

4.2. Potential strategies for regulating tumor exosome production

As discussed in the previous sections, the special physicochemical properties of the TME are favorable factors for promoting exosome signaling. Therefore, reversal therapy by regulating the physicochemical properties of the TME has the potential to regulate the biogenesis of exosomes. For example, treating A549 cells with aspirin can reduce the enhanced exosome secretion caused by hypoxia by inhibiting the upregulation of HIF1a-COX2 [180], suggesting that increasing oxygen levels in the TME may suppress exosome secretion by tumor cells. In this context, nanocatalytic oxygen generation systems hold promise for inhibiting tumor-derived exosome release by restoring the oxygen level in the TME. Similarly, the use of alkaline nanomaterials such as $CaCO_3$ [181], $Mg(OH)_2$ [182], and layered double hydroxides (LDHs) [183], is expected to help regulate the pH of the TME and inhibit tumor exosome secretion by neutralizing excess acid.

5. Exosome-based therapeutic strategies for cancer management

5.1. Utilizing the anti-tumoral cell-derived exosomes

While immune cells infiltrating the TME are frequently educated into tumor-supportive roles in the inflammatory TME, exosomes exhibiting tumoricidal properties can be generated by culturing immune cells of allogeneic or autologous origin *in vitro*. This particular subset of exosomes holds promising clinical applications (Table S3 in Supporting information).

5.1.1. NK cell-derived exosomes (NEOs)

NK cells, a class of killer immune cells not restricted by MHC, have gained increasing recognition in tumor immunotherapy [184]. Relevant studies have demonstrated that NEOs exert substantial stimulatory effects on peripheral blood mononuclear cells. These responses include the upregulation of human leukocyte antigen DR isoforms (HLA-DR) and costimulatory molecules on monocytes, alongside with an elevated expression of CD25 on T cells [185]. Notably, these effects are maintained even in the presence of lipopolysaccharide and IL-10/TGFβ. Moreover, NEOs exhibit an increase in the fraction of $CD56^+$ NK cells, suggesting promising potential for applications in cancer treatment [185,186]. In addition to immune regulation, NEOs possess inherent anti-tumor capacity [187]. Upon injection, NEOs are rapidly internalized by tumor cells [188], and then the internalized NEOs release the tumoricidal substances, such as perforin, miRNAs, and other factors, to induce tumor cell apoptosis [189,190].

5.1.2. M1 TAMs-derived exosomes

In cancer treatment strategies, inhibiting M2 TAMs or reversing M2 TAMs into M1 TAMs has potential therapeutic effects. Recent studies indicate that exosomes derived from M1 TAMs possess pro-inflammatory factors, amplifying the anti-tumor effect and converting M2 TAMs into the M1 phenotype, thereby counteracting the immunosuppressive TME [191,192]. It is demonstrated that M1 TAM-derived exosomes significantly enhance the cytotoxicity of breast cancer cells to PTX drugs by promoting the pro-inflammatory phenotype of TAMs in the TME [193]. Moreover, subcutaneous injection of M1 TAM-derived exosomes demonstrates a tropism toward lymph nodes, primarily being taken up by local macrophages and dendritic cells (DCs), inducing the release of the Th1 cytokine repertoire [193,194]. Exosomes derived from M1 TAMs have also demonstrated efficacy in enhancing cancer vaccine efficacy by creating a pro-inflammatory microenvironment in lymph nodes. A recent study has shown that M1 TAM-derived exosomes are more potent immune enhancers than CpG oligonucleotides when used in combination with lipid calcium phosphate nanoparticle-based vaccines [195]. Similarly, hybrid membrane vesicles based on M1 TAM-derived exosomes can promote tumor regression by delivering doxorubicin (DOX) to induce immunogenic cell death (ICD) in tumor cells, thereby activating antitumor immune responses [196].

5.1.3. DC-derived exosomes

As the most efficient antigen-presenting cells, DC cells can activate naive CD4 and CD8 T cells by engulfing, processing, and pre-

senting tumor antigens, thereby initiating specific anti-tumor immune responses [197,198]. Recent studies have demonstrated that exosomes derived from DCs (DC-exo) retain the fundamental functions of DCs [199,200]. The DC-exo membrane surface maintains functional MHC-I and MHC-II, co-stimulatory molecules (*i.e.*, CD80, CD86) and adhesion molecules (*i.e.*, intercellular adhesion molecule 1 (ICAM1)), enabling them to induce T cell immune responses [201,202]. After stimulating DCs with tumor antigens, their exosomes were gathered and injected into tumor-bearing mice. These DC-exo triggered tumor-specific CD8 T cell responses *in vivo*. A single intradermal injection of DC-exo demonstrated superior anti-tumor efficacy in eradicating established tumors compared with injection of DCs [203,204].

5.2. Instigating exosomes for anti-tumor drug delivery

Exosomes, with their unique biological characteristics, have emerged as promising candidates for delivery of therapeutic cargoes [205–207], as summarized in Table S3. One notable attribute is their inherent ability to efficiently traverse biological barriers, including the blood-brain barrier, due to their small size, lipid bilayer structure, and more importantly, specific membrane receptors from origin cells [208,209]. Moreover, the stability of exosomes in circulation further enhances their suitability as carriers [210,211]. Unlike free drugs or molecules, exosomes can shield their cargoes from degradation, prolong their half-life in the blood, and provide sustained and controlled release at designated sites [212]. Furthermore, benefiting from the abundance of host cell-specific receptors retained on the exosome membrane, selective killing of tumor cells can be achieved through targeting homologous receptors [205,213]. Therefore, harnessing the properties of exosomes derived from tumor cells and TME-resident cells holds immense potential in the development of anti-tumor treatments. For instance, long-term use of DOX chemotherapy poses a serious risk of cardiotoxicity, leading to complications such as arrhythmia and congestive heart failure, and imposing limitations on the widespread clinical application of DOX [214]. Capitalizing on the homologous targeting capacity of tumor exosomes offers a solution, enabling DOX to be precisely directed to tumor cells while minimizing detrimental side effects. Studies have revealed that DOX-loaded exosomes derived from breast cancer cells, in contrast to DOX alone, exhibit superior targeting and delivery of DOX to tumor cells, resulting in a substantial inhibition of tumor growth [215,216]. Additionally, neutrophils possess exceptional chemotactic ability at inflammatory sites, and their exosomes retain this characteristic. In the study of glioma, neutrophil-derived exosomes are found to effectively penetrate the blood-brain barrier and accumulate at glioma sites. By loading DOX, they effectively inhibit tumor growth and prolong the survival time of tumor-bearing mice [217]. Another innovative approach involves using tumor exosomes to modify DOX-loaded nanoparticles, promoting their accumulation within tumor cells. This strategy has achieved a synergistic effect of chemotherapy and photothermal therapy on breast cancer treatment [218].

5.3. Engineered exosomes have potential anti-cancer therapeutic capabilities

In addition to loading drugs to achieve the effect of attenuating toxicity and increasing efficacy, exosomes are also a druggable material that is very suitable for biological modification (Table S3) [219]. First, stem cell-derived exosomes themselves have anti-inflammatory activity and have been shown to significantly combat virus-induced excessive inflammatory responses in coronavirus disease 2019 (COVID-19) clinical trials [220–222]. However, natural exosomes cannot achieve real-time response to physiological signals or controlled release of drugs due to their poor targeting ability. Therefore, synthetic biology technology has been used to express the targeted molecules on the surface of exosomes to enhance their active targeting function [223]. Studies suggest that exosomes can express ligands of inflammatory factors on their membrane surface through genetic engineering, which has the potential to neutralize excessive inflammatory factors in the microenvironment. It is found that highly expressing tumor necrosis factor receptor 1 (TNFR1) on the surface of cell membrane nanovesicles competitively binds TNF-α, which can resolve the inflammation and promote wound healing in burn models [224]. Dual expression of immune checkpoints PD-L1 and fibrinogen-like protein 1 (FGL1) in exosomes from mesenchymal stem cells significantly promoted the survival of organ transplant models by inhibiting excessive activation of immune cells [225]. In addition, BCMA nanovesicles constructed using the affinity of BCMA receptors for the pro-oncogenic cytokine proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF) also inhibited the progression of MM by binding to these factors [226]. These studies have shown the potential of expressing anti-inflammatory molecules through exosome regulation in the inflammatory environment.

6. Conclusions and challenges

In summary, our review presents an overview of the pervasive role of the inflammatory response throughout tumor genesis and progression, highlighting its dual nature as both a trigger and a promoter. In the complex microenvironment containing cancer cells, immune cells, and stromal cells, the inflammatory communication mediated by exosomes derived from these diverse cell types emerges as a pivot in shaping the inflammatory TME. The heterogeneous cargoes of exosomes contribute to both pro- and anti-tumor effects within the TME. Unveiling the intricate dynamics of exosome-mediated signaling lays the foundation for developing targeted therapeutic strategies that could effectively modulate the inflammatory TME and enhance cancer treatment outcomes.

However, targeting the inflammatory TME with therapeutic strategies still presents numerous challenges [227]. Exosomes are continuously secreted by tumor cells and other resident cells within the TME, posing significant obstacles to their efficient clearance. While single-session exosome clearance based on dialysis may offer some degree of efficacy, its effectiveness is limited. Increasing clearance frequency may enhance the effect, but inevitably increases treatment costs. Moreover, exosomes inherently play a crucial role in intercellular signaling, and excessive clearance may lead to unexpected adverse effects. Therefore, there is an urgent need to develop precise clearance strategies targeting inflammatory TME exosomes. On the other hand, drug-specific inhibition of tumor exosome generation emerges as a promising alternative for cancer treatment. Due to substantial heterogeneity observed across various cancer types and individuals, personalized treatment plans may be necessary for each case because this heterogeneity manifests in the differential expression levels of signaling molecules that enhance the exosome secretion pathway. Therefore, identifying potential molecules that are highly expressed in specific cancer cells and promote exosome secretion is the key step for clinical translational potential.

Current clinical trials have demonstrated the wide-ranging applications of exosomes in various fields, including exosome-based cell-free therapy, biomarkers, drug delivery systems, and the development of anti-tumor vaccines (Table S4 in Supporting information) [228]. These applications hold tremendous potential for transformative changes in the medicine and biotechnology industries. Unfortunately, a significant obstacle to the clinical translation of exosomes lies in the procurement of high-purity, clinical-grade exosomes on a large scale and the establishment of standardized purification protocols. The absence of harmonized stan-

dards for isolation, identification, and quality control hinders the attainment of high-purity and stable-quality exosomes. Besides, research on exosome quality control needs to be reinforced to establish a holistic quality control system that ensures the safety and quality of isolated exosomes.

Overall, as a regulatory component of tumor progression, exosomes play a key role in tumor progression and the formation of the inflammatory microenvironment. Although the complex regulatory mechanisms of exosomes in the formation of TME remain to be further explored, a better understanding will help improve targeted anti-tumor treatment through multifaceted exosomes.

CRediT authorship contribution statement

Chao He: Writing – original draft, Visualization, Formal analysis, Data curation. **Wanpin Yu:** Visualization, Formal analysis, Data curation. **Qingyuan Zhao:** Visualization, Formal analysis, Data curation. **Huina Liu:** Investigation. **Yu Wang:** Investigation. **Yue Xiong:** Investigation. **Yuqing Zeng:** Investigation. **Jing Zhao:** Investigation. **Zhi Ping Xu:** Writing – review & editing, Supervision, Conceptualization. **Lingxiao Zhang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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