Platelet-circulating tumor cell crosstalk: A pivotal target in cancer diagnosis and therapy (Review)

LIFANG ZHANG[1*], YE YUAN[2,3*], YAN DENG[1,4], LIN WANG[1,3-5] and FENGHUA CHEN[1,3]

[1]Department of Clinical Laboratory, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, P.R. China; [2]Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, P.R. China; [3]Hubei Key Laboratory of Regenerative Medicine and Multi-disciplinary Translational Research (Huazhong University of Science and Technology), Wuhan, Hubei 430022, P.R. China; [4]Research Center for Tissue Engineering and Regenerative Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430022, P.R. China; [5]Hubei Provincial Engineering Research Center of Clinical Laboratory and Active Health Smart Equipment, Wuhan, Hubei 430022, P.R. China

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Abstract. Platelets, while essential for hemostasis, have been recognized as critical mediators in cancer metastasis. The crosstalk between platelets and circulating tumor cells (CTCs) constitutes a key driver of metastasis, emerging as a focal point in oncology research. Elucidating the underlying mechanisms provides novel insights into tumor dissemination. The present review systematically traces the evolution of platelet-CTC crosstalk, from receptor-mediated adhesion to bidirectional molecular exchange, and its implications for metastatic progression. Additionally, the diagnostic significance of platelet-CTC complexes as potential biomarkers for cancer detection and prognosis is highlighted. Finally, promising therapeutic strategies targeting the platelet-CTC crosstalk are discussed. By integrating current knowledge, it was demonstrated that targeting platelet-CTC crosstalk holds potential for improving cancer diagnosis and therapy, while also identifying avenues for future translational research.

Correspondence to: Dr Fenghua Chen or Dr Lin Wang, Department of Clinical Laboratory, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, 1277 Jiefang Avenue, Wuhan, Hubei 430022, P.R. China
E-mail: chfh100@hust.edu.cn
E-mail: lin_wang@hust.edu.cn

*Contributed equally

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Contents

1. Introduction

Platelets are universally recognized for pivotal role in hemostasis. However, emerging evidence has revealed their substantial involvement in cancer progression (1). This seminal study revealed how platelets become indispensable accomplices of circulating tumor cells (CTCs). The molecular crosstalk between platelets and CTCs plays a vital role in tumor metastasis, the primary cause of cancer-related mortality. CTCs, identified as malignant cells shedding from primary tumors into the vasculature, serve as the precursors to metastasis by disseminating via the bloodstream to distant organs (2). Understanding CTCs helps further explore platelet roles in CTC generation and metastasis. Platelets confer multifaceted protection to CTCs through direct or indirect interactions: i) shielding from immune surveillance and hemodynamic shear forces, and ii) facilitating endothelial adhesion and extravasation (3,4). Mechanistically, platelet-derived bioactive molecules (for example, TGF-β) induce epithelial-mesenchymal transition (EMT), enabling tumor cell detachment and intravasation (3). Furthermore, platelet-tumor aggregates formed via surface receptor interactions enhance CTC survival and hematogenous spread (5,6).

As time goes by, our comprehension of the platelet-CTC crosstalk has been continuously deepened, gradually revealing its significant relationships in multiple aspects such as promoting the survival of tumor cells, immune escape and metastatic

dissemination (7). Extending the study of Wang *et al* (7), these mechanisms underlying platelet-CTC crosstalk were further elucidated and their diagnostic and therapeutic potential were explored. The present review synthesizes contemporary insights into the following aspects: i) the historical context and progression of platelet-CTC crosstalk; ii) the molecular mechanisms underlying platelet-CTC interactions; iii) the bidirectional interactions between platelets and CTCs; iv) the diagnostic utility of platelet-CTC-derived biomarkers in liquid biopsies; and v) emerging therapeutic strategies targeting the platelet-CTC interface.

2. Historical context and evolution of platelet-CTC crosstalk

Platelets are primarily recognized for their critical function in hemostasis; however, their multifaceted roles in oncogenesis have garnered increasing scientific interest. Seminal insights into this relationship emerged in the late 19th century. In 1868, Trousseau (8) reported an association between malignancy and spontaneous coagulation, implicating platelet involvement. Subsequently in 1869, Ashworth documented the presence of aberrant neoplastic cells within the circulatory system, now acknowledged as the inaugural identification of CTCs (9). In 1877, Billroth (10) observed 'thrombi with tumor components' within the tumor metastasis, further establishing a direct connection between cancer cells and blood platelets. Advancing to the mid-20th century, a comprehensive analysis of blood smears from 14,000 patients revealed a significant correlation between increased platelet levels and cancer incidence (11). The findings indicated that thrombocythemia was notably more prevalent in malignancies of the lung, stomach, colorectal tract, breast and ovary. In 1968, Gasic *et al* (12) observed that thrombocytopenia was associated with cancer metastasis in murine models. Injecting mice with antiplatelet serum significantly reduced the number of metastatic foci; this effect was reversible through platelet-rich plasma infusion. These findings underscore platelets' facilitatory role in metastatic dissemination.

In the late 20th century, research elucidated complex bidirectional interactions between tumors and platelets. Numerous malignancies induce platelet aggregation both *in vitro* and *in vivo*, resulting in thrombocytopenia, frequently associated with pulmonary platelet sequestration (13). By 2011, mechanistic studies revealed that platelets contribute to cancer progression via internalization of RNA from tumor-derived extracellular vesicles (EVs), establishing an RNA transfer network within the bloodstream by releasing pro-tumorigenic vesicles (14). Concomitantly, tumor-secreted cytokines are internalized by platelets, recruiting them to the neoplastic site to support angiogenesis (15). Platelets sequester these proteins via α-granules, thereby modulating specific cellular pathways through regulated exocytosis (16). Clinical investigations concurrently identified thrombocytosis as an independent prognostic factor in primary lung carcinoma, suggesting platelet count as a straightforward biomarker for risk stratification (17,18). Collectively, these advances highlight platelets' integral roles beyond hemostasis, encompassing tumor proliferation, metastasis and vascular remodeling.

The advent of microfluidic technology in the 21st century has revolutionized the research of platelet-CTC crosstalk. In 2017, microfluidic-based isolation leveraged platelet-derived surface markers on CTCs, confirming platelet-CTC co-localization (19). In 2021, Lim *et al* (20) discovered using centrifugal microfluidic technology that 90.7% of CTCs were platelet-coated, and platelet-encased CTC clusters correlated with rapid disease progression. Recent investigations (21) have elucidated the molecular mechanisms underlying the crosstalk between platelets and CTCs. The interplay provides a critical scientific foundation for advancing metastasis research and harbors significant potential for clinical applications. Since the initial recognition of platelet-tumor interactions in the 19th century, the field has undergone substantial evolution, with contemporary studies comprehensively exploring the platelet-CTC crosstalk to uncover pro-tumorigenic effects (Fig. 1).

3. Interplay between platelets and CTCs

Molecular mechanism of platelet-CTC crosstalk. The interplay between platelets and CTCs is primarily mediated by direct surface receptor binding and by extracellular proteins that facilitate receptor bridging (Fig. 2). Building on the previous study of Erpenbeck and Schön (22), the adhesive mechanisms underlying platelet-CTC crosstalk were refined, clearly revealing the physical basis of their interaction. Key mechanisms include: i) the engagement of platelet C-type lectin-like receptor 2 (CLEC-2) with Podoplanin expressed on tumor cells, which induces platelet activation and facilitates tumor cell metastasis (6); ii) the interaction of the platelet glycoprotein (GP) Ib-IX-V complex with tumor cells via von Willebrand factor (vWF), mediating adhesion (22); iii) platelet GPIIb/IIIa (αIIbβ3 integrin) binding to ligands such as fibrinogen and vWF, enhancing platelet-tumor cell aggregation (23-25); iv) metastatic potential is augmented by platelet GPVI receptor interactions with galectin-3, collagen, or fibrin on tumor cells (26,27); v) integrin αvβ3 on tumor cells binding to the Arg-Gly-Asp (RGD) sequence, promoting adhesion (28); vi) the activation of protease-activated receptors (PAR) on tumor cells by thrombin, enhancing their interaction with platelets (22); vii) integrin α6β1 binding to ADAM9 on tumor cells, promoting metastasis (29); viii) platelet-derived acidic sphingomyelinase (Asm) inducing p38K phosphorylation in tumor cells, thereby activating integrin α5β1 and facilitating adhesion and metastasis (30,31); and ix) P-selectin on the surface of platelets binds to sialyl Lewis^x (SLe^x) on the surface of CTCs (22,32). This complex subsequently interacts with endothelial P-selectin, resulting in CTCs rolling and vascular retention (22,32). Collectively, these molecular interactions represent potential therapeutic targets for cancer treatment.

Platelet-mediated effects on CTCs. Platelets confer critical protective effects on CTCs during metastasis (Fig. 3A). First, platelets bind to CTCs through glycan-lectin interactions (such as CLEC-2, galectins) to form a 'protective shield' (21,33). This interaction helps CTCs evade the damaging effects of fluid shear stress by promoting thrombus formation (34). Furthermore, it enables CTCs to escape immune surveillance, particularly the cytotoxic effects of natural killer

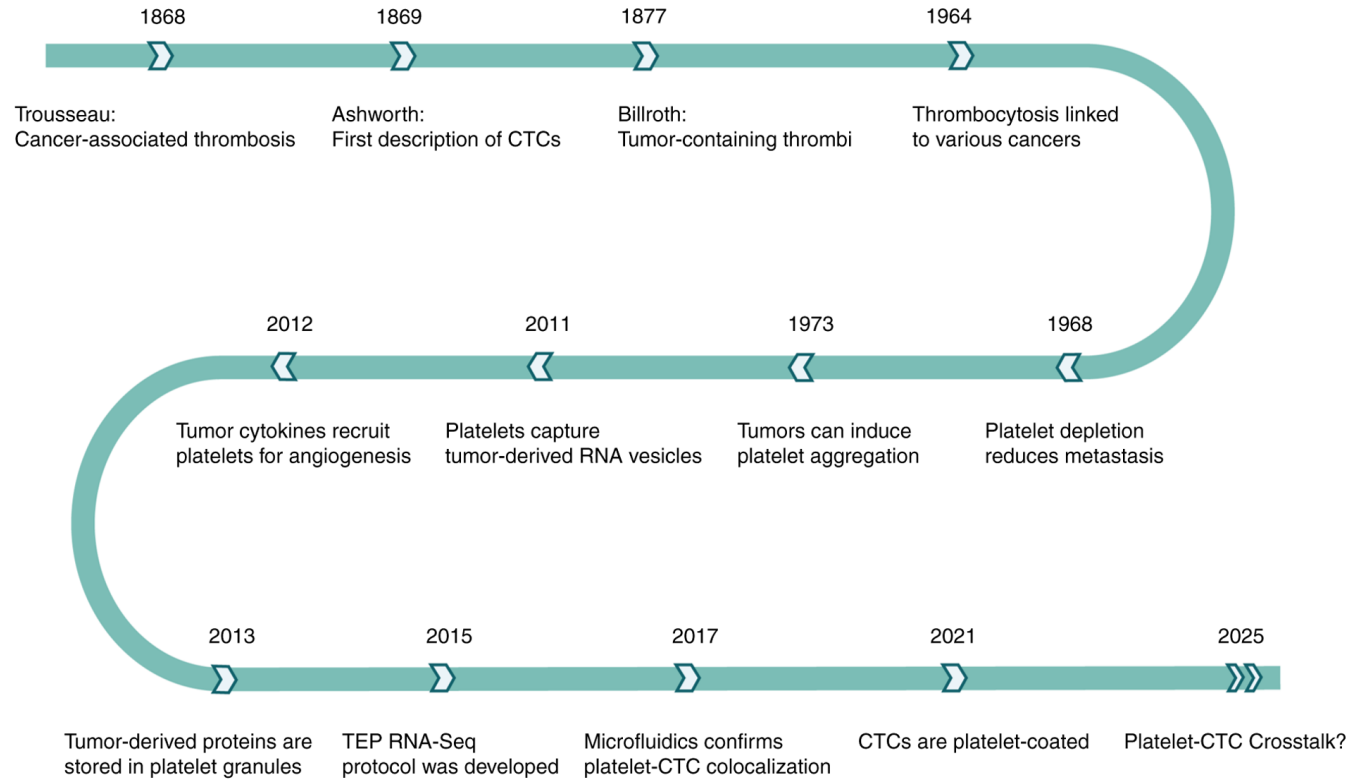

Figure 1. Historical timeline of platelet-CTC crosstalk. The present review emphasizes contemporary advancements in platelet-CTC crosstalk, with its historical progression illustrated in the figure. CTC, circulating tumor cell. Created with Adobe Illustrator 2020.

cells, thereby significantly enhancing CTC survival within the circulation (4,35,36). Hemodynamic analysis indicates that rolling CTCs induce local vortex formation, which may potentiate platelet recruitment to the CTC surface (37). Upon adhesion, platelets enhance CTC stabilization at endothelial sites by reducing cellular motility and mitigating mechanical constraints through physical encapsulation (37). Additionally, shear forces exhibit positive correlation with platelet density during adhesive events, while CTC arrest propensity inversely correlates with cellular size and stiffness. By contrast, platelet rigidity demonstrates negligible influence on adhesion efficacy (37).

Secondly, platelet adhesion to CTCs is facilitated through surface adhesion molecules, including P-selectin, CLEC-2 and GPIIb/IIIa. This interaction promotes CTC-endothelial adhesion and vascular retention, establishing critical prerequisites for metastatic colonization in distant organs (38-41). A previous study by Schlesinger (41) summarized the role of platelet receptors in tumor metastasis, which advanced our comprehension of platelet-CTC adhesion. Notably, surgical stress induces TLR4-dependent ERK5 phosphorylation, resulting in GPIIb/IIIa integrin activation and subsequent platelet-CTC aggregation (42). These aggregates exhibit enhanced entrapment by neutrophil extracellular traps, thereby promoting their retention within the pulmonary microvasculature (42). Heparanase released from α-granules cooperates with P-selectin to enhance platelet adhesion and promote thrombogenicity, facilitating metastasis (43). Furthermore, tissue factor (TF)-induced coagulation facilitates the coating of CTCs by platelets, leading to the formation of circulating tumor microemboli (CTM) (44).

Additionally, platelets secrete multiple bioactive mediators that collectively facilitate metastatic progression. The platelet release contains TGFβ, ATP, and serotonin, which, in combination with matrix metalloproteinases (MMPs) and histamine, synergistically enhance tumor cell invasiveness, increase vascular permeability, and promote extravasation and metastatic niche formation (45-49). For example, TGFβ released via platelet-CTC crosstalk can activate the metastatic capacity of CTCs by triggering metabolic reprogramming and bioenergetic adjustment (50). On the other hand, TGFβ activates the TGFβ/Smad pathway, inducing SERPINE1/PAI-1 expression to activate PI3K/AKT signaling, thereby enhancing CTC metastatic competence (51). Molecular analyses reveal that platelet-CTC crosstalk upregulates key oncogenic pathways in CTCs, including *MYC, IL33, VEGFB, PTGER2, PTGS2* and *TGFβ2* expression profiles (52). Regulation of angiogenesis is a key mechanism in tumor progression, with extensive evidence indicating that platelets directly contribute to this process, likely through factors released upon their activation (53). Ghosh *et al* (54) developed an angiogenesis-enabled tumor microenvironment (TME) chip that recapitulates multicellular interactions among tumor cells, endothelial cells and platelets in ovarian cancer, providing direct evidence of platelet-mediated angiogenesis enhancement. Furthermore, platelets orchestrate immune-modulatory functions through chemokine release (particularly CXCL7 and CXCL5 from α-granules), facilitating immune cells' recruitment and pre-metastatic niche establishment (55,56).

Platelets significantly facilitate EMT during the dissemination of CTCs via diverse molecular mechanisms (57). TGFβ secreted by platelets triggers EMT by activating both

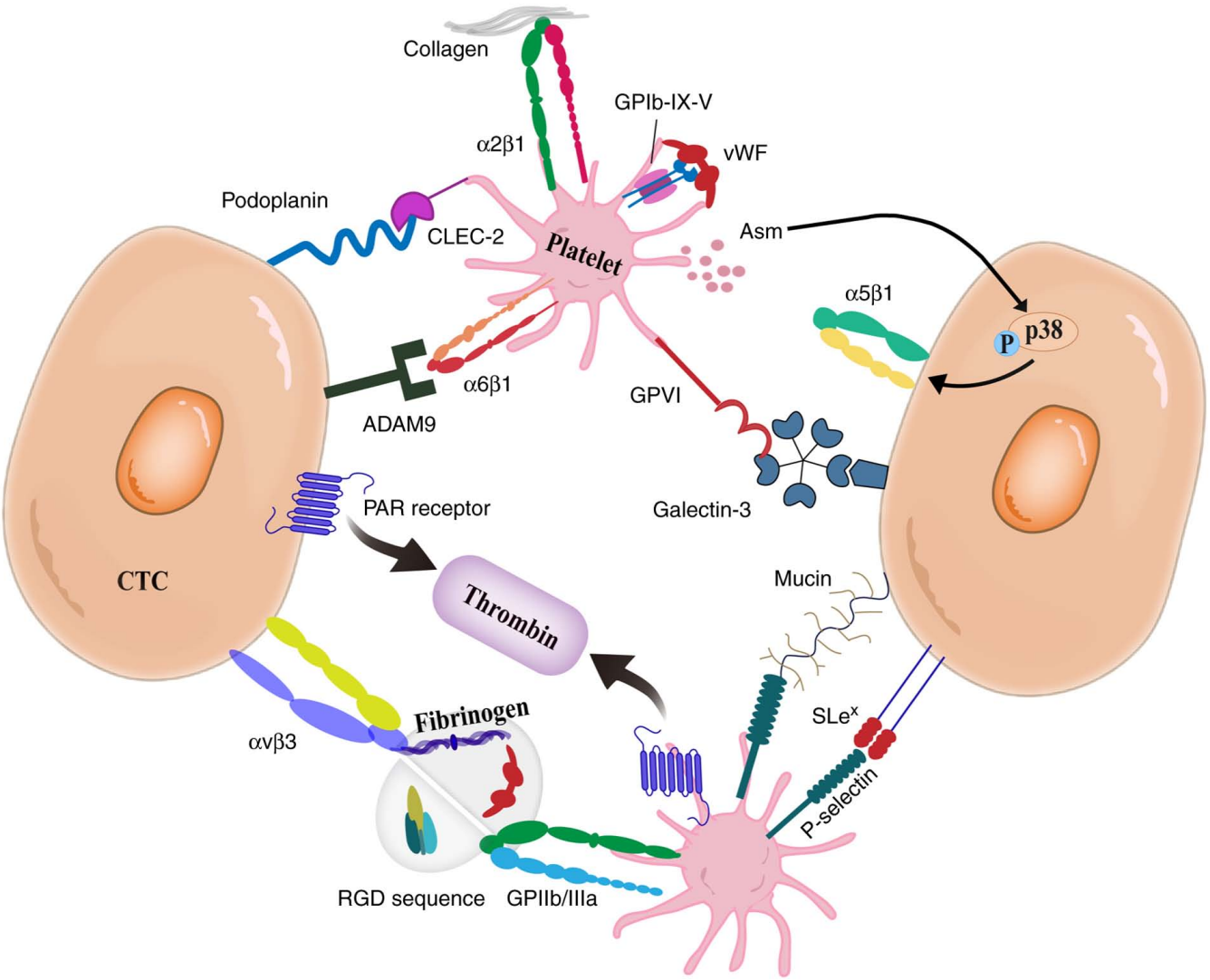

Figure 2. Receptor pairs governing platelet-CTC crosstalk. The depicted molecular interactions encompass: CLEC-2 (platelets) binding to podoplanin (cancer cells); GP Ib-IX-V complex (platelets) interacting with vWF (cancer cells); GPIIb/IIIa (αIIbβ3 integrin) (platelets) binding to ligands such as fibrinogen and vWF; GPVI (platelets) recognizing galectin-3, collagen, and fibrin on cancer cells; integrin αvβ3 (cancer cells) engaging RGD motifs; PAR (cancer cells) mediating thrombin-dependent platelet activation; integrin α6β1 (platelets) binding to ADAM9 (cancer cell); platelet-derived Asm inducing p38K phosphorylation and integrin α5β1 activation in tumor cells; P-selectin (platelets) interacting with sLe^x and mucins on cancer cells. These receptor-ligand engagements collectively enhance platelet adhesion to CTCs, facilitating vascular retention, extravasation and metastatic dissemination. CTC, circulating tumor cell; GP, glycoprotein; vWF, von Willebrand factor; RGD, Arg-Gly-Asp sequence; Asm, acidic sphingomyelinase; SLe^x, sialyl $Lewis^x$; PAR, protease-activated receptor. Created with Adobe Illustrator 2020.

TGFβ/Smad and NF-κB signaling pathways (46). Furthermore, platelet-derived growth factor-D (PDGF-D) promotes EMT by upregulating transcriptional regulators such as Twist1 and Notch1 in colorectal cancer cells, as well as interacting with PDGFRβ in tongue squamous cell carcinoma cells, thereby inducing phosphorylation of key kinases including p38, AKT and ERK (58,59). Platelets also secrete lysophosphatidic acid (LPA), which binds to LPA receptors on tumor cells to enhance their invasive and migratory capacities (57,60). Additionally, platelet-derived microvesicles modulate EMT-associated gene expression in tumor cells through the transfer of regulatory RNAs, including mRNA and microRNA (miRNA) (61). Building on Wang *et al*'s (57) detailed delineation of platelet-induced EMT signaling pathways, the present review integrates recent advances to provide a more comprehensive mechanistic overview. For instance, platelets contribute to CTC plasticity by maintaining a mesenchymal phenotype during circulation, enabling more efficient transition to an epithelial state upon reaching distant metastatic sites. This epithelial-mesenchymal plasticity augments tumor cell invasiveness and metastatic potential (52). These multifaceted roles establish platelets as critical mediators of cancer metastasis and provide a mechanistic basis for therapeutic strategies targeting platelet-CTC crosstalk. However, while current research predominantly focuses on platelet-mediated EMT in CTC generation, few investigations address how platelets support CTC colonization via mesenchymal-epithelial transition (MET) in distant organs.

Tumor-induced platelet responses. Emerging evidence demonstrates a complex bidirectional interplay between platelets and tumor cells (7) (Fig. 3B). This interaction induces platelet

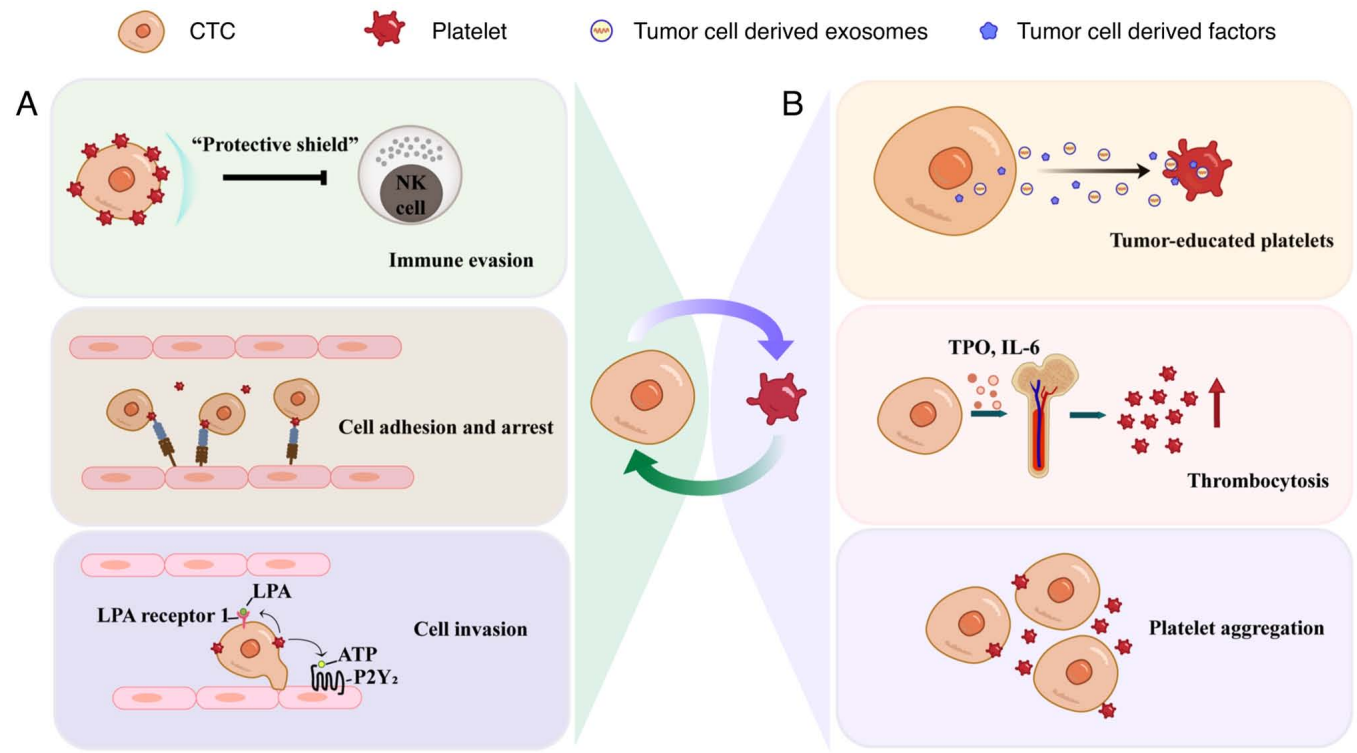

Figure 3. Bidirectional interactions between platelets and CTCs. (A) Platelet-mediated tumor promotion: i) Platelets create a protective shield around CTCs, safeguarding them from fluid shear stress and immune attack. ii) Platelet surface receptors enhance cancer cell adhesion and vascular retention. iii) Platelet-derived LPA binds to LPA receptor 1 on cancer cells, promoting invasion. Platelet-released ATP interacts with endothelial $P2Y_2$ receptors to facilitate CTC extravasation. (B) Tumor-mediated platelet modulation: i) Platelets uptake and enrich tumor-specific biomolecules, leading to altered DNA/RNA/protein expression profiles characteristic of tumor-educated platelets. ii) Tumor-secreted TPO or IL-6 stimulates megakaryopoiesis and thrombopoiesis in bone marrow, resulting in thrombocytosis. iii) Tumor cells activate platelets and induce their aggregation. CTC, circulating tumor cell; ATP, adenosine triphosphate; LPA, lysophosphatidic acid; IL-6, interleukin-6; TPO, thrombopoietin. Created with Adobe Illustrator 2020.

activation, phenotypic transformation and transcriptomic reprogramming, culminating in the formation of tumor-educated platelets (TEPs). TEPs are characterized by their capacity to sequester and enrich tumor-specific substances (including proteins, nucleic acids, EVs) during their interaction with tumors, leading to distinct alterations in DNA, RNA and protein expression profiles (62). A recent study has demonstrated that platelets actively internalize DNA-containing EVs and membrane-free DNA fragments, thereby sequestering tumor-derived DNA (63). These platelets play pivotal roles in tumor growth, angiogenesis and metastasis (41). Through interaction with cancer cells, platelets are 'educated' and carry tumor-related biological information (64). Due to the short lifespan and enclosed membrane structure, TEPs provide real-time molecular snapshots of tumor activity; therefore, they are regarded as promising indicators for cancer detection and disease monitoring (65).

The tumor-induced platelet education process operates through several critical aspects. Firstly, tumor cells initiate platelet aggregation via direct binding to platelet surface receptors or through extracellular protein-mediated bridging, which is known as 'tumor cell-induced platelet aggregation' (TCIPA) (33). In metastatic models, TCIPA formation occurs within 1 min of tumor cell intravasation, shielding tumor cells from immune attacks and facilitating tumor growth and metastasis (33,56,66). Beyond inducing TCIPA, Strasenburg *et al* (66) elucidated multiple mechanisms of tumor-mediated platelet activation, substantially expanding our understanding of this process. Secondly, tumor-derived factors, including thrombopoietin and interleukin-6, stimulate megakaryopoiesis and platelet generation in bone marrow, leading to paraneoplastic thrombocytosis, a well-established poor prognostic indicator across multiple malignancies (67). Furthermore, tumor cells trigger platelet degranulation, releasing immunosuppressive (for example, CD40L) and procoagulant (for example, TF) mediators that reshape the TME (68,69). Elevated tumor TF expression initiates the coagulation cascade, inducing platelet activation and fibrin production. The resulting fibrin mediates TCIPA and enhances adhesion of CTM to the mesothelium, ultimately promoting polyclonal metastasis (70). Fibrinogen, upon conversion to fibrin, may form a matrix scaffold that influences the recruitment of immune cells, mediates inflammatory responses, stimulates angiogenesis, and increases vascular permeability, collectively facilitating the development of a pre-metastatic niche that supports tumor progression (71). Collectively, tumor cells orchestrate the function and quantity of platelets through multiple mechanisms, establishing a microenvironment conducive to tumor development and metastasis (72).

4. Diagnostic significance of platelet-CTC complexes in cancer

Cancer diagnosis has historically relied on biopsy, a method offering high specificity but constrained by invasiveness, spatial resolution limitations, and incomplete capture of tumor heterogeneity. To address the increasing need for early cancer

detection and monitoring, non-invasive approaches have been investigated, including circulating tumor DNA/RNA (ctDNA/RNA) and CTCs (73-76). ctDNA/RNA analysis enables plasma-based sequencing. In addition, CTCs can be enriched by size, density, or surface markers, followed by quantification using fluorescence immunostaining or morphological examination (77). Moreover, CTCs can be captured intact or through secreted exosomes for nucleic acid analysis, enhancing their utility as tumor biomarkers (78).

Platelets, as abundant and readily isolatable blood components, interact with CTCs to form platelet-CTC complexes, thereby presenting novel diagnostic opportunities. Platelet-related indices, including platelet count, mean platelet volume, and platelet-to-lymphocyte ratio, are associated with tumor progression (79,80). However, these parameters may be confounded by inflammation or chemotherapy-induced bone marrow suppression (79-81). Technological advancements now facilitate precise analysis of platelet-CTC complexes, enhancing diagnostic accuracy and specificity. For instance, a microfluidic platform was developed to isolate platelet-covered CTCs through a two-stage strategy: Initial removal of unbound platelets, followed by antibody-mediated CTC capture targeting platelet-specific markers (19). The shielding of CTC surface markers (for example, EpCAM) by platelet encapsulation impairs antibody-dependent capture and can also alter cellular morphology and molecular profiles, complicating subsequent analysis. To address this, bifunctional monomers or zwitterionic 3D network structures can be employed to suppress platelet adhesion and preserve CTC integrity (82,83). This technology represents a promising tool for cancer metastasis research and non-invasive cancer diagnosis, though further mechanistic and clinical validation remains essential.

Although anucleate, platelets harbor diverse biomolecules, including RNA, DNA and proteins derived from megakaryocytes or the TME. Their 7-to-10-day circulatory lifespan confers superior stability compared with ctDNA/RNA or exosomes, making platelets ideal for longitudinal monitoring. During circulation, platelets continuously assimilate and enrich tumor-related substances, culminating in the formation of TEPs (84). TEPs exhibit diagnostic utility across multiple cancer types, including pan-cancer detection and companion diagnostics (85). The RNA profiles of TEPs, including miRNA, lncRNA, mRNA, and small nuclear RNA (snRNA), exhibit significant potential for tumor diagnosis (Table I) (67,75,86-92). Specifically, dysregulation of snRNAs (for example, U1, U2 and U5), which mediate RNA splicing, is mechanistically linked to tumor progression and displays diagnostic potential in malignancies such as lung cancer (67,93). Previous studies have detailed the diagnostic utility of snRNA, mRNA and proteins from TEPs, highlighting the great potential of TEP RNA profiles in cancer diagnosis and prognosis monitoring (67,84). Particularly, platelet RNA-seq emerges as a highly promising screening methodology (94). This approach offers several advantages, including minimal invasiveness, relatively low cost, and absence of radiation exposure. Moreover, it has the potential to identify primary tumor origins (95). Protocols, such as thromboSeq, were proposed based on TEP RNA analysis for cancer diagnosis and therapeutic monitoring. Notably, TEP-derived RNA signatures also enable dynamic monitoring of tumor progression. Comparative efficacy of TEP RNA sequencing across tumor types is systematically summarized in Table I (96).

Platelets accumulate tumor-derived DNA across a wide spectrum of neoplastic conditions, from advanced malignancies with high ctDNA load to low-burden diseases such as early-stage cancers and precancerous colorectal polyps (63). Compared with other blood components, including red blood cells and mononuclear cells, platelets exhibit superior efficiency in the uptake of tumor-derived DNA, suggesting their role as a reservoir for genetic material derived from tumors (63). An important advantage of this platelet-based capture is that the DNA is shielded from nuclease activity, thereby preserving low-frequency mutations that might otherwise be degraded (63). Consequently, platelet DNA analysis emerges as a highly promising tool for liquid biopsy. However, the extraction of platelet DNA necessitates an initial platelet isolation step to avoid contamination from other cellular components, rendering this method more technically complex than ctDNA analysis. Furthermore, the field currently lacks standardized protocols, large-scale clinical validation, and robust evidence supporting its diagnostic utility. Future research in large-scale clinical cohorts is warranted to translate this discovery into improved strategies for cancer diagnosis and monitoring.

In addition to RNA and DNA, platelets contain a diverse array of biologically active proteins that represent a promising source for cancer biomarkers. Utilizing advanced proteomics approaches, researchers have identified protein panels exhibiting differential expression patterns between ovarian cancer (FIGO stages III-IV) and benign adnexal lesions, with diagnostic accuracies showing high sensitivity (96%) and specificity (88%) (97). Similarly, targeted methodologies involving nano liquid chromatography-tandem mass spectrometry have revealed seven potential platelet protein markers associated with early-stage malignancies (98). Nevertheless, the underlying molecular mechanisms remain insufficiently characterized. Therefore, further research is essential to elucidate the mechanisms of these proteins.

5. Therapeutic strategies targeting the platelet-CTC crosstalk

Antiplatelet agents. Extensive preclinical and clinical evidence demonstrates that common antiplatelet agents, including aspirin, clopidogrel and c7E3/ReoPro, exert significant antitumor effects (99). The multifaceted mechanisms of aspirin include: Direct suppression of tumor cell proliferation, inhibition of platelet-CTC crosstalk, and attenuation of platelet-derived pro-angiogenic and growth factors, cytokines and chemokines (100). Notably, aspirin may exert anticancer properties through non-COX-dependent pathways, including the inhibition of inflammatory processes and the induction of apoptosis, as well as the suppression of signal transduction mediated by IκB kinase β and ERK (99,101). In 2016, the U.S. Preventive Services Task Force endorsed low-dose aspirin for cancer prevention in selected populations (aged 50-69 years), albeit with the caveat that its benefits may be offset by the risk of major bleeding (102,103).

In addition to aspirin, other antiplatelet agents also exhibit significant roles in cancer therapy. Preclinical studies

Table I. TEP and CTC profiling in cancer diagnosis.

First author/s, year	Tumor type	Analysis type	Detection method	Main findings	Diagnostic performance	(Refs.)
Heinhuis *et al*, 2020	Sarcoma	Platelet RNA	ThromboSeq + SVM	TEP RNA distinguishes sarcoma from controls	Diagnostic accuracy: 87%, AUC: 0.93	(87)
Antunes-Ferreira *et al*, 2023	NSCLC	Platelet RNA	ThromboSeq + PSO-SVM	TEP RNA effectively identifies patients with NSCLC	HighSens: Sensitivity 95%, Specificity 36%; HighSpec: Sensitivity 65%, Specificity 94%	(88)
Gao *et al*, 2023	Ovarian cancer	Platelet RNA	RNA-seq + MRGF	TEP RNA combined with CA125 improves diagnosis	AUC: 0.918; Combined with CA125 AUC: 0.922	(89)
Sol *et al*, 2020	Glioblastoma	Platelet RNA	ThromboSeq + digitalSWARM	TEP RNA detects glioblastoma with high accuracy	Detection accuracy: 95%, AUC: 0.97	(90)
Mantini *et al*, 2021	Pancreatic cancer	Platelet RNA	RNA-seq + miRNA-seq + Proteomics	Differential expression of RNA and proteins in pancreatic cancer	Differentially expressed miRNAs: 41; mRNAs: 1878; Proteins: 52	(91)
Łukasiewicz *et al*, 2021	Endometrial cancer	Platelet RNA and ctDNA	RNA-seq + ctDNA-seq + AI	TEP RNA and ctDNA are useful for diagnosis and histology	Tumor-educated platelets AUC: 0.975; ctDNA AUC, 0.698	(92)
Xu *et al*, 2022	CRC	Platelet RNA	RNA-seq + PSO-SVM	Distinguishes CRC from controls	AUC: 0.928-0.915	(94)
Xiao *et al*, 2022	RCC	Platelet RNA	RNA-Seq + SVM + RFE	RCC detection with gene markers	Accuracy: 100%-95.9%	(96)
Pereira-Veiga *et al*, 2019	Advanced/ Metastatic breast cancer	Circulating tumor cells	Negative Enrichment + qPCR	Prognostic signature identified	N/A	(76)

AUC, area under the curve; RCC, renal cell carcinoma; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; miRNA, microRNA; HighSens, a highly sensitive test designed to minimize false negatives; HighSpec, a highly specific test aimed at reducing false positives. AI, artificial intelligence; PSO-SVM, particle swarm optimised support vector machine; SVM, support vector machine; MRGF, minimum redundant gene filtering; RFE, recursive feature elimination.

demonstrated the therapeutic potential of $P2Y_{12}$ inhibitors (for example, clopidogrel and ticagrelor) in disrupting platelet-tumor interactions, thereby inhibiting cancer cell migration and metastasis (104-106). Experimental models demonstrate that ticagrelor and EP3 antagonist DG-041 inhibit platelet-induced phenotypic changes in colon cancer cells (106). Such changes include the downregulation of E-cadherin, upregulation of Twist1, enhanced cell motility and increased platelet aggregation (106).

Some antiplatelet agents inhibit platelet-CTC crosstalk by targeting specific platelet surface receptors. Notably, multiple surface proteins, including GPVI, CLEC-2, GPIIb/IIIa, etc., represent validated therapeutic targets for attenuating tumor progression and metastasis (107). For instance, GPIIb/IIIa antagonists (for example, eptifibatide) have demonstrated efficacy in inhibiting cancer cell metastasis both *in vitro* and in animal models (108,109). Furthermore, activated GPIIb/IIIa receptors serve as dual-function targets for molecular imaging probes, enabling tumor visualization, and chemotherapeutic agents, facilitating precise therapeutic delivery (110,111). GPVI blockers (for example, revacept) reduce thrombosis by disrupting platelet-collagen interactions and concurrently block platelet-induced EMT and COX-2 expression in cancer cells (112). Targeting podoplanin on CTCs selectively inhibits the binding of CLEC-2 receptors on platelets to podoplanin, thereby preventing platelet-mediated tumor protection (113). Additionally, inhibitors of GPIbα and P-selectin exhibit potential in preclinical studies for inhibiting the interaction between platelets and cancer cells (39,114). Several published reviews have summarized various antiplatelet agents for cancer therapy, synthesizing fragmented findings in the field and further advancing the understanding of targeting platelets for cancer treatment (78,107). Based on current advances, integrating antiplatelet agents into comprehensive therapeutic strategies, such as in combination with chemotherapy or targeted therapy, may enhance efficacy through complementary mechanisms.

Engineered platelet technologies. Engineered platelet technologies represent a promising paradigm for cancer therapy, leveraging fabrication techniques such as drug loading, genetic engineering and membrane modification to create intelligent drug delivery systems. Concerning the combination therapy with chemotherapeutic agents, two principal strategies have been established. Firstly, the incorporation of doxorubicin (DOX) into platelets significantly enhances therapeutic efficacy against lymphoma (Fig. 4A) (115). Secondly, small EVs derived from platelets can be exploited to encapsulate DOX, subsequently facilitating targeted delivery to CTCs (Fig. 4B) (116). An innovative approach involves disrupting CTC clusters through platelet-CTC crosstalk; loading platelet decoys or lyophilized platelets with tissue-type plasminogen activator facilitates dissociation of these clusters, thereby inhibiting metastatic potential (117). Within the domain of genetic engineering, a study by Li *et al* (118) utilized lentiviral vector-mediated transduction of hematopoietic stem cells to generate platelets expressing tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (Fig. 4D). These engineered platelets substantially reduced hepatic metastasis in a prostate cancer mouse model while preserving native hemostatic function (118). Collectively, these advancements not only enhance treatment specificity but also minimize off-target effects.

Furthermore, engineered platelets represent a promising platform for integration with tumor immunotherapy, enabling novel therapeutic strategies. One approach utilizes engineered platelets as carriers for immune checkpoint blockade. Surface conjugation of anti-PD-L1 antibodies onto platelets leverages their inherent tumor tropism, facilitating targeted accumulation within post-resection inflammatory niches (119). Upon activation, platelets release microparticles encapsulating anti-PD-L1 antibodies, which block the PD-L1/PD-1 interaction between tumor cells and T cells, consequently reversing immunosuppression and potentiating T cell-mediated antitumor responses (Fig. 4C) (119). Engineered platelets can also augment chimeric antigen receptor T (CAR-T) cell therapy. Surface-anchored anti-PD-L1 antibodies obstruct the PD-1/PD-L1 pathway, preventing CAR-T cell exhaustion, while activated platelets secrete cytokines such as IL-15 to enhance CAR-T cell proliferation and activity (120). Additionally, platelet-derived microparticles and chemokines enhance CAR-T cell infiltration into tumors (120). Beyond immune modulation, a distinct strategy involves loading engineered platelets with cytotoxic complexes, such as granzyme B and perforin, enabling immune-independent cytotoxicity against CTCs through mechanisms mimicking T cell effector functions, thereby inhibiting metastasis (121). These strategies enhance therapeutic efficacy synergistically when combined with chemotherapy or immunotherapy.

However, research on engineered platelets as carriers for radiosensitizers remains limited but promising; targeted tumor delivery improves radiotherapy efficacy while sparing normal tissues (122,123). *In vitro* megakaryocyte cultures provide platelets for engineering, yet scaling clinical-grade, donation-independent production requires overcoming yield and quality barriers (124).

Nanostrategies for disrupting platelet-CTC crosstalk. Nanotechnology demonstrates significant potential in modulating platelet-CTC crosstalk. For instance, perfluorocarbon nanoparticles inhibit platelet activation, thereby enhancing T cell infiltration into tumors and improving immunotherapy efficacy (125). Similarly, chlorogenic acid nanoparticles also suppress platelet activation, disrupting the tumor vascular barrier to augment chemotherapeutic drug permeability (126). Additionally, nanoparticles functionalized with activated platelet membranes target CTC-associated microthrombi, significantly reducing lung metastasis in a breast cancer model (Fig. 4E) (127). Photodynamic nanostrategies enable the release of nitric oxide, which suppresses platelet activation by downregulating the expression of P-selectin and blocking the activated configuration of GPIIb/IIIa (128). This intervention not only reduces tumor-derived procoagulant factors secretion but also avoids hemorrhagic risks associated with systemic anticoagulation. Collectively, these approaches provide a novel therapeutic paradigm for inhibiting tumor metastasis through precise platelet function modulation.

Several nanostrategies disrupt platelet-CTC crosstalk without direct targeting. For example, MMP2-responsive polymer-lipid-peptide nanoparticles encapsulate DOX and an anti-platelet antibody R300 (129). Upon MMP2

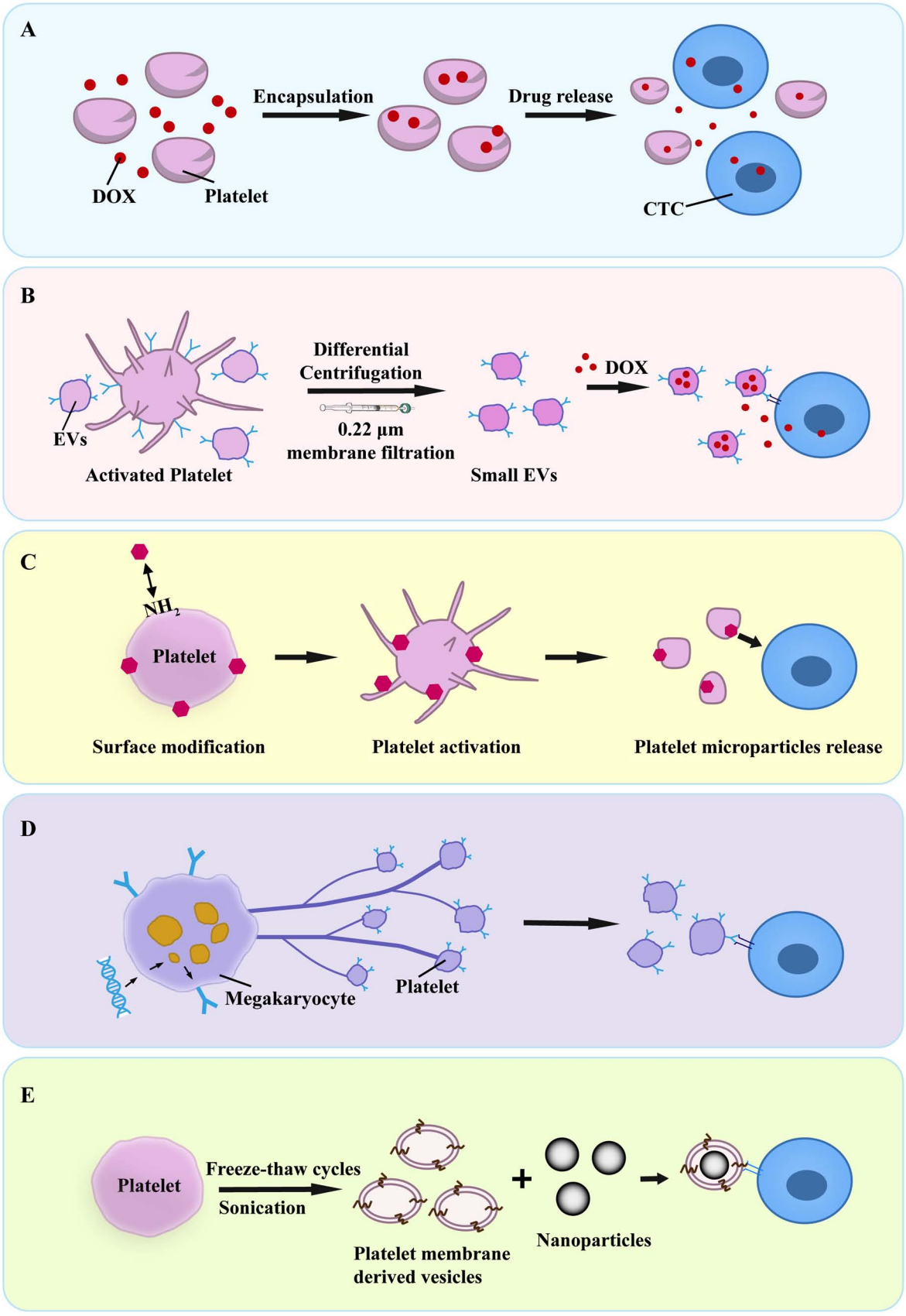

Figure 4. Five strategies of engineered platelet technology. (A) Drug-loaded platelets are prepared through co-incubation of DOX with platelets, subsequently targeting CTCs via 'tumor cell-induced platelet aggregation' and releasing DOX. (B) Following platelet activation, EVs are released, purified by centrifugation and filtration, and subsequently loaded with DOX. The resulting drug-carrying EVs adhere to CTCs and release DOX within the bloodstream. (C) Drugs are loaded onto platelets via surface modification, and drug-loaded microparticles are released upon platelet activation. (D) Megakaryocytes are genetically engineered to differentiate into tumor-resistant platelets. (E) Membrane-derived vesicles are generated from platelets using repeated freeze-thaw cycles and ultrasonication. The purified vesicles encapsulate nanoparticles via electrostatic interactions. This approach combines platelet engineering with nanotechnology. DOX, doxorubicin; CTCs, circulating tumor cells; EVs, extracellular vesicles. Created with Adobe Illustrator 2020.

activation in the TME, the release of R300 induces platelet micro-aggregation and depletion, which facilitates vascular permeabilization and DOX delivery for enhanced anti-cancer efficacy (129). Furthermore, strategies focusing on adhesion disruption include CD44-targeted DOX-loaded liposomes that incorporate the Lys-Leu-Val-Phe-Phe (KLVFF) peptide motifs that self-assemble into nanofiber networks on CTC surfaces, physically impeding platelet aggregation (130). By blocking platelet-CTC crosstalk, such approaches effectively suppress tumor invasion and metastasis. These nanotechnological innovations illustrate promising avenues for cancer therapy, offering novel insights for developing precise and efficient treatment strategies.

Therapeutic strategies targeting CTCs. Beyond the aforementioned strategies, substantial advancements have been achieved in direct approaches specifically targeting CTCs. An intelligent nano-diagnostic system was developed for targeting CTCs of metastatic breast cancer (131). This nano-diagnostic system is composed of targeted multi-responsive nanomicelles encapsulating near-infrared fluorescent superparamagnetic iron oxide nanoparticles, featuring dual-mode imaging and dual toxicity. It tracks and eliminates CTCs before colonization at distant sites, thereby impeding metastatic progression (131). Furthermore, CTCs exhibit unique functional properties that render them ideal targets for personalized drug sensitivity testing. *In vitro* isolation and culture of CTCs, followed by pharmacological screening, can predict patient-specific therapeutic responses, mitigating the risk of ineffective or adverse treatments (132).

6. Conclusion and perspective

The present review systematically examines the mechanisms, diagnostic applications and therapeutic implications of platelet-CTC crosstalk. Beginning with historical observations such as cancer-related thrombocytosis, the evolution of research toward molecular-level insights is traced. A systematic overview of adhesion molecules between CTCs and platelets is provided, clarifying the physical basis of their interactions, a perspective that distinguishes the present study from Yang *et al* (21), who focused primarily on platelets as CTC 'shelters'. The review further offers a broader examination of CTC effects on platelets, covering platelet education (leading to TEP formation), TCIPA, enhanced thrombocytosis and platelet activation. Beyond existing concepts, particular emphasis is placed on the novel capacity of platelets to capture tumor-derived DNA, adding a molecular dimension to TEP research.

A key focus lies in the clinical translational potential of TEPs. In addition to systematically summarizing the diagnostic performance of TEP RNA-seq across multiple cancer types in tabular form, the review highlights the promising applications of RNA, DNA and protein profiles in TEPs as emerging biomarkers, an aspect not sufficiently explored in the study by Yang *et al* (21). Moreover, given the extensive reviews on CTC detection technologies elsewhere, only a brief overview was provided. Therapeutically, antiplatelet agents and strategies targeting platelet-CTC crosstalk were reviewed to highlight promising avenues for future therapeutic development. Furthermore, advances in smart delivery systems enable exploration of engineered platelets, leveraging their natural homing properties for drug loading, and their combination with chemotherapy or immunotherapy, thereby revealing potential therapeutic avenues. Progress in nanotechnology targeting this interaction was also discussed, broadening research perspectives in the field.

The present review advances the field by synthesizing fundamental research on platelet-CTC crosstalk, organized around several integrative themes. Its uniqueness lies in several key integrative aspects: i) a dedicated focus on the bidirectional crosstalk in the vascular niche; ii) an expansion of the TEP concept to include the novel dimension of tumor-DNA capture for diagnostics, complemented by a systematic consolidation of the current landscape of TEP RNA-seq for cancer diagnosis and its clinical translational potential; and iii) a comprehensive, cross-disciplinary synthesis of next-generation therapeutic platforms (for example, engineered platelets and nanotherapeutics), moving beyond traditional antiplatelet agents. By bridging molecular mechanisms with translational applications, the present review offers a forward-looking perspective and a strategic resource for ongoing research and therapeutic development.

Looking forward, critical research directions warrant further investigation: Elucidating the precise mechanisms through which platelets facilitate CTC extravasation across vessel walls and influence MET during metastatic colonization; investigating variations in platelet-CTC crosstalk across diverse cancer types to enable precise therapeutic targeting; advancing the clinical translation of TEP-based diagnostics, particularly validating the efficacy of integrated platelet DNA analysis in large-scale clinical cohorts; and overcoming challenges in the large-scale *ex vivo* culture of functional platelets to realize the potential of engineered platelet therapies. Future efforts include preclinical evaluation of translationally promising engineered platelet strategies, leveraging their inherent tumor-homing properties for drug delivery, and exploring synergistic combinations with multimodal treatments. Progress in these areas may inform novel therapeutic strategies to inhibit metastatic progression and enhance patient survival outcomes.

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Availability of data and materials

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Authors' contributions

LZ wrote the original draft and created the visualizations. YY acquired funding, conceived the study, performed critical revision, and provided substantial improvement of the manuscript. YD reviewed the manuscript, contributed to visualizations, provided constructive feedback, and polished the language. FC and LW jointly supervised the study. FC oversaw the research design and project administration. LW led the investigation, provided resources, and performed technical validation. All authors read and approved the final version of the manuscript and take full responsibility for the integrity and accuracy of all aspects of the work. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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