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The role of platelets in tumor immune evasion and metastasis: mechanisms and therapeutic implications

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Abstract
Only circulating tumor cells (CTCs) that successfully evade immune surveillance upon entering the bloodstream can lead to clonal expansion and metastasis. Cancer progression is accompanied by pathophysiological processes such as platelet activation and thrombosis. Platelets secrete a variety of growth factors to stimulate cancer cell proliferation, regulate tumor angiogenesis, and subsequently mediate surface changes in cancer cells to promote invasion and progression. As part of a dangerous alliance, CTCs and platelets induce mutual activation. Activated platelets aggregate and encapsulate tumor cells, forming microtumor thrombi containing fibrin clots that act as protective barriers. These platelets interact with immune cells, including NK cells, macrophages, neutrophils, and T cells, to facilitate cancer metastasis and progression through various mechanisms. The formation of a favorable tumor microenvironment (TME) and pre-metastatic niche aids cancer cells in evading immune surveillance. Multiple signaling pathways and immune checkpoints are also involved in this process. Given the significant role of platelets in tumor immune evasion, anti-cancer strategies targeting platelets and their potential use as "bionic drug delivery systems" for anti-tumor drugs hold broad prospects in emerging tumor therapies.

Keywords Platelet, CTC, Immune cell, Immune escape, Signaling pathway, Therapy

Introduction

Platelets are non-nucleated cytoplasmic fragments released by megakaryocytes in the bone marrow, primarily responsible for maintaining hemostasis and vascular integrity. Upon disruption of endothelial continuity or exposure to the subendothelial matrix, as well as during inflammation-induced endothelial damage, platelet activation is triggered. This activation results in the adhesion of platelets and the release of multiple bioactive factors, leading to firm attachment to the injured vessel wall and the formation of platelet aggregates to seal the wound [1]. Additionally, activated platelets play a role in wound healing and tumor cell metastasis. Thrombocytosis and hypercoagulability observed in cancer patients are associated with an increased risk of thromboembolic events and poor prognosis, thereby elevating the risk of metastasis [2].

Platelets modulate the tumor microenvironment (TME) by interacting with tumor epithelial cells, endothelial cells, pericytes, fibroblasts, immune cells, and other components. This complex interplay influences various stages of tumorigenesis through angiogenesis induction, promotion of sustained and uncontrolled clonal proliferation, stimulation of invasion and metastasis,

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assistance in evading immune checkpoint regulation and prevention of cell death [3].Furthermore, platelets may possess the capability to initiate TME formation in the presence of premetastatic niche, thereby acting as a "fertilizer" for cancer cell metastasis within the framework of the "seed and soil" hypothesis [4].

Although circulating tumor cells (CTCs) simultaneously encounter red blood cells, leukocytes, and platelets in the bloodstream, platelets—despite being anucleate cytoplasmic fragments—are uniquely positioned to rapidly adhere to CTCs via glycoprotein receptors (e.g., P-selectin, GPIIb/IIIa), thereby initiating microthrombus formation and immune evasion [5]. Research has demonstrated that platelets play a pivotal role in each stage of the metastatic cascade, including facilitating the growth and proliferation of primary tumor cells, local invasion, intravasation into lymphatic or blood vessels, survival during circulation, immune evasion, extravasation to invade distal organ parenchyma, and colonization of distant organs, ultimately leading to clinically significant metastases [6]. Circulating tumor microemboli (CTMs), composed of non-discrete phenotypic populations such as mesenchymal CTCs and homologous or heterotypic clusters, exhibit enhanced metastatic potential and survival advantages compared to individual CTCs. Platelet-rich CTMs, in particular, demonstrate superior metastatic capabilities [7].

Activated platelets modulate the levels of growth factors, chemokines, proteolytic enzymes, and microparticles in the TME through the secretion of various bioactive molecules, thereby facilitating the proliferation and invasion of CTCs. Additionally, platelets promote tumor-induced angiogenesis by releasing of vascular endothelial growth factor (VEGF), supporting the formation of new blood vessels that nourish tumors and enable further extravasation [8]. By secreting transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF), platelets induce epithelial-mesenchymal transition (EMT) in tumor cells, enhancing their aggressiveness and stemness. This process facilitates the binding of CTCs to endothelial cells and transendothelial migration, which is essential for tumor extravasation, dissemination, and colonization. Moreover, platelet-derived microparticles (PMPs), which contain bioactive components and nucleic acids from the platelet cytoplasm, are shed from the plasma membrane and contribute significantly to cancer progression [9].

Platelet activation, aggregation, and adsorption

Platelet activation and adhesion at the site of intimal injury involve intricate interactions between platelets and the subendothelial matrix, which is rich in adhesion ligands and membrane receptors. Specifically, the glycoprotein complex GPIb-IX-V facilitates initial platelet rolling and adhesion to von Willebrand factor (vWF) at the site of endothelial injury, which subsequently promotes more robust binding via the platelet GPIIb/IIIa receptors. Additionally, platelet GPVI and α2β1 receptors directly bind to collagen, further stimulating platelet activation and aggregation [10].

Platelets within the TME can interact with CTCs that enter the bloodstream. Physical adhesion, primarily mediated by the pairing of adhesion molecules with their specific receptors, is a prerequisite for this interaction (Figure 1). During this process, platelets exhibit both systemic and localized responses to cancer. They continuously absorb and enrich tumor-associated free proteins, nucleic acids, vesicles, and particles, thereby forming a significant component of what is known as the "tumor circulating complex." This leads to altered RNA and proteome expression profiles in platelets, resulting in unique tumor-promoting phenotypes. These circulating platelets, termed tumor-educated platelets (TEPs) Figure 2 , represent a subset of highly activated platelets that can serve as liquid biopsy markers to assist in cancer diagnosis and prognosis [11–15]. In addition to direct platelet-tumor interactions within the TME, tumors systemically alter megakaryocytes in the bone marrow, spleen, and lungs, leading to the production of pre-educated platelets. This process is particularly significant given the limited lifespan of platelets (7–10 days in humans and 3–5 days in mice), suggesting that sustained TEP generation primarily stems from tumor-induced megakaryocyte reprogramming rather than transient education within the TME. Studies have shown that tumors increase megakaryocyte numbers and modify their transcriptional profiles via cytokines or extracellular vesicles, resulting in platelets that inherently carry tumor-specific biomolecules and splice variants (Fig. 2) [14, 16]. These findings underscore the systemic nature of platelet education, where tumor-derived signals reshape hematopoiesis to favor the release of TEPs, which subsequently contribute to metastasis and immune evasion.

Subsequently, CTCs induce platelet activation via multiple mechanisms, and their metastatic potential is contingent upon this platelet activation. For instance, the overexpression of the CD97 receptor on the surface of tumor cells can trigger platelet activation. Additionally, soluble mediators such as matrix metalloproteinases (MMPs), thromboxane A2 (TXA2), tissue factor (TF), P2Y receptors, thrombin, and adenosine diphosphate (ADP) are released into the extracellular space, further amplifying platelet activation and enhancing adhesion and aggregation. This phenomenon, known as Tumor Cell-Induced Platelet Aggregation (TCIPA), facilitates the survival of CTCs in circulation [18, 19]. Notably, MMP-2/9 plays a crucial role in this process, while

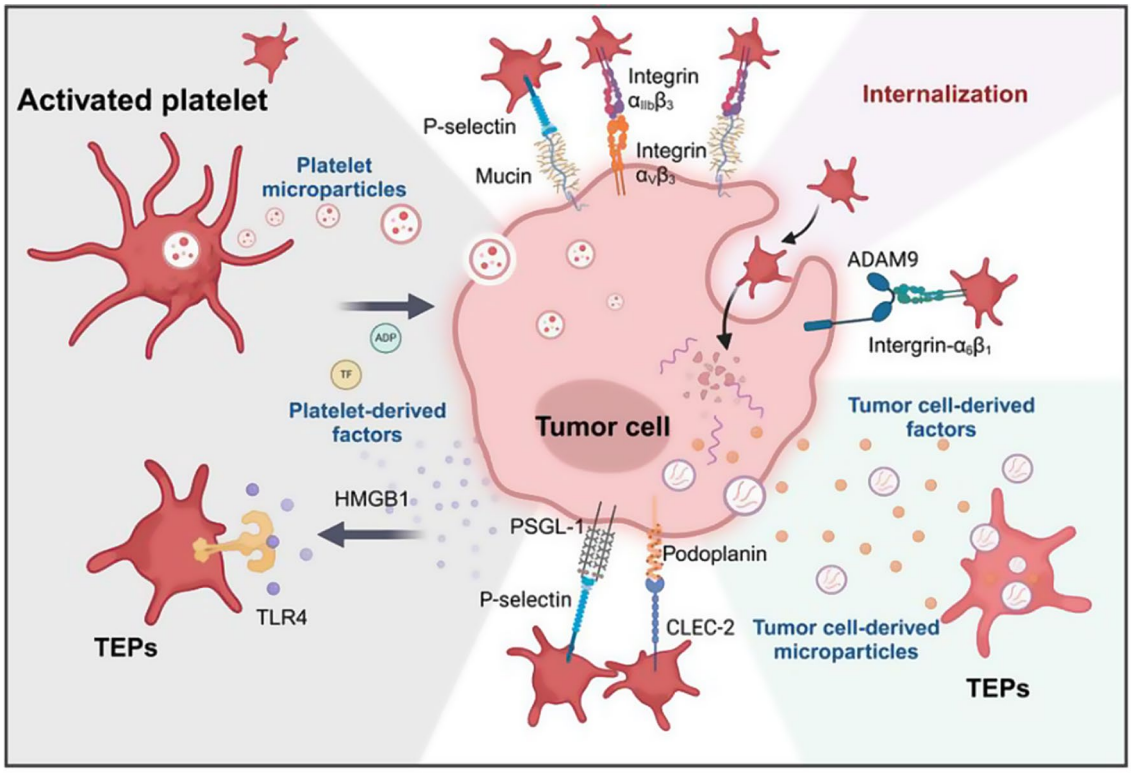

Fig. 1 Interactions between platelets and tumor cells can lead to platelet activation and aggregation, thereby promoting the formation of TEPs (right panel). Concurrently, these interactions facilitate tumor progression through the release of multiple platelet-derived microparticles and their associated contents (left panel). The cross-talk between platelets and circulating tumor cells (CTCs) is primarily mediated by several receptor-ligand pairs, including GPIIb/IIIa (integrin αIIbβ3) - αVβ3, P-selectin - PCLP1 (podoplanin-like protein 1)/PSGL-1 (p-selectin glycoprotein ligand 1)/mucin/CD44, glycoprotein VI (GPVI) - galectin-3, C-type lectin-like receptor 2 (CLEC-2) - podoplanin (PDPN), GPIbα - vWF, and ADAM9 - integrin α6β1. Reprinted from [17]

platelet components such as thrombospondin-1 (TSP1) and clusterin enhance MMP-9 expression through the p38 mitogen-activated protein kinase (p38MAPK) pathway, creating a positive feedback loop that increases cancer cell aggressiveness. Furthermore, CTCs can directly or indirectly induce platelet aggregation, for example by secreting interleukin-6 (IL-6), which leads to the release of thrombopoietin (TPO). ADAMTS13, a protease responsible for cleaving and inactivating vWF, also plays a role in platelet activation. High mobility group box 1 (HMGB1, a highly conserved nuclear protein, promotes TCIPA by binding to toll-like receptor 4 (TLR4) on platelets, thereby activating the ERK5-GPIIb/IIIa pathway [20, 21].

TEPs release a variety of secretory vesicles containing bioactive molecules, including lysosomes, alpha granules, and dense granules. These vesicles enhance platelet activation and aggregation, promoting tumor proliferation and metastasis. Activation of the G-protein-mediated signaling pathway results in enhanced secretion of storage particles, which function as a positive feedback mechanism to amplify the initial signal. This process rapidly activates platelets and recruits them into the expanding thrombus. The expression of genes associated with platelet activation, such as the integrin subunit α2b (ITGA2b) gene encoding the platelet protein CD41, is essential for effective platelet aggregation [22]. These events enable TEPs to cross-link via adhesion molecules like GPIIb/IIIa and bind to soluble fibrinogen, forming fibrin clots that facilitate the entanglement of tumor cells within platelet and fibrin networks inside the vasculature, thereby reducing exposure of CTCs surfaces. Additionally, TEPs can provide a protective barrier for CTCs by attaching to them through receptor-ligand interactions, as illustrated in Fig. 1. By binding to CD36 and CD47 receptors on tumor cells, TEPs mediate the formation of CTMs, allowing CTCs to adhere closely to the vascular wall and avoid rapid clearance from circulation or mechanical destruction due to high hemodynamic shear forces [23].

Significant progress has been made in understanding the role of platelets in tumor immune evasion. However, current research predominantly focuses on local platelet-tumor interactions, with insufficient attention to systemic regulatory mechanisms such as bone marrow megakaryocyte reprogramming. Furthermore, the clinical application of antiplatelet therapies remains controversial due to spatiotemporal heterogeneity in efficacy

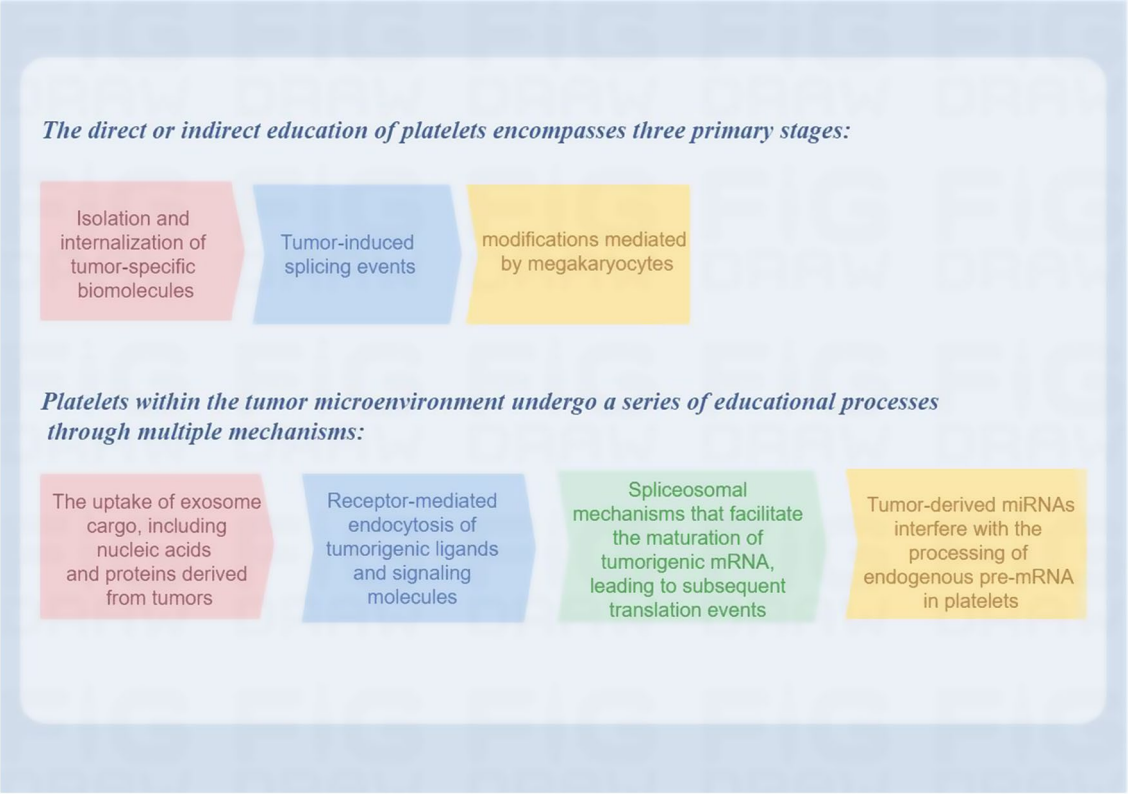

Fig. 2 Mechanisms of platelet education within the tumor microenvironment

and potential pro-metastatic risks. This review systematically integrates preclinical and clinical evidence to advance three key aspects of current knowledge: (1) We elucidate the continuum of tumor-induced remote megakaryocyte education via extracellular vesicles/cytokines that generate TEPs, providing new insights into sustained platelet activation; (2) We present a balanced analysis of antiplatelet strategies' dual effects—short-term metastasis suppression versus potential long-term vascular compromise—highlighting the need for personalized therapeutic approaches; (3) We explore the potential of platelet-inspired delivery systems (e.g., metabolic-modulating liposomes) to overcome limitations of conventional therapies. While these findings do not resolve all existing controversies, they establish a more comprehensive framework for understanding the platelet-tumor-immune triad and identify critical translational priorities, including dynamic TEP monitoring and optimized targeted delivery systems.

The interaction between platelets and immune cells facilitates the immune evasion of tumor cells

A summary of platelet-mediated immune cell modulation is provided in Table 1, highlighting key molecular mechanisms and functional outcomes.

NK cell

The aggregation of platelets around CTCs serves as a physical barrier, specifically providing steric hindrance that protects CTCs from immune-mediated clearance by natural killer (NK) cells and T lymphocytes. GPIbα on the surface of platelets interacts with Mac-1 expressed by NK cells, potentially modulating the cytolytic activity of these cytotoxic lymphocytes [24]. Moreover, the immune recognition by NK cells adheres to the principles of "missing self" and "induced self": cells deficient in major histocompatibility complex class I (MHC-I) expression or expressing stress-induced ligands that activate NK receptors are preferentially targeted for elimination. Although CTCs often exhibit reduced MHC-I expression, they can extend pseudopods around platelets and undergo membrane fusion, facilitating the transfer of platelet-derived MHC-I-containing vesicles to the tumor cell surface. Consequently, CTCs may acquire a "pseudo-normal" phenotype, thereby evading immune surveillance [25].

On the other hand, platelets can inhibit immune recognition of CTCs by NK cells through multiple mechanisms, thereby evading immune clearance and enhancing CTC survival. Specifically, PDGF directly suppresses NK cell effector functions, reducing their cytotoxic activity and interaction with target cells. TGF-β1 inhibits NK cell activation by suppressing mTOR activity and downregulating the expression of the C-type lectin-like NKG2D

Table 1 Mechanisms of platelet-immune cell interactions in tumor immune evasion

Immune Cell	Interaction Mechanisms	Key Molecules /Pathways	Functional Consequences	Ref
NK Cells	1. Platelet aggregates form physical barriers shielding CTCs from NK contact. 2. Transfer of platelet MHC-I to CTCs masks "missing self" signals. 3. Secretion of TGF-β1 and PDGF suppresses NK cytotoxicity.	TGF-β1, PDGF, ADAM10/17, NKG2D, GITRL, PD-L1	Inhibits NK cell activation and cytotoxicity, promoting CTC survival and metastasis.	[24–29]
Neutrophils	1. Induces neutrophil extracellular trap (NET) formation. 2. Polarizes N1 (anti-tumor) to N2 (pro-tumor) phenotypes. 3. Platelet-neutrophil aggregates (PNAs) protect CTCs from shear stress.	TLR4-ERK5, CXCL4, PAF-PAFR, G-CSF, vWF	Enhances pro-inflammatory microenvironment, vascular permeability, and CTC adhesion.	[30–35]
Macrophages	1. Recruits macrophages to tumor sites. 2. TEP-derived miRNAs (e.g., miR-183) drive M2 polarization. 3. CD47-SIRPα axis blocks phagocytosis.	PAF, IL-6/STAT3, CD47-SIRPα, TGF-β1	Promotes immunosuppression, EMT, and angiogenesis.	[36–40]
Dendritic Cells	1. Inhibits DC maturation and antigen presentation. 2. Downregulates co-stimulatory molecules (CD80/CD86). 3. Upregulates PD-L1 expression.	VEGF, TGF-β1, PF4, 5-HT	Impairs T cell priming and induces immune tolerance.	[41–44]
MDSCs	1. Recruits MDSCs via CXCL4/CXCL7. 2. TGF-β1 expands and activates MDSCs. 3. PDGF-BB induces CAF-derived CXCL12 to recruit MDSCs.	TGF-β/Smad, CXCL4, PDGF-BB/CXCR4	Suppresses T/NK cell function and drives fibrotic/immune checkpoint resistance.	[45–49]
T Lymphocytes	1. GARP/TGF-β axis inhibits CTLs and expands Tregs. 2. PF4 suppresses IL-2 production. 3. Platelet-derived PD-L1 directly inhibits T cell proliferation.	GARP-TGF-β, PD-1/PD-L1, PF4-CXCR3	Attenuates anti-tumor immunity and fosters immunosuppressive niche.	[50–56]
B Lymphocytes	1. Modulates humoral immunity via CD40L. 2. Potential involvement in Breg-mediated IL-10/TGF-β secretion (requires validation).	CD40-CD40L, IL-10, IL-35	May contribute to immunosuppression (mechanistically unclear).	[57]–[58]

receptor, a critical immune checkpoint protein for NK cell anti-tumor activity. Furthermore, TGF-β1 also inhibits the release of anti-tumor cytokines, such as interferon gamma (IFN-γ), through the canonical Smad2/3 pathway-dependent inhibition of the "master regulator" transcription factor T-bet. Additionally, to a lesser extent, the expression levels of NKp30, NKp44, NKp46, and NKp80 are downregulated [26, 27]. The secretion of the enzyme ADAM10/17 triggers the downregulation of NKG2D and the shedding of its ligands, including MICA and MICB. Platelets directly reduce the expression of CD226 and CD96 on the surface of NK cells and transfer inhibitory ligands such as glucocorticoid-induced TNF receptor ligand (GITRL), receptor activator of nuclear factor kappa-B(NF-kB) ligand (RANKL), programmed death-ligand 1 (PD-L1), PCLP1, and CD96 to the surface of CTCs [28, 29]. The microparticles (MPs) released by TEPs constitute approximately 90% of circulating MPs, and the encapsulated miR-183 may suppress the cytolytic activity of NK cells by silencing their activation receptor DAP12 [30].

Neutrophils

Inflammation is a complex physiological process that plays a pivotal role in various pathological conditions, including chronic inflammation within the TME, which is a hallmark of malignant tumors. Tumor-associated neutrophils (TANs) are regulated by TEPs to modulate the inflammatory microenvironment of tumors. This regulation is achieved through enhanced phagocytosis, degranulation, release of cell-free DNA fragments, and improved antigen presentation [31]. Platelets play a crucial role in modulating the differentiation of TANs into distinct phenotypes. Specifically, the N1 phenotype enhances anti-tumor responses through direct cytotoxic effects on tumor cells and by stimulating T cell-mediated immunity. Conversely, the N2 phenotype facilitates tumor progression by suppressing T cell activity and upregulating angiogenic factors such as VEGF and MMP-9 [32].

Platelets engage in complex interactions with neutrophils via multiple intermediates, such as platelet P-selectin and neutrophil PSGL-1. TGF-β1 facilitates the recruitment of additional neutrophils to the tumor site, leading to the formation of platelet-neutrophil aggregates (PNAs) that shield CTCs from cyclic shear stress [33]. Moreover, TEPs can directly induce neutrophil extracellular trap (NET) formation through the TLR4-ERK5 signaling pathway. The interaction between platelet GPIb and neutrophil CD18, along with tumor-derived granulocyte colony-stimulating factor (G-CSF), vWF, and CXCL4(a CXC chemokine ligand), also plays a crucial role in this process. NETs promote angiogenesis and facilitate CTC capture and adhesion to the vascular endothelium, thereby contributing to inflammation, tissue damage, thrombosis, and tumor metastasis [34].

Platelet-activating factor (PAF) can additionally recruit neutrophils to the tumor site and direct their differentiation into the N2 phenotype via PAF-PAF receptor (PAFR) signaling. This pathway facilitates the upregulation of immunosuppressive factors such as arginase 1 (Arg1) and death receptor 5 (DR5, also known as TRAIL-R1), and inhibits apoptosis induced by tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [35]. Moreover, platelets independently regulate neutrophil expansion by circulating pre-cancerous serum amyloid A (SAA) protein [36].

Macrophages

In the TME, platelets interact with CTCs and facilitate the accumulation of macrophages, including tumor-associated macrophages (TAMs), through chemokines such as macrophage migration inhibitory factor (MIF), CCL2, and CXCL12. TAMs can be broadly categorized into two phenotypes: M1-type macrophages, which are classically activated and facilitate anti-tumor immune responses, and M2-type macrophages, which are alternatively activated. Unlike M1-type macrophages, M2-type macrophages exhibit diminished antigen-presenting capacity and secrete chemokines and MMPs. Consequently, M2-type macrophages primarily exert immunosuppressive effects and contribute to cancer cell metastasis [37].

As significant contributors to the release of miRNAs in blood, TEPs upregulate the expression levels of A2M, MYLK, and TGFB3 in M2 macrophages, thereby promoting their polarization and supporting tumor progression. PAF binds to PAFR on macrophages, inducing M2-like characteristics and activating the IL-6/STAT3 axis to facilitate EMT in tumor cells [38, 39]. The M2 phenotype may also be associated with TEPs binding to PSGL-1 on TAMs via P-selectin, which upregulates the transcription of complement C5 through activation of the JNK/STAT1 pathway. This subsequently leads to the release of C5a and STAT4, inhibiting CD8 + T cell activity and promoting tumor immune escape. The lactic acid level is associated with this process [40]. Additionally, CD47 blocks phagocytosis by binding to signal regulatory protein alpha (SIRPα) on macrophages, while the recruitment of regulatory T cells (Tregs) further inhibits the activation of CD47-targeted therapies aimed at enhancing tumor-specific T cell immunity [41].

Dendritic cells

Dendritic cells (DCs), as the primary antigen-presenting cells (APCs), play a crucial role in regulating the activation of antigen-specific T lymphocytes and serve as a bridge between the innate and adaptive immune systems. However, the functionality of DCs varies depending on the stage of tumor development. In advanced stages, infiltrating DCs can acquire an immunosuppressive phenotype, contributing to tumor immune tolerance and progression. For example, the differentiation of immature DCs into tolerogenic phenotypes promotes immune evasion. Additionally, specific subsets of DCs, such as plasmacytoid dendritic cells (pDCs) that secrete IFNγ, can induce immunosuppression by activating regulatory T cells (Tregs) through the expression of inducible costimulator (ICOS) ligands [42, 43].

In this context, the mechanism by which platelets inhibit the function of DCs merits further exploration. TEPs release a variety of factors, such as VEGF, which diminishes the antigen-presenting capacity of DCs and thereby impairs their immune surveillance function. TGF-β1 directly inhibits the activation and maturation of NK cells and DCs. Both 5-hydroxytryptamine (5-HT) and TGF-β1 can suppress the upregulation of key T-cell co-stimulatory molecules on the surface of DCs, increase interleukin-10 (IL-10) levels, and consequently reduce the ability of DCs to stimulate T cells, thus inhibiting cellular immunity. Platelet factor 4 (PF4) enhances the reactivity of DCs to TLR ligands [44]. Moreover, soluble mediators released by TEPs decrease the T cell activation capability of DCs. Platelet concentrates also inhibit the production of IL-6, IL-8, IL-12, tumor necrosis factor (TNF), TGF-β, and prostaglandin E2 (PGE2) in DCs, while enhancing the expression of PD-L1 on DCs [45].

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells (MDSCs) constitute a heterogeneous population of immature bone marrow-derived cells that are induced by soluble factors derived from tumors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF), during cancer progression. These cells are characterized by their diverse composition of granulocytes and/or monocytes, originating from a mixture of DCs, macrophages, and granulocyte precursors. As key immunosuppressive cells within the TME, MDSCs induce significant systemic and local immunosuppression, maintain the quiescence of cancer stem cells, and promote cancer invasion and metastasis [46]. MDSCs exhibit a close relationship with platelets. Firstly, PSGL-1 on the surface of MDSCs binds to P-selectin on platelets, activating platelet recruitment via the PSGL-1/P-selectin pathway. Secondly, platelets can enhance the formation and recruitment of MDSCs, augment their immunosuppressive activity, and facilitate the immune escape of CTCs [47].

TEPs directly induce the production of MDSCs via CXCL4, which in turn negatively regulates the function of CD8 + T cells. Additionally, TEPs recruit pre-tumorigenic immune cells, including neutrophils and MDSCs, to the premetastatic niche by releasing inflammatory

chemokines such as CXCL5 and CXCL7. MDSCs promote tumor cell proliferation by delivering energy-rich lipid vesicles, inhibite the activation and proliferation of T cells and NK cells through upregulation of Arg-1, inducible nitric oxide synthase (iNOS), and reactive oxygen species (ROS), interfere with the antigen-presenting capacity of B cells, and stimulate the expansion of Treg cells, thereby driving sustained immunosuppression [48, 49]. Studies based on ITP have shown that TGF-β1 derived from TEPS induces the amplification and functional reprogramming of MDSCs via the TGF-β/Smad signaling pathway. Moreover, PDGF stimulation markedly enhances the proliferation of cancer-associated fibroblasts (CAFs) and upregulates CXCL expression, contributing to the recruitment of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) and leads to significant tumor fibrosis. This results in reduced lymphocyte infiltration and resistance to PD-1 antibody therapy [50].

T lymphocyte

In platelet-T lymphocyte aggregation, platelets modulate T cell immune responses through direct cell-cell interactions or soluble mediators, exhibiting complex and often opposing regulatory effects across various disease states. Notably, the mechanism of platelet-mediated immune evasion has emerged as a focal point in the development of novel immunotherapies [51]. For instance, activated platelets markedly diminish the antitumor efficacy of T cell-based immunotherapies, such as bispecific antibodies (bsAbs)-mediated T cell recruitment, via a TGF-β-dependent pathway. This to impaired reactivity of both CD4 + and CD8 + T cells [52].

Glycoprotein A repeat dominance (GARP) protein is prominently expressed on the surface of platelets and plays a crucial role in the secretion, maturation, and activation of TGF-β. This leads to the formation of the GARP/TGF-β axis, which is essential for sustaining primary tumor growth and facilitating distant metastasis. TGF-β1 directly inhibits the activation, proliferation, effector differentiation, and cytotoxicity of cytotoxic T lymphocytes (CTLs), while simultaneously promoting the production of Tregs, thereby reducing tumor immune sensitivity. Additionally, TGF-β1 can indirectly weaken CTLs by inducing the expression of the key transcription factor forkhead box P3 (FoxP3), conferring a regulatory and immunosuppressive phenotype on Tregs. Furthermore, thrombin is involved in the cleavage of GARP from platelets and the subsequent release of active TGF-β, further supporting cancer immune escape [53, 54]. Simultaneously, this intricate process releases particles containing a variety of signaling molecules, including PF4 (CXCL4), serotonin, and proteases, which induce NK cells and T cells to become non-reactive. Notably, PF4 inhibits the release of IL-2, with its levels inversely correlated with the proliferation and cytotoxic capacity of CD4 + and CD8 + T lymphocytes. This phenomenon may be attributed to PF4 inducing the expression of immunomodulatory molecules on lymphocytes or directly interacting with T lymphocytes and their receptors via CXC chemokine receptor 3 (CXCR3) [55].

The heat shock protein Gp96 plays a crucial role in mediating DCs antigen presentation and proinflammatory cytokine secretion. However, when platelet-specific binding to Gp96 occurs, this process is inhibited, thereby affecting antigen presentation and subsequent T lymphocyte activation. Furthermore, platelets can directly bind to CD3ε on CTLs via the platelet protein TLT-1, leading to the inhibition of T cell proliferation and cytotoxicity [56, 57]. Additionally, CTCs facilitate a certain degree of downregulation of MHC-I, which reduces the presentation of tumor antigens to T cells through MHC molecules without adequately inducing an NK cell response [17].

B lymphocyte

Platelet regulation of B cell-mediated humoral immunity, particularly in the context of immune escape, remains underexplored. PMPs, which are a rich source of CD40 ligand (CD40L), modulate B cell humoral immunity via CD40-CD40L axis signaling. This interaction synergizes with CD4 + T cells to stimulate the production of antigen-specific IgG and influences the formation of germinal centers [58]. Conversely, immunoglobulin deposition triggers Fc receptor and complement-mediated chronic inflammation, fostering an environment conducive to cancer development. Regulatory B cells (Bregs) inhibit the anti-tumor response of T cells by producing cytokines such as IL-10, IL-35, and TGFβ. The role of platelets in these processes warrants further investigation [59].

Immune-associated signaling pathways

Platelets are recognized as a significant source of bioactive molecules that modulate multiple signaling pathways in various cell types. The equilibrium between immune defense and self-tolerance is delicately regulated by pairs of immune checkpoint molecules. For instance, platelet endothelial cell adhesion molecule 1 (PECAM-1), functioning as an immune checkpoint molecule, negatively regulates the cytotoxicity of monocytes and macrophages. Additionally, PECAM-1 promotes atypical TGF-β signaling in T cells, which is independent of Smad, thereby inhibiting T cell immune function [60]. PECAM-1 interacts with Pyk2, serving as a crucial mediator for anchor-independent growth and anoikis resistance in tumor cells [61]. CTCs acquire platelet-derived regulator of G protein signaling 18 (RGS18), which upregulates human leukocyte antigen E (HLA-E) expression through the AKT-GSK3β-CREB signaling pathway

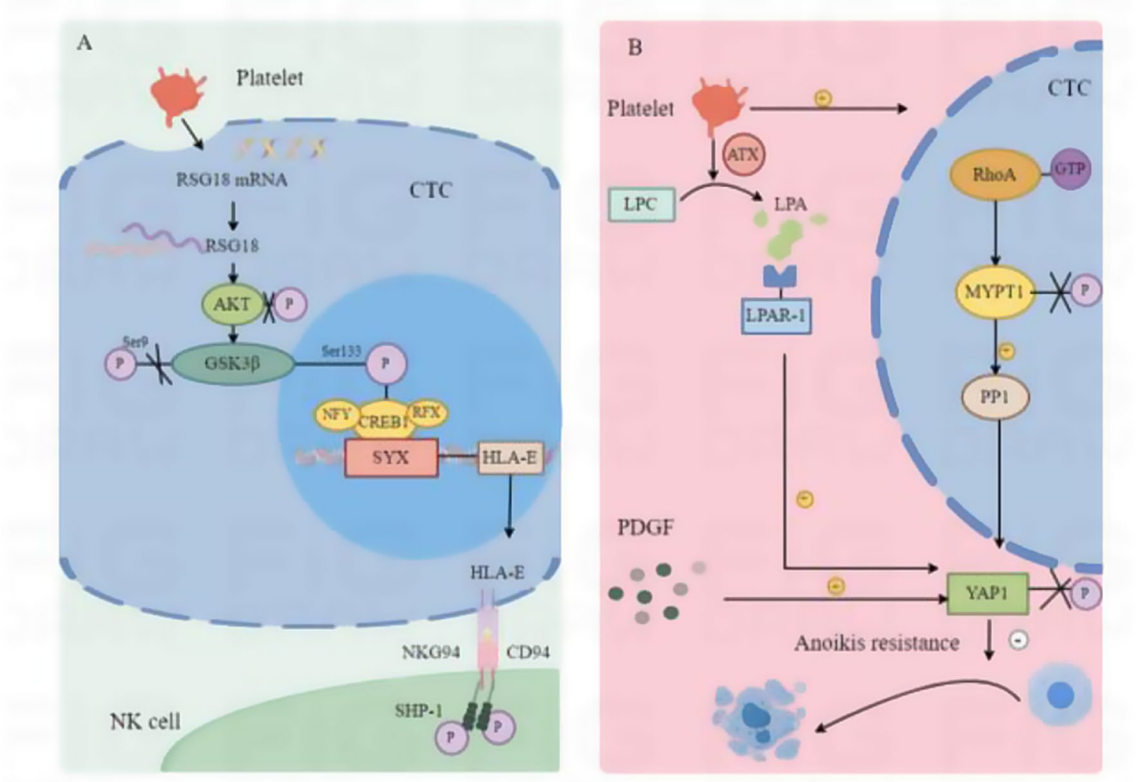

Fig. 3 **A**. Tumor cells facilitate immune evasion through interactions with CD94-NKG2A on NK cells. Upon upregulation of RGS18, AKT phosphorylation is attenuated, leading to the stabilization of GSK3β by inhibiting serine residue 9 phosphorylation. Subsequently, GSK3β enhances CREB1 activity via phosphorylation at serine residue 133. Activated CREB1 exhibits predominantly nuclear subcellular localization and forms a transcriptional positive regulatory complex with RFX and NFY within the nucleus. This complex binds to the HLA-E promoter, which contains intact SXY modules and partial enhancer A and ISRE sites. Consequently, overexpression of RGS18 results in increased HLA-E levels in three PDAC cell lines. **B**. Platelets mediate tumor cell resistance to apoptosis through various mechanisms

(Fig. 3A). Elevated HLA-E interacts with CD94-NKG2A on NK cells, forming an immune checkpoint pair that activates intracellular phosphatase SHP-1 to inhibit NK cells cytotoxicity and CTC-mediated immune surveillance [62].

Different degrees of platelet activation may underlie the varying levels of PD-L1 expression on platelet surfaces. As a ligand for programmed cell death protein-1 (PD-1), PD-L1 plays a crucial role in negatively regulating immune cell function within the TME, directly contributing to host immunosuppression or immune evasion, and potentially influencing the efficacy of immune checkpoint therapies [63]. Research on non-small cell lung cancer (NSCLC) has demonstrated that platelet-derived PD-L1 not only reflects overall PD-L1 expression in tumors but also predicts the therapeutic response to immune checkpoint inhibitors (ICIs). Furthermore, it enhances the therapeutic effect of ICIs by modulating the growth of PD-L1-negative tumors. Platelet-derived PD-L1 can directly interact with T cells, inhibiting their activation and proliferation, thereby suppressing the cytotoxicity of CD4 + and CD8 + T cells, making it a valuable prognostic and predictive biomarker for cancer patients [64, 65]. Additionally, platelet activation promotes the proliferation of Tregs and is positively correlated with PD-1/PD-L1 signaling. Moreover, platelet-derived EGF can induce PD-L1 expression in tumor cells via the p-ERK1/2/p-c-Jun pathway in an EGF/EGFR-dependent manner [66].

TEPs secrete adenosine triphosphate (ATP), which directly interacts with the endothelial purinergic receptor P2Y2 (P2RY2). This interaction promotes endothelial barrier opening, thereby altering vascular permeability and facilitating CTC extravasation, thus establishing a foundation for CTCs to interact with platelets. In this dynamic process, the RhoA-myosin phosphatase targeting subunit 1 (MYPT1)-protein phosphatase 1 (PP1) pathway mediates the dephosphorylation of Yes-associated protein 1 (YAP1), thereby stimulating cell proliferation and migration and promoting nuclear translocation (Fig. 3B). Consequently, platelets decrease the susceptibility of tumor cells to anoikis, aiding in immune evasion, while upregulating the expression of pro-survival genes, which facilitates invasion and metastasis [67, 68]. Furthermore, TEPs secrete autotaxin, an enzyme with lysophospholipase D catalytic activity. This enzyme binds to

the integrin αvβ3 on CTCs and catalyzes the conversion of lysophosphatidylcholine (LPC) to lysophosphatidic acid (LPA). Subsequently, LPA binds to the LPA receptor 1 (LPAR-1) on tumor cells in an autocrine manner, thereby activating anoikis resistance in CTCs through the RhoA-Gα12/13-YAP1 pathway [69, 70].

As a chemoattractant, PDGF has been demonstrated to induce anoikis through its binding to the PDGF receptor α (PDGFR-α). The underlying mechanism remains to be fully elucidated but may involve the activation of the RhoA/PP1 cascade leading to YAP1 activation or Src-family kinase-dependent tyrosine phosphorylation, which regulates YAP transcriptional activity [71]. Notably, PDGF-BB has been shown to inhibit anoikis and upregulate the expression of the oncogene MYC via the Hippo/YAP signaling pathway, thereby promoting tumor progression [72]. Additionally, PDGF can confer apoptosis resistance in CAFs by activating the Ras/PI3K/Akt pathway, which subsequently inhibits T cell responses. In glioblastoma, PDGFR-α modulates cytoskeletal reorganization, upregulates extracellular signal-regulated kinases (ERK1/2), PI3K, and Rho-associated coiled-coil containing protein kinase (ROCK) pathways, and facilitates anchorage-independent growth of CTCs [73]. Overexpression of multiple EGF-like domain 11 (MEGF11) has been implicated in conferring anti-anoikis properties. TSP1 exerts immunosuppressive effects by modulating innate and adaptive immune cells through CD47-dependent mechanisms, promotes anoikis resistance via interaction with the calreticulin-LRP1 complex, and stimulates PI3K-dependent Akt activation while downregulating apoptotic signaling pathways [74].

Additional mechanisms of immune evasion

Studies on hepatocellular carcinoma have demonstrated that PDGF serves as a critical link between TGF-β signaling and nuclear beta-catenin accumulation during EMT. This process endows a subpopulation of tumor cells with characteristics of cancer stem cells, thereby promoting tumor progression [75]. Platelets, acting as significant sources of TGF-β1, activate the TGF-β/Smad and NF-κB signaling pathways in CTCs, accelerating EMT and consequently increasing PD-L1 expression. PDGF-D can induce EMT via the mTOR, Notch, NF-κB, CXCL4, and Bcl-2 signaling pathways [76]. EMT-induced immune escape is a critical mechanism of immune resistance, mediated through multiple pathways. For instance, the mesenchymal characteristics of tumor cells lead to the downregulation of NK cell surface activation receptors or restrict the expression of NKG2D ligands such as ULBP1/6 on CTCs [77, 78]. The inhibitory checkpoint CD155 on the surface of CTCs is transcriptionally regulated by the FAK/JNK/c-Jun signaling cascade in a platelet-contact-dependent manner. Specifically, the interaction between CD155 and its receptor TIGIT on NK cells inhibits NK cell cytotoxicity, thereby evading innate immune surveillance mediated by this pathway [79].

The overexpression of the tryptophan catabolic enzyme indoleamine 2,3-dioxygenase (IDO) in tumor cells results in the suppression of effector T cell and NK cell responses, while promoting the differentiation of Tregs and the generation of MDSCs. These processes play a critical role in facilitating tumor immune escape [80, 81]. Additionally, human leukocyte antigen G (HLA-G), a non-classical MHC class I molecule with immunosuppressive properties, expressed by CTCs, can bind to various inhibitory receptors on immune cells, such as immunoglobulin-like transcript 2 (ILT2), thereby mediating potent inhibition [82]. Similarly, CTCs utilize abnormally expressed mucins and associated glycans, including sialic acid Tn (sTn) antigens, to interact with inhibitory receptors on DCs, TAMs, and NK cells, leading to comprehensive immunosuppression through receptor masking or inhibition of cytolytic activity. For instance, MUC1 binds to siglec on DCs, shielding TLRs and inducing an immature DC phenotype. The remodeling of the glycocalyx by mucins in cancer cells is directly linked to the immunosuppressive TME, potentially triggering MDSC recruitment and activation, as well as the induction of NK and T cell inhibition via the TLR2/MyD88/IL-6/JAK1/2 signaling axis [83, 84].

Recent studies have demonstrated that the overexpression of podoplanin (PDPN) on platelets is positively correlated with the expression of immune checkpoint molecules such as PD-L1, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene 3 (LAG-3) in invasive bladder cancer and NSCLC. This overexpression can inhibit the proliferation and survival of IL-7-mediated effector T cells and is associated with increased tumor infiltration by Foxp3 + Tregs [85]. Additionally, TXA2, secreted by platelets, exerts immunosuppressive effects and participates in Th1 differentiation and Th17 expansion. It may also inhibits Th2 differentiation while promoting Treg differentiation both in vivo and in vitro. TXA2 has been shown to activate p38MAPK in T cells during allergic responses, promote the binding of transcription factors NFE2 and PBX1 to IL-9 promoters, thereby inhibiting IL-9 transcription and limiting the differentiation of T cells into Th9 cells [86]. DC-derived TXA2 and its receptor TP are believed to modulate adaptive immune responses by regulating interactions between T cells and DCs, such as restraining T cell activation [87]. TCIPA is regarded as a key target for protecting CTCs from immune surveillance, thereby promoting tumor growth and metastasis primarily through glycoprotein and lipoxygenase (LOX)-dependent pathways. For instance, overexpression of 12-LOX has

been shown to upregulate MMP9 mRNA, protein levels, and secretions in cancer cells via activation of the PI3K/AKT/NF-κB signaling pathway, ultimately facilitating cellular invasion [88].

TEPs-derived thrombin catalyzes the transformation of fibrinogen and mediates the release of pro-inflammatory cytokines such as IL-6, TNF, and monocyte chemotactic protein-1 (MCP-1). This process leads to the accumulation of various tumor-infiltrating immunosuppressive cell populations, including MDSCs, M2-like TAMs, and Tregs. Thrombin also activates protease-activated receptors (PARs), thereby reducing CTL infiltration via thrombin-PAR1 signaling. This process upregulates immunosuppressive genes such as colony-stimulating factor 2 (Csf2) and prostaglandin-endoperoxide synthase 2 (Ptgs2), and promotes tumor invasion through the PAR1-PDK1-AKT signaling pathway. Consequently, thrombin couples coagulation with immune escape mechanisms, fostering an immunosuppressive microenvironment [89, 90]. Thromboglobin and CD44 facilitate the interaction between CTCs, whereas CD44 and intercellular adhesion molecule-1 (ICAM-1), as markers of tumor stem cells, independently promote the clustering of CTCs. Specifically, CD44 enhances stem-like properties through the activation of p21-activated kinase 2 (PAK2)/protein tyrosine kinase 2 (PTK2) or EGFR signaling pathways, while ICAM-1 confers stem-like characteristics by upregulating cell cycle-related pathways [91]. Notch1 signaling is activated in CTCs and CTMs through direct contact with ROS derived from PMN-MDSCs and jagged canonical Notch ligand 1 (JAG1) expressed on PMN-MDSCs. Subsequently, Nodal, which is induced by Notch1 activation, interacts with the receptor Cripto on PMN-MDSCs to facilitate cellular aggregation [75]. Platelet-derived stromal cell-derived factor-1α (SDF-1α, also known as CXCL12) regulates PDGF-BB expression via the SDF-1α/CXCR4 axis, thereby playing a crucial role in pericellular recruitment and neovascularization within tumors microenvironments. Conversely, tumor-derived PDGF-BB, through phosphorylation of PDGF receptor β (PDGFR-β), induces SDF-1α expression by activating hypoxia-inducible factor 1α (HIF-1α) in endothelial cells, which in turn promotes platelet survival [92, 93].

Platelet-based antitumor therapeutic strategies

Currently, platelet-based antitumor therapeutic strategies can be categorized into two primary approaches: one involves directly inhibiting platelet function using conventional antiplatelet agents; the other employs a targeted delivery system for antitumor drugs utilizing platelets or platelet membrane coatings. Emerging evidence underscores the dual role of platelet-derived TXA2 in promoting metastasis through both direct tumor-platelet interactions and immune evasion. A seminal study by Yang et al. revealed that aspirin inhibits platelet COX-1/TXA2 signaling, thereby restoring T cell immunity by suppressing the ARHGEF1-RHOA pathway, which otherwise dampens TCR-driven activation and effector functions. This mechanism explains the reduced metastatic burden observed with aspirin use in preclinical models and aligns with clinical data showing decreased metastasis in cancer patients on low-dose aspirin regimens [94]. Complementing these findings, Lucotti et al. demonstrated that platelet-derived TXA2 orchestrates early metastatic niche formation by recruiting $CX3CR1^{+}$ monocytes/macrophages via endothelial activation (e.g., CCL2/MCP-1 release). COX-1 inhibition or TXA2 receptor antagonism (e.g., picotamide) abrogated this process, highlighting a temporal window where targeting platelet TXA2 disrupts macrophage-dependent dissemination [95].

Emerging nanotechnologies hold significant promise in antitumor therapy. By conjugating nanoparticles with apoptosis-inducing molecules such as TRAIL, TNF, Fas ligand (FasL), and liposomes encapsulating small interfering RNA (siRNA), these systems can deliver these agents to CTCs via vWF interactions, thereby facilitating direct cytotoxicity [96, 97]. Recently developed platelet membrane hybrid liposomes (PM-Lipo) have been engineered to concurrently deliver glycolysis inhibitors, namely quercetin (Que) and shikonin (SHK), thereby achieving metabolic reprogramming of platelets. This approach not only inhibits platelet activation and their interaction with CTCs but also reshapes the tumor immune microenvironment. Concurrently, the inhibition of glycolysis in CTCs diminishes their metastatic and invasive potential [54]. Nanoparticles coated with platelet membranes, when loaded with drugs or agents for enhancing local immune activation such as the targeted delivery of the TLR agonist resiquimod (R848) to tumor sites, can effectively reprogram M2 macrophages into M1 macrophages. This not only delays tumor growth but also inhibits metastasis and recurrence. This vector system offers significant advantages including enhanced biocompatibility and natural targeting affinity [98].

Several immune escape mechanisms, target molecules, and interaction pathways discussed above offer promising directions for drug development aimed at inhibiting tumor metastasis. For instance, immune agents such as sorafenib and regorafenib have been shown to decrease ADAM9 expression, thereby preventing the shedding of MHC-1 from tumor cells and enhancing NK cell activation [99]. Circulating PMPs and the regulatory microRNAs derived from them can metastasize to tumor cells within solid tumors, modulate gene expression in CTCs, and influence tumor progression. These mechanisms play a crucial role at multiple stages of cancer development,

and elucidating these mechanisms will uncover potential targets for cancer therapy [100]. For example, in NSCLC, platelet-derived miR-223 enhances the invasion of tumor cells by targeting the tumor suppressor protein Band4.1-like protein-3 (B4GALT3) [101]. TEPs and their derivatives, including RNA and proteins, hold promise as biomarkers for cancer diagnosis, real-time monitoring, and prognostic prediction. Additionally, the platelet-to-lymphocyte ratio (PLR) can serve as a valuable tool for developing prognostic and personalized treatment strategies [102, 103]. The intricate interplay between platelets and tumor cells presents both opportunities and challenges for therapeutic intervention. While targeting platelet-mediated pathways holds promise for inhibiting metastasis, emerging evidence reveals a paradoxical duality: antiplatelet and anticoagulant therapies may exert context-dependent effects that can inadvertently promote cancer progression under certain conditions. This complexity necessitates a nuanced understanding of their mechanisms and temporal dynamics.

Large-scale clinical trials have uncovered unexpected pro-tumorigenic effects associated with prolonged antiplatelet regimens. The DAPT trial demonstrated that extended (30-month) dual antiplatelet therapy (DAPT) with P2Y12 inhibitors (clopidogrel or prasugrel) plus aspirin significantly increased cancer incidence and cancer-related mortality, particularly after 24 months of treatment [104]. This temporal pattern suggests a cumulative disruption of platelet-mediated immune surveillance or vascular integrity. Similarly, the PLATO and PEGASUS trials revealed elevated cancer mortality with ticagrelor, with independent audits identifying discrepancies in cancer death reporting—highlighting potential underestimation of risks [105]. The ASPREE trial further challenged conventional assumptions by showing increased cancer mortality in healthy elderly recipients of long-term low-dose aspirin [10], while the TRACER trial implicated PAR-1 antagonists like vorapaxar in elevating solid cancer incidence among cardiovascular patients [106]. These findings collectively suggest a class effect wherein sustained platelet or coagulation inhibition may inadvertently facilitate cancer progression, especially in patients with occult malignancies.

Animal studies provide mechanistic clarity for these clinical observations. In B16F10 melanoma models, short-term thrombin inhibition effectively blocked metastasis, whereas prolonged administration of direct thrombin inhibitors (e.g., hirudin or ximelagatran) doubled lung metastatic burden [107]. This temporal dichotomy mirrors clinical findings and implies adaptive changes in the tumor microenvironment. The 4T1 breast cancer model revealed a striking context-dependence: DAPT induced vascular mimicry (VM) in primary tumors, marked by PAS+/CD31- pseudovessel formation and worsened survival, yet suppressed metastasis in the absence of primary lesions [108]. This paradox underscores how platelet inhibition may destabilize vascular integrity in established tumors while retaining antimetastatic effects in early dissemination. Dabigatran, a direct thrombin inhibitor, promoted lung metastasis not through anticoagulation but by impairing platelet-dependent endothelial protection, as evidenced by elevated vascular permeability biomarkers (e.g., SDC-1 and Ang-2) [109]. Similarly, GPVI inhibition reduced metastasis in galectin-3-expressing tumors but risked hemorrhage due to compensatory CLEC-2 activation, illustrating the delicate balance between antimetastatic efficacy and vascular homeostasis [110].

The pro-tumorigenic effects of prolonged antiplatelet/anticoagulant therapy emerge through intersecting pathways: Endothelial Barrier Disruption: Chronic platelet inhibition interferes with CLEC-2/podoplanin and GPVI signaling, destabilizing endothelial junctions and facilitating tumor cell extravasation [10, 109]. DAPT exacerbates this by shifting platelets toward a pro-angiogenic phenotype (elevating VEGFA/PDGF while reducing TSP-1/PF4) and inducing VM via VE-cadherin/Slpi upregulation [108]; TGF-β/PAI-1 Axis Dysregulation: Anticoagulants reduce PAI-1 levels, unleashing plasmin-mediated TGF-β activation that drives EMT and fosters a pro-thrombotic, pro-metastatic niche [106]; Immune Evasion: Ticagrelor and clopidogrel impair NK cell cytotoxicity by suppressing platelet-derived MHC-I transfer to tumor cells, while ticagrelor's prolactin-elevating effects may stimulate hormone-sensitive cancers [105].

Antiplatelet and anticoagulant therapies play a crucial role in managing thrombosis in cancer patients, yet their dual effects—both inhibiting platelet-mediated immune evasion and metastasis while potentially promoting cancer progression—demand a refined therapeutic approach. Notably, aspirin's antimetastatic effects operate through a bifunctional mechanism: (1) immune reactivation (via blockade of the TxA_2-COX-1 axis to restore T cell cytotoxicity) and (2) niche suppression (by attenuating macrophage-driven early metastasis). To optimize outcomes, a paradigm shift is needed: (1) personalizing P2Y12 inhibitor duration (e.g., limiting to <24 months in high-risk patients) and prioritizing safer agents like non-anticoagulant heparin derivatives (e.g., Succ-100-LMWH) that target selectins without bleeding risks [107]; (2) combining anticoagulants such as COX-1 inhibitors (e.g., aspirin) or P2Y12 antagonists with TGF-β inhibitors or VM-targeting agents to counteract pro-metastatic effects; and (3) adopting biomarker-driven strategies (e.g., galectin-3 or TGF-β monitoring) to identify at-risk patients. Despite decades of interest in antiplatelet therapy for cancer, its clinical adoption remains limited by cost-effectiveness and implementation challenges.

Future research should focus on spontaneous metastasis models and therapies innovation that selectively disrupt procancer platelet functions while preserving vascular and immune homeostasis, ultimately bridging the gap between preclinical promise and clinical utility.

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Author contributions
XZ devised the study. JG were involved in the conception of the study and critically revised the manuscript. JG and XZ were involved in writing the article. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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The authors declare no competing interests.

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