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REVIEW

The role of tumor-platelet interplay and micro tumor thrombi during hematogenous tumor metastasis

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Abstract

Background In addition to their pivotal roles in coagulation and thrombosis, platelets are crucial in tumor progression, with plenty of clinical and experimental data demonstrating that the interplay of platelets and tumor cells is essential for hematogenous tumor metastasis. After detach from primary sites, tumor cells intravasate into the blood circulation becoming circulating tumor cells and induce platelet activation, aggregation and encasement around tumor cells to form micro tumor thrombi, which create a permissive tumor microenvironment for metastasis. Platelets in micro tumor thrombi protect tumor cells from immune surveillance and anoikis (detachment-triggered apoptosis) through various pathways, which are significant for tumor cell survival in the bloodstream. Moreover, platelets can facilitate tumor metastasis by expediting epithelial-mesenchymal transition (EMT), adhesion to the endothelium, angiogenesis, tumor proliferation processes and platelet-derived microvesicle (PMV) formation.

Conclusions Here, we provide a synopsis of the current understanding of the formation of micro tumor thrombi and the role of micro tumor thrombi in tumor hematogenous metastasis based on the tumor-platelet interplay. We also highlight potential therapeutic strategies targeting platelets for tumor treatment, including cancer-associated platelet-targeted nanomedicines.

Keywords Platelets · micro tumor thrombi · Tumor-platelet interplay · Hematogenous metastasis · cancer therapy

1 Introduction

The prognosis of tumor patients has substantially improved due to standardized therapy, including surgical excision, chemotherapy and radiotherapy. However, the development of metastasis, which represents advanced disease, has become the major cause of cancer-related death [1]. Therefore, unraveling the mechanism of tumor metastasis is of great importance to improve the prognosis of patients with advanced tumors. Hematogenous tumor metastasis commonly involves the following events: (i) invasion of tumor cells into the extracellular matrix (ECM) of primary sites and intravasation; (ii) escape from immune surveillance and acquisition of anoikis resistance, which are vital for circulating tumor cells (CTCs) survival in blood circulation; and (iii) adhesion to blood vascular endothelium, extravasation and invasion of metastatic sites, in which tumor cells adapt to the new microenvironment and proliferate (Fig. 1).

Generated from megakaryocytes in bone marrow, platelets are small enucleated cells circulating in the bloodstream. Physiologically, platelets are essential in coagulation and thrombosis processes, maintaining the integrity of vascular walls. Upon vascular injury, platelets adhere to disrupted vascular endothelium through the interaction of (GP)Ibα and von Willebrand factor (vWF). Platelet surface integrins could bind to collagen on disrupted endothelium surface, thus leading to platelet activation and thereafter release of ADP, TXA_2 and serotonin that facilitate platelet aggregation. Recently, platelet-derived microvesicles (PMVs) have attracted much attention due to their participation in many physiological and pathological conditions. In fact, PMVs are the major part of microvesicles in blood circulation [2]. PMVs are derived from inversion of the plasma membrane and carry cytosolic components to the outer space. Due to their origin, PMVs contain platelet-derived components encapsulated with a lipid bilayer mirroring the platelet membranes. Thus, PMVs could be deemed mediators of platelet

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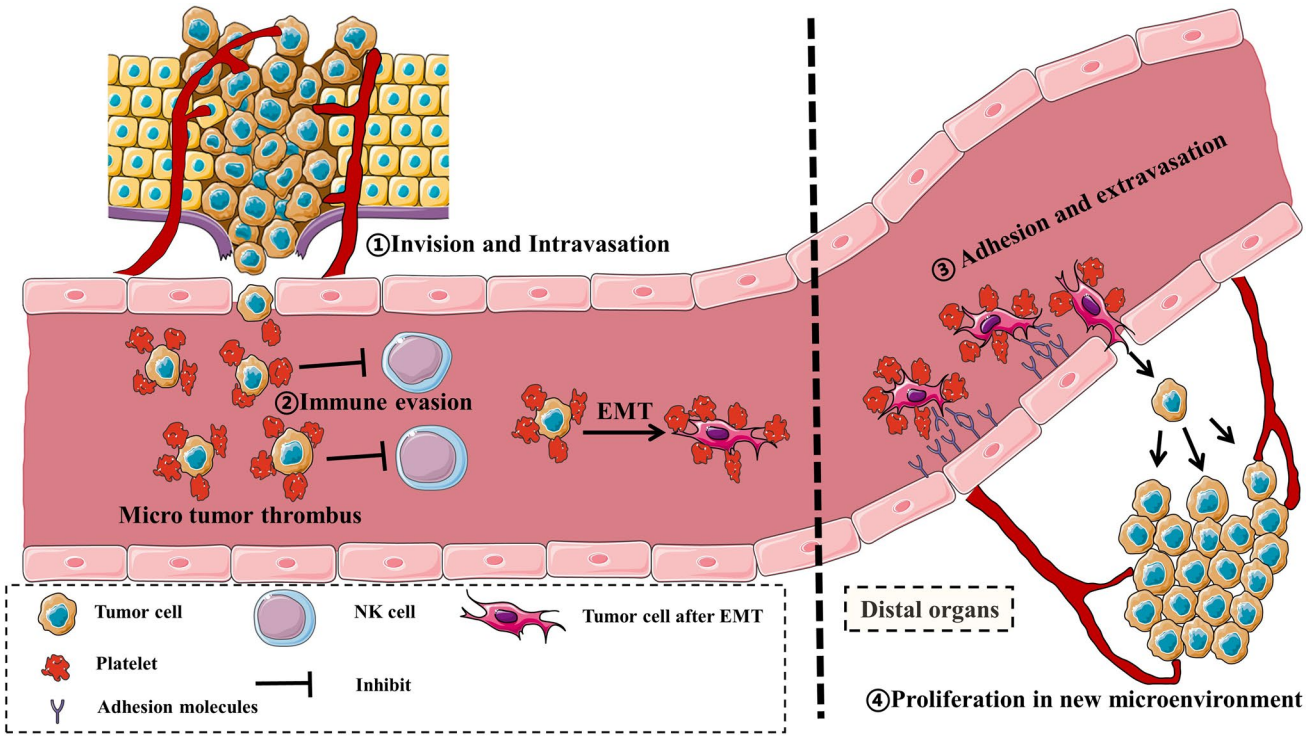

Fig. 1 Overview of the tumor hematogenous metastasis process. Tumor cells migrate from primary sites and undergo intravasation by breaking through the extracellular matrix (ECM) and vascular endothelium. In circulation, circulating tumor cells (CTCs) induce platelet activation and aggregation. Activated platelets encase CTCs to form micro tumor thrombi and protect CTCs from immune surveillance mediated by NK cells. In addition, platelets trigger CTCs to undergo the epithelial-mesenchymal transition (EMT) process, during which tumor cells obtain mesenchymal traits and enhanced invasiveness. Platelets facilitate CTC adhesion to the vascular endothelium and extravasation to distal organs, in which tumor cells adapt to the local microenvironment and proliferate into metastatic foci

functions and play their roles through both internal bioactive components and external surface ligands [3].

Patients with tumor thrombi have much higher metastatic rates and poorer prognoses than other patients [4]. During intravasation, cells within the tumor mass can secrete microvesicles that induce tumor-derived signatures in platelets [5]. Moreover, those cells could detach and intravasate, becoming CTCs. After contact with platelets, CTCs can be activated and encased by platelets, thus forming a micro tumor thrombi [6, 7]. The storage of a plethora of cytokines and platelets has recently been indicated to participate in the regulation of inflammatory responses, including tumor progression [8]. During tumor-induced inflammation, platelets are the first responding cells because they are small, abundant and store numerous bioactive molecules [9]. Activated platelets can aid in tumor progression and metastasis via various pathways: (i) platelets are able to secrete immunosuppressive cytokines and transfer inhibitive ligands to the CTC surface to protect CTCs from immune surveillance; (ii) platelet derived growth factors can facilitate tumor proliferation and EMT; and (iii) by regulating immune cells, including neutrophils, monocytes and macrophages, platelets create a permissive microenvironment for CTC metastasis.

2 Micro tumor thrombi formation

During hematogenous metastasis, CTCs in the bloodstream have to survive in high shear forces and bypass immune surveillance to form metastatic foci [10]. To escape from shear forces and immune surveillance, tumor cells trigger abnormal platelet activation and aggregation (tumor cell-induced platelet aggregation, TCIPA), which leads to tumor thrombi formation [6, 7]. CTCs achieve this via direct cell interaction and secretion of tumor-derived releasates (Fig. 2). Podoplanin (PDPN), a membrane protein expressed on some tumor cells, including osteosarcoma, squamous cell carcinoma and brain tumors, is the ligand of C-type lectin receptor type 2 (CLEC-2), which is expressed almost exclusively on platelets [11–13]. Through such direct binding, tumor cells can stimulate platelets, induce TCIPA, and expedite hematogenous tumor metastasis [11, 14, 15]. Studies have shown that abrogation of either PDPN or CLEC-2 function could

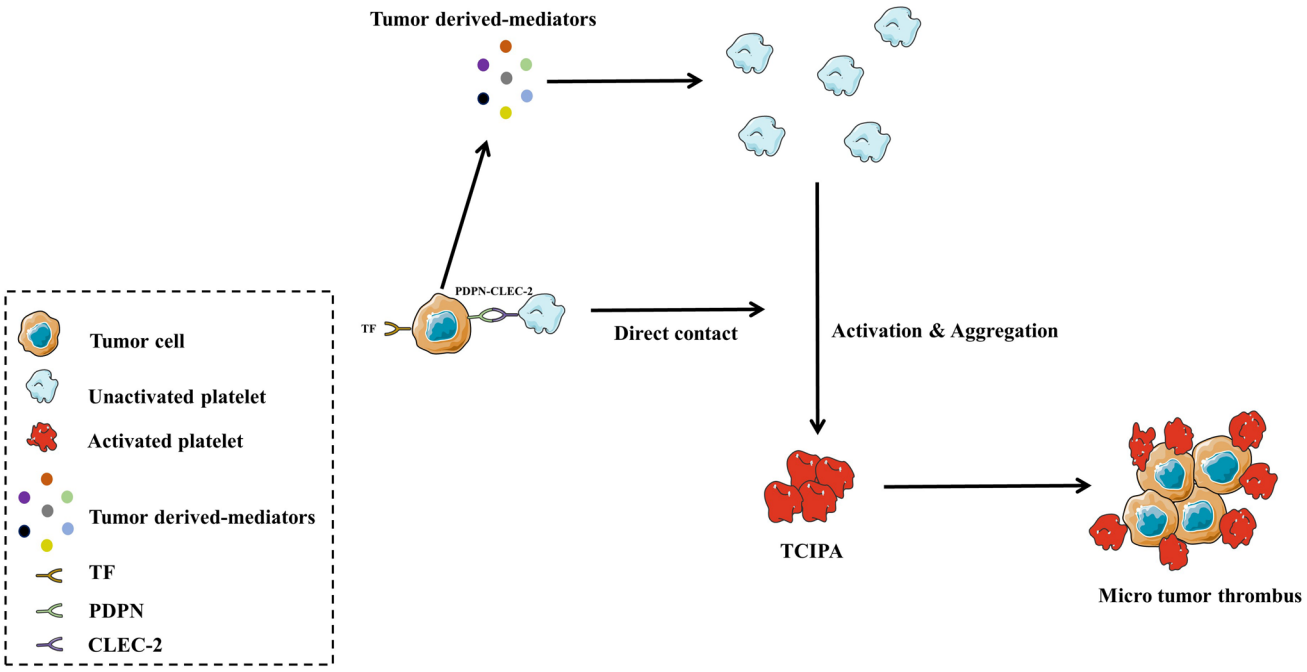

Fig. 2 Schematic diagram of micro tumor thrombi formation. Circulating tumor cells (CTCs) induce platelet activation via direct contact and tumor-derived mediators (TF, thrombin and ADP, etc.). Activated platelets are capable of encasing CTCs, leading to the formation of micro tumor thrombi and the tumor microenvironment

significantly impede tumor hematogenous metastasis in mouse models [12, 16, 17]. Disruption of the PDPN and CLEC-2 interaction leads to blockade of platelet and CTC adhesion, which is detrimental for CTC survival in the circulation. After direct contact, stimulated platelets secrete the chemokines CXCL5 and CXCL7, leading to neutrophil recruitment and tumor microenvironment formation [18].

Aside from their direct interactions with cells, tumor cells can release numerous mediators (e.g., tissue factor (TF) [19], thrombin [20], ADP [21], TXA_2 [22], matrix metalloproteinases (MMPs) [23], high-mobility group box1 (HMGB1) [24], CD97 [25], cancer cell-derived IgG [26], and mucins [27]) to initiate platelet activation and subsequent micro tumor thrombi formation. In fact, patients with tumors are more prone to thrombocytosis and elevated biomarkers of platelet activation, and the risk of venous thromboembolism in tumor patients is much higher than that in the general population (5–15% for tumor patients vs. 1–2 cases per 1000 people per year in the general population) [11, 28, 29]. Tumor patients exhibit overexpression of TF and coagulation factor VII, which are critical in the extrinsic coagulation pathway [30]. TF expressed on tumor cell membranes and secreted as tumor-derived microparticles can initiate the extrinsic coagulation pathway by interacting with coagulation factor VII and coagulation factor X [19, 31]. Thrombin generated from the extrinsic coagulation cascade and some types of tumor cells (e.g., pancreatic and lung cancer cell lines) can activate platelets and accelerate tumor thrombosis [20, 32]. Moreover, a study indicated that platelets could upregulate TF expression in ovarian cancer [33], implicating the interplay between tumor cells and platelets via TF.

ADP and TXA_2 are classical platelet agonists that participate in the coagulation cascade and induce thrombosis [34]. ADP expressed by tumor cells can interact with platelet receptors P_2Y_{12} and P_2Y_1, which contributes to TCIPA and the release of ADP and TXA_2, which are stored in platelet granules [28]. Increased ADP and TXA_2 expression in the tumor anoxic microenvironment leads to positive feedback in the platelet activation cascade, which is conducive to the generation of metastatic foci [21, 22, 32].

MMPs are proteolytic enzymes that participate in ECM degradation and remodeling, which are crucial in the processes of tumor invasion and metastasis [35]. Interestingly, MMPs derived from tumor cells are indicated to elicit platelet activation and TCIPA [36]. MMP-1 released from breast cancer cells could foster ADP release, triggering TIPCA through a positive feedback pathway [28]. Tumor cell derived MMP-2 can induce TCIPA by binding to platelet integrin $\alpha_{IIb}\beta_3$ [37, 38]. In turn, activated platelets can release factors that upregulate MMP expression in melanoma cells [23]. Moreover, MMPs restored in platelet α-granules are released upon platelet activation and can degrade the basement membrane, thus supporting tumor metastasis [39].

Some tumor cells can release high-mobility group box 1 (HMGB1), which binds to platelet toll-like receptor 4 (TLR4), leading to platelet activation and tumor extravasation [24]. Both primary and metastatic tumors have been suggested to express CD97, which can activate platelets and enhance lysophosphatidic acid release, leading to increased tumor invasiveness and transendothelial migration [25, 40]. In contrast to B lymphocytes, tumor cells have been reported to produce immunoglobin G (IgG), which can bind to platelet FcgRIIa, thus initiating platelet activation [26, 41]. Shao et al. demonstrated that cancer mucins bind to both platelets and neutrophils and trigger their mutual activation [27, 42].

Among all the mediators listed above, some could serve as biomarkers for cancer-associated thrombosis and are related to tumor prognosis. Circulating TF-positive microparticles are related to venous thromboembolism in many tumor types (including pancreatic cancer, colorectal cancer and glioma) [43–45]. High expression of PDPN is associated with worse prognosis in glioma [46]. Moreover, PDPN expression in glioma patients has a positive correlation with the D-dimer level [47], which is a classical marker reflecting coagulation function.

Overall, tumor cells are capable of inducing platelet activation by various pathways. Activated platelets surround tumor cells and form micro tumor thrombi that are conducive to tumor cell survival in the blood circulation. Releasates from activated platelets recruit leukocytes and form tumor niches facilitating tumor development and metastasis.

3 Role of micro tumor thrombi during hematogenous metastasis

3.1 Immune evasion

Tumor cells entering the blood circulation as CTCs are prone to be recognized and eliminated by cytotoxic immune cells (e.g., natural killer (NK) and $CD8^+$ T cells) [48]. This process is called immune surveillance. CTCs are capable of inducing platelet activation and aggregation via direct interaction and release of various mediators. Activated platelets can encase CTCs via integrins, fibrin, and P-selectin, shielding them physically and immunologically from immune surveillance and leading to distant metastasis [14, 42, 49, 50]. It has been demonstrated that platelets protect CTCs from both NK and $CD8^+$ T cells. Nieswandt et al. first used thrombocytopenic mice to indicate that platelets impede NK-cell-mediated cytolysis of tumor cells [51]. Palumbo et al. further substantiated this hypothesis using mice lacking Gαq (a G protein vital for platelet activation) and fibrin [52]. Deficiency in any of them resulted in diminished tumor cell survival. Moreover, the diminution of tumor cell survival was obliterated in mice with NK-cell depletion [53]. Platelets impede NK-cell-mediated cytolysis via cell contact and cytokine interactions [54]. Platelets can transfer ligands that are suppressive for NK-cell function to the CTC surface, such as MHC class I [55], glucocorticoid-induced TNF-related protein ligand (GITRL) [56], receptor activator of NF-kB ligand (RANKL) [57], and PD-L1 [58]. Placke et al. revealed that platelets encasing CTCs could transfer MHC class I molecules onto the tumor cell surface, thus disrupting immune recognition and immune surveillance by NK cells [55]. Recently, Zaslavsky et al. reported that PD-L1-negative tumors could escape immune surveillance with the help of platelet-derived PD-L1 [59]. In addition to direct contact with tumor cells, platelets activated by CTCs can secrete transforming growth factor-β (TGF-β), which is capable of downregulating NKG2D on NK cells and suppressing antitumor immunity [60]. In fact, it has been reported that platelets are the major source of TGF-β in both the tumor microenvironment and human body [61–63]. Furthermore, platelets express TGF-β-docking receptor glycoprotein A repetitions predominant (GARP), which can activate latent TGF-β in nearby platelets [61]. In addition to inhibiting NK-cell activity, TGF-β can convert $CD4^+$ T cells into regulatory T cells that lead to immunosuppression in the tumor microenvironment [64]. TGF-β and lactate are major platelet-derived mediators that dampen $CD4^+$ and $CD8^+$ T-cell activity [61]. Moreover, TGF-β has been proven to be capable of downregulating NK-cell function by impeding cytokine production and degranulation [60, 65].

As regulators of inflammation, platelets can modulate not only NK cells and $CD8^+$ T cells but also neutrophils, monocytes and macrophages [66]. Neutrophils are recruited to inflammatory sites via L-selectin and PECAM-1 [66, 67]. Activated platelets can trigger neutrophil extracellular trap (NET) formation by binding to neutrophils, which is mediated by the binding of platelet P-selectin and neutrophil P-selectin glycoprotein ligand-1 (PSGL-1) [68]. Platelet ICAM-2, CD40L, GPIb and GPIIb/IIa can facilitate the binding between platelets and neutrophils [66]. GSF released by tumor cells can promote neutrophil production and NET formation [69]. Tumor cell-derived HMGB1 is capable of inducing NET formation through ligation with RAGE (receptor for advanced glycation end products) or TLR4 on neutrophils [70]. In addition, tumor-primed platelets could facilitate tumor cell-induced NET formation [71]. Neutrophil extracellular traps (NETs) consist of nuclear or mitochondrial DNA decorated by histones and proteins secreted from activated neutrophils [72]. Conventionally, the major role of NETs is to assist neutrophils in eliminating pathogens [73]. In recent years, NETs have been indicated to be involved in tumor progression, dissemination and metastasis [74]. CTCs can be entrapped by NETs via β1-integrin-mediated interactions, thus preventing immune surveillance and promoting tumor thrombosis and metastasis [75]. NETs can augment tumor growth through

direct alteration of metabolic programming [76]. Recently, NETs were found to be engaged in tumor relapse, during which NETs could reinvigorate dormant tumor cells and lead to metastasis [77]. Monocytes adhered to platelets are activated by direct binding and release procoagulant and TF-positive microvesicles [66]. TF-positive CTCs could activate procoagulant proteins and coat themselves with fibrin, which led to immune evasion and increased adherence to distant sites. Platelet-derived TGF-β suppresses macrophage proinflammatory function and may correlate with the polarization of the M2 phenotype, which exerts immunosuppressive and proangiogenic functions [78, 79]. In general, platelets induce CTC immune evasion by interacting with immunocytes in direct and indirect manners (Fig. 3).

3.2 Anoikis resistance

Anokis is a form of programmed cell death due to the loss of interaction between the cell and ECM [80]. Platelets were indicated to induce CTC anokis resistance by several pathways (Fig. 3). Platelet-derived autotaxin converts lysophosphatidylcholine to lysophosphatidic acid, which can adhere to the CTC LPAR-1 receptor and initiate CTC anokis resistance via the RhoA-Gα12/13-YAP-1 pathway [25, 81, 82]. Through initiating RhoA-MYPT1-PP1-mediated YAP1 dephosphorylation as well as facilitating its nuclear translocation, platelets impede apoptosis in tumor cells and upregulate gene expression with a prosurvival trait [82]. Li et al. reported that plateletderived growth factorBB inhibited anoikis and promoted tumor progression via the Hippo/YAP signaling pathway [83]. PDGF, a growth factor secreted from platelets, has been reported to induce fibroblast apoptosis resistance through the Ras/PI3K/Akt pathway [84]. Cacic et al. found that platelet microparticles could protect acute myelogenous leukemia cells from daunorubicin-induced apoptosis via overexpression of miR-125a and miR-125b, thus leading to chemotherapy resistance [85].

3.3 Promotion of proliferation

Platelets can release various mitogenic proteins and growth factors to boost tumor cell proliferation [14, 28, 86], including TGF-β, PDGF, VEGF, platelet factor 4 (PF4), insulin-like growth factor (IGF)-I, stromal cell-derived factor-1 (SDF-1) and angiopoietin (Fig. 3). Platelet-derived TGF-β can foster tumor growth by binding to the tumor cell receptor TGFβR1 in ovarian cancer [62, 87]. PDGF receptor (PDGFR) is normally expressed on mesenchymal cells, while epithelial tumor cells can express PDGFR via the EMT process induced by TGF-β, thus

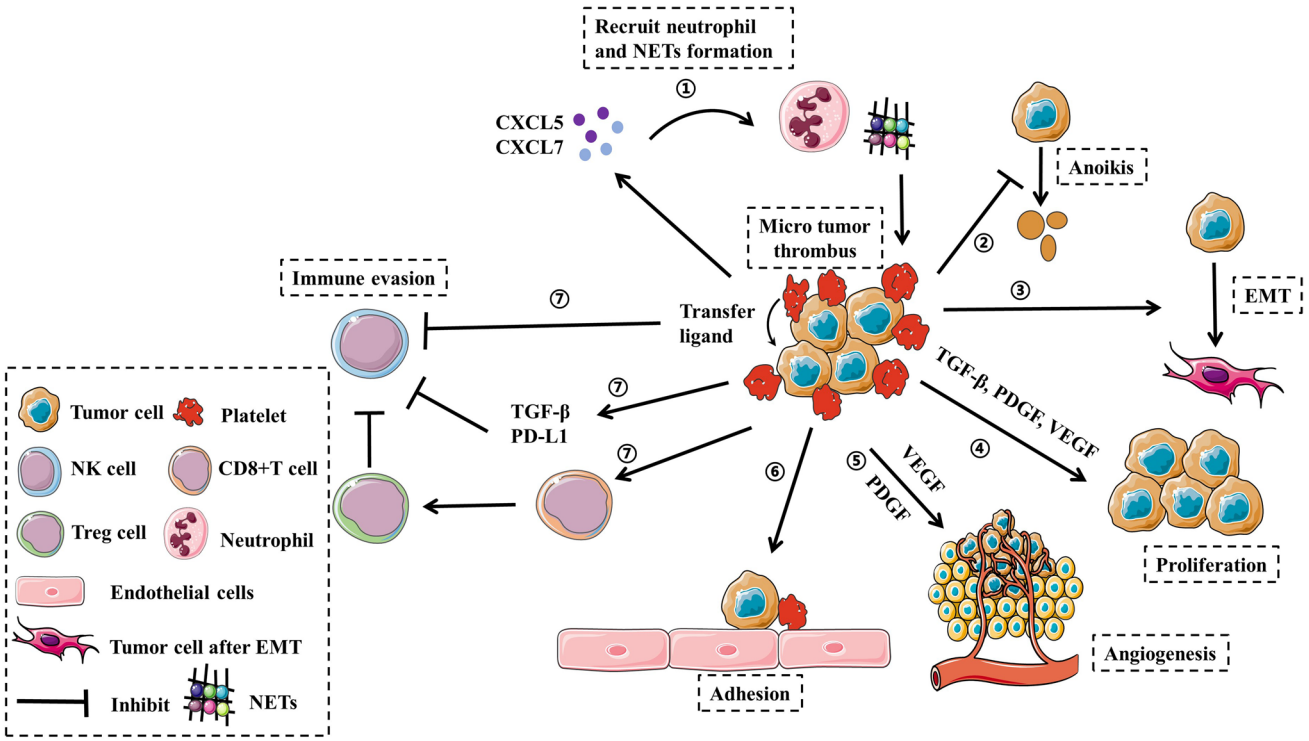

Fig. 3 Role of micro tumor thrombi in hematogenous tumor metastasis. Platelets in micro tumor thrombi could induce CTC anokis resistance and immune evasion, allowing CTCs to survive in blood circulation. In addition, platelets in micro tumor thrombi are indicated to enhance tumor progression and metastasis via several mechanisms, including EMT, tumor proliferation, angiogenesis and adhesion

leading to a proliferation response to PDGF [88]. VEGF released by platelets was indicated to increase tumor cell proliferation in breast cancer via interplay with VEGFR-2 and the integrin signaling pathway [89]. The role of PF4 in tumor proliferation is controversial. Pucci et al. reported that PF4 is a cancer-enhancing endocrine signal and can accelerate tumor growth in lung cancer [90]. However, Wang et al. demonstrated that PF4 can be a potential anti-tumor target due to its inhibitory role in tumor angiogenesis [91]. Platelet-derived SDF-1 can initiate intracellular signaling through several diverse pathways, leading to upregulated proliferation in ovarian cancer [92].

In addition to releasing of growth factors, platelets can expedite tumor growth by direct contact [39]. The interaction of platelet-expressed CLEC-2 and tumor cell-expressed PDPN can stimulate proliferation in lung cancer [93]. Contact of ADP and the P_2Y_{12} receptor expressed on platelets results in tumor growth via the ASK1-JNK/P38 signaling pathway [94].

3.4 Facilitation of EMT

EMT is a process during which epithelial cells lose their epithelial identity and obtain mesenchymal traits, which is associated with tumor invasiveness and metastasis [95]. A recent study suggested that retarding tumor-platelet crosstalk using activated platelet-targeting nanoparticles could suppress the tumor EMT process and metastasis in breast cancer [96]. In fact, platelets were found promote EMT via several pathways (Fig. 3) [97]. TGF-β is the major cytokine mediating the acceleration of the EMT effect by platelets [97, 98]. In ovarian cancer, patients with higher TGF-β levels were found to have elevated platelet counts [97]. Ovarian cancer cells cocultured with platelets showed increased TGF-β levels and higher expression of mesenchymal markers [97]. The TGF-β type I receptor inhibitor A83-01 inhibited EMT and platelet-mediated tumor progression in vitro and in vivo [97], indicating that platelets induce the EMT process via a TGF-β-dependent pathway. Moreover, direct platelet-tumor cell interactions were demonstrated to synergistically enhance the EMT process and metastasis with platelet-derived TGF-β via the TGF-β/Smad and NF-kB pathways in colorectal cancer [98]. In line with this, PDPN-CLEC-2 and integrin α2β1 interactions could trigger TGF-β release from platelets and accelerate the EMT process [99–101]. In addition to TGF-β, TANK-binding kinase 1 (TBK1) mediates the platelet-induced EMT process [102]. TBK1 activation paralleled the platelet-induced EMT process in mammary carcinoma cells. The platelet-induced EMT process and NF-kB activation were impeded via ablation of TBK1 expression, suggesting that TBK1 is involved in platelet-induced EMT and NF-kB signaling.

3.5 Mediation of tumor cell adhesion

Platelet membranes express various adhesion molecules, including integrins ($\alpha_{IIb}\beta_{III}$, $\alpha_2\beta_1$, $\alpha_5\beta_1$, $\alpha_6\beta_1$, $\alpha_L\beta_2$, $\alpha_v\beta_3$), glycoprotein (GP) Ib-IX-V, CLEC-2, GPVI and P-selectin [103–105]. These molecules mediate the adhesion of platelets, endothelial cells, and CTCs [106]. Platelet $\alpha_{IIb}\beta_{III}$ and P-selectin mediate tumor cell rolling, tethering and stable adhesion along the endothelium under dynamic flow conditions [107]. P-selectin has been reported to exert a pivotal role in the interaction of platelets, endothelial cells, and CTCs [42]. In platelets, P-selectin is normally stored in α-granules and can be translocated to the platelet surface upon platelet activation, leading to the contact of platelets, endothelial cells, and CTCs [108]. In addition, P-selectin induces the interaction of platelets, endothelial cells and neutrophils by binding to mucins and PSGL-1 [109].

Integrin $\alpha_6\beta_1$ expressed on platelets can bind to ADAM9 expressed on tumor cells, which induces tumor metastasis [110]. Expressed on tumor cells, $\alpha_v\beta_3$ can facilitate the interaction among tumor cells, platelets and vasculature [111]. When it colocalizes with $\alpha_v\beta_3$, nectin-like molecule 5 (NECL5) is capable of inducing tumor cell adhesion of the endothelium via contact with CD226 on the platelet surface [112].

As a key receptor for collagen, platelet GPVI can facilitate tumor cell adhesion to endothelial cells, promoting tumor cell arrest and metastasis [113]. Tumor cell-derived galectin-3 could interact with GPVI on platelets to promote tumor cell extravasation and metastasis [114].

3.6 Induction of angiogenesis and modulation of endothelial cells

During tumor progression and metastasis, tumor cells require angiogenesis to generate new microvessels that provide sufficient nutrients and growth factors to support tumor growth [115]. Platelets have been found to participate in both early and advanced stages of cancer during angiogenesis and are pivotal in stabilizing neovascularization (Fig. 3) [116]. Platelet α-granules contain multiple molecules that can regulate angiogenesis and are released upon platelet activation [104, 117]. Molecules, including VEGF, PDGF, epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF), are proangiogenic factors and can induce angiogenesis [118]. Moreover, platelet α-granules also contain anti-angiogenic factors, including angiostatin, PF4, thrombospondin-1 (TSP1) and endostatin [117]. Platelets can release different kinds of angiogenic molecules according to external stimuli [117, 119]. Platelets stimulated by ADP can expedite the release of proangiogenic factors such as VEGF via activation of the PAR1 receptor, while platelets stimulated by TXA_2 induce the release of antiangiogenic factors such as endostatin through activation of PAR4 [117]. As

an agonist of platelet activation, thrombin also participates in angiogenesis by facilitating the release of proangiogenic factors as well as increasing the permeability of the endothelial cell barrier [120]. Thrombin-, ADP- and TF-stimulated platelets are prone to secrete a plethora of VEGF, which is the most efficient proangiogenic factor [121]. PMVs contain plentiful RNAs, receptors and proteins and were shown to exert proangiogenic effects just as strong as platelets in angiogenesis through the PI3-kinase, Src kinase and ERK signaling pathways [49, 122]. In addition to secreting angiogenic molecules and PMVs, platelets were found to induce angiogenesis via direct contact with endothelial cells [123]. Integrin $\alpha_{IIb}\beta_{III}$ and tetraspanin were reported to participate in the direct interaction of platelets and endothelial cells as well as in platelet-induced angiogenesis [124].

In addition to the induction of angiogenesis, platelets also modulate endothelial cells to facilitate the intravasation and extravasation of tumor cells during metastasis. Tumors in primary sites induce local angiogenesis to intravasate into the blood circulation, since new blood vessels have infirm tight junctions and are easy to cross [125]. During this process, platelets secrete factors (e.g., VEGF and TGF-β) to coordinate angiogenesis and disrupt endothelial cell function [126]. After tumor cell intravasation into the bloodstream, platelets further promote the transendothelial migration of tumor cells, which is the process by which tumor cells cross the endothelial barrier. Ward et al. showed that platelet interaction with tumor cell CD97 led to bidirectional signaling that caused platelet release of ATP and tumor cell activation of CD97/LPAR dependent RHO signaling [25]. Platelet-derived ATP resulted in disruption of endothelial tight junction thus increasing vascular permeability [127], while RHO signaling activation made tumor cells more invasive. The bidirectional signaling mentioned above coordinated tumor cell transendothelial migration, which is crucial for tumor metastasis.

3.7 Platelet-derived microvesicle (PMVs)

Upon activation, platelets can release PMVs that contain mRNA, microRNA, DNA, proteins, cytokines, and second messengers [128, 129]. As extracellular membrane vesicles, PMVs have been found to promote metastasis through multiple mechanisms: (i) delivery of membrane receptors to tumor cells and stromal cells; (ii) transfer of mRNA, protein and second messengers that lead to epigenetic alteration in recipient cells; and (iii) direct activation of target cells through PMV surface ligands [130]. Recent studies have shown that PMVs can transfer their membrane receptors, including CXCL4, CD41, CD61 and CD62, to tumor cells to increase tumor migration, metastasis and adhesion [128, 131]. PMVs, which are rich in mRNAs and microRNAs, can regulate the gene expression of recipient cells. With a plethora of genetic material, PMVs can also regulate the gene expression of tumor cells. In an ovarian cancer cell line, PMVs induced the EMT process and increased tumor progression by delivering miR-939 [132]. In breast cancer cells, PMVs delivered TPM3 mRNA to tumor cells, thus augmenting tumor invasion [133]. However, another study pointed out that PMVs infiltrated solid tumors and transferred miRNAs to tumor cells to induce apoptosis and inhibit tumor growth [134]. In the tumor microenvironment, PMV surface phosphatidylserine can bind to the phosphatidylserine receptor on immune cells, thus inhibiting the antitumor immune response and initiating an immunosuppressive environment [135]. In lung cancer, PMVs acted as a chemoattractant for 4 of 5 lung cancer cell lines and promoted proliferation via the MAPK-p42/44 and PI-3 K-AKT signaling pathways [136].

4 Therapeutic strategies targeting platelets for tumor treatment

Current platelet-based antitumor therapeutic strategies can be classified into two major approaches. One method is directly abrogating platelet function via antiplatelet agents. The other method is delivering antitumor or antiplatelet drugs through cancer-associated platelet-targeted nanomedicines [86, 137]. Antiplatelet agents including nonsteroidal anti-inflammatory drugs (NSAIDs) and antagonists targeting integrins, ADP, CLEC-2 and P-selectin have shown therapeutic potential for tumor treatment [138, 139]. For example, the classical antiplatelet agent aspirin was found to have an antitumor effect in colorectal cancer as early as 1988 [140]. Since then, the antitumor effect of aspirin has gradually been extended to other types of tumors, including breast cancer, gastric cancer, liver cancer, and ovarian cancer [141–143]. Nevertheless, most studies focusing on these agents were in the early stage and could not reach a unified conclusion. In the ASPREE trial, McNeil et al. enrolled 19,114 community-dwelling persons with 70 years of age or older and randomly divided them into a low-dose aspirin group (100 mg of enteric-coated aspirin) and a placebo group [144–146]. The ASPREE trial results showed that use of low-dose aspirin caused higher risk of death from any cause and higher cancer-related death compared to placebo, indicating the clinical application of aspirin for primary prevention of tumor in patients older than 70 years old should be cautious. Moreover, the side effects of antiplatelet agents, including hemorrhage and thrombocytopenia, limit their clinical application [147]. Strategies targeting downstream signaling following platelet activation, such as TGF-β, PDGF, and VEGF signaling, have shown potential therapeutic value with better safety profiles [148–150]. Lenvatinib, an

inhibitor of VEGF and PDGF receptors, has shown activity with noninferior efficacy to sorafenib (a first-line treatment for unresectable hepatocellular carcinoma) in terms of overall survival in advanced hepatocellular carcinoma [151]. Bintrafusp Alfa, a reprogrammed antibody that can simultaneously inhibit TGF-β and PD-L1, has been proven to exert antitumor effects by overcoming immune evasion both in vitro and in vivo [152, 153].

Another category of platelet-based therapy accomplishes targeted therapy using cancer-associated platelet-targeted nanomedicines that could adhere to platelets via their platelet adhesion molecules [154]. With the design of nanoparticles with antibodies targeting platelet receptors, including P-selectin, GPIb and GPIIb/IIIa, tumors can be imaged and localized in vivo [155]. Similarly, the coating of antitumor agents with platelet membranes has been shown to exert tumoricidal effects and is not affected by tumor heterogeneity [156]. A P-selectin-targeting peptide was applied, and nanoparticles with PSN peptide modification exhibited increased accumulation at both the primary tumor site and metastases due to their ability to capture activated platelets [96]. Therefore, nanoparticles could inhibit tumor metastasis in nearly every crucial stage in a consecutive manner. Coating of drugs with platelet membranes by using mesoporous silica nanoparticles, vascular disruption agents and antiangiogenic drugs achieved significant vascular disruption and antiangiogenic efficacy because the platelet membrane could aggregate at the damaged vessel walls of the tumor through targeted adhesion [157]. Likewise, the TLR agonist R848 coated with platelet membranes initiated a local immune response and caused tumor regression in colorectal and breast tumor models [158]. Platelets conjugated with anti-programmed cell death-ligand 1 (aPDL1) antibody could induce an immune response and inhibit tumor metastasis in breast tumors through the release of aPDL1-decorated PMVs [159]. A type of bioengineered platelet composed of internal-loaded doxorubicin and external-loaded aPDL1 has been reported to decrease tumor recurrence and metastasis in a postsurgical melanoma model [160]. In summary, the major advantages of cancer-associated platelet-targeted nanomedicines are as follows: (i) they protect nanoparticles from elimination in the circulation; (ii) they have relatively high targetability due to the close interplay between platelets and CTCs; and (iii) they exhibit increased circulation period and loading capacity [161]. However, there are still limitations that need to be overcome before these cancer-associated platelet-targeted nanomedicines can be clinically applied. For example, all of these nanomedicines have more or less bleeding risk and some nanomedicines are found not only in tumor tissues but also in the liver, which may lead to liver toxicity [86]. Therefore, the design of more specific and tolerable agents is necessary for the clinical application of nanomedicines.

5 Conclusion

As a critical process during tumor metastasis, tumor cells that undergo intravasation become CTCs with no tumor stroma component and have to cope with high shear force, immune surveillance and anokis to achieve distal metastasis. To survive in the circulation, tumor cells interact with platelets to form micro tumor thrombi, during which process platelets are activated and educated by direct contact as well as the action of tumor cell-derived bioactive molecules. Activated platelets then aggregate and encase tumor cells to form micro tumor thrombi, interact with tumor cells and immune cells to form a permissive tumor microenvironment, and foster tumor progression and metastasis through various pathways. Therefore, therapies targeting platelets and their corresponding signaling pathways have encouraging therapeutic prospects for tumor treatment. Unraveling the interplay between platelets and tumor cells during micro tumor thrombi formation and tumor metastasis will provide a deeper understanding of the mechanism of tumor progression and will be conducive to designing novel therapeutic agents that specifically target tumor lesions without apparent effects on platelet physiological functions.

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Declarations

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Competing interests The authors declare that they have no competing interests.

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