Am J Cancer Res 2025;15(2):407-425
www.ajcr.us /ISSN:2156-6976/ajcr0160570

Review Article

Advances and potentials in platelet-circulating tumor cell crosstalk

Jie Yang, Pingyao Xu, Guiji Zhang, Dongsheng Wang, Bo Ye, Lichun Wu

Department of Clinical Laboratory, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, University of Electronic Science and Technology of China, Chengdu, Sichuan, The People's Republic of China

Received September 16, 2024; Accepted January 27, 2025; Epub February 15, 2025; Published February 28, 2025

Abstract: Tumor metastasis leads to circulating tumor cells (CTCs) that separate from primary malignant tumors and enter blood circulation. CTCs survive and engage with other cells to cope with obstacles, including shear stress, disease, immune attacks, and drugs. Platelets are the best partners for CTCs. Platelets provide a good protective layer for CTCs to ensure that are not monitored and cleared by the native immune system, and protected from shear stress and survive better. Here, we review current reports on platelet-CTC interaction and the clinical relevance of their combination and summarize new techniques for CTC capture and treatment based on platelet-CTC interaction. We discuss current data, identify its shortcomings, and suggest future developments.

Keywords: Circulating tumor cells, platelets, clinical relevance, tumor metastasis, liquid biopsy

Introduction

Circulating tumor cells (CTCs) shed or migrate into the circulation from the primary tumor site owing to the metastatic characteristics of the tumor. CTCs undergo epithelial-mesenchymal transformation (EMT) and interact with other cell types in the circulation [1]. They adhere to the vascular endothelium and exude into the distal organs, eventually developing into macroscopic metastases [1]. CTCs circulate as individual cells or cell clusters that appear to have higher metastatic potential and shorter half-lives [2]. As a key component of the metastasis cascade, CTCs have unique phenotypic and genotypic characteristics and have been used as a non-invasive source of cancer cells for tumor phenotypic and genotypic analysis [3]. Additionally, CTCs serve as clinical indices for identifying tumor surface markers and mutations, evaluating and monitoring treatment responses, and assessing patient prognosis [1, 3]. Therefore, exploring the characteristics of CTCs is critical for understanding the biology and progression of blood-borne metastatic tumors. However, the accuracy and sensitivity of CTC liquid biopsies using clinical blood collection cannot be guaranteed because of low quantification (1-10 cells per 10 ml of blood) [4]. One of the main reasons for this is that CTCs enter blood vessels through active invasion or passive shedding, and face mechanical stress, foreign microenvironments, and immune surveillance, which results in a short half-life and a high apoptosis rate.

During blood transmission, CTCs interact with all types of blood cells including platelets, neutrophils, monocytes/macrophages, endothelial cells, and cancer-associated fibroblasts [1]. These interactions are broadly classified into two categories: direct cell-cell interactions, especially within heterogeneous CTC clusters, and indirect regulation of phenotypic molecules of interacting cells [1]. CTCs survive in harsh environments and take root in distant organs, benefiting from the manipulation of the cellular function of surrounding normal cells. Among circulating cells, platelets are the most closely associated with and have the greatest influence on CTCs [5]. Under platelet shelters, CTCs are protected from the destruction of shear stress and evade surveillance by the immune system. Hence, exploring the mechanism of

https://doi.org/10.62347/JAYK5667

interaction between platelets and CTCs and using it as a theoretical basis to achieve efficient capture and targeted therapy of CTCs will greatly improve the efficacy and prognosis of patients with tumors.

Here, we review current reports on platelet-CTC interaction and the clinical relevance of their combination and summarize new techniques for CTC capture and treatment based on platelet-CTC interaction. We discuss the current literature, identify gaps in the knowledge, and suggest ideas for future studies.

Platelets in cancer

Platelets play crucial roles in human health and disease. Platelets act as "scanners" in the immune system, sense the presence of bacteria, and communicate with lymphocytes to regulate immune cell exosmosis in the circulation [6]. Therefore, platelets are important for the recovery from inflammation [7]. Platelets also play a critical role in clotting and wound healing [8]. Platelet-rich plasma-activated tendon-derived stem cells promote regeneration of ruptured Achilles tendon in rats [9]. Ristocetin-induced platelet aggregation has been used to monitor bleeding tendency in chronic lymphocytic leukemia treated with irutinib [10]. The role of platelets in tumors has been extensively. The Indian physician Sushruta discovered a relationship between tumors and blood changes as early as 1000 BC [11]. In 1878, Billroth et al. [11] discovered tumor cells in blood clots. Since platelets have not yet been discovered, only alterative characteristics caused by tumors were noticed in the blood; however, the blood components associated with tumors were unclear. Gasic et al. [12] first reported the relationship between platelets and tumor metastasis in 1968 and found that platelets caused tumor metastasis. As technology continues to evolve, the complex interactions between platelets or megakaryocytes and tumors as well as the role of platelets in promoting tumor metastasis, are being increasingly understood [13].

Tumor-platelet interaction is a vital component of cancer metastasis, and platelets have an impact on the primary site as well as on tumor cells entering the bloodstream [11]. Platelets create an environment in which multiple pro-angiogenic factors are provided to tumors, thereby stimulating the expression of these factors [14]. Furthermore, circulating vascular endothelial growth factor levels have been reported to be a prognostic factor for diagnosis and treatment evaluation in patients with tumors [15]. When CTCs enter the circulation, platelets, the first circulating cells, encounter CTCs during metastasis [16]. The ability of platelets to protect tumor cells from normal immune responses in the circulation significantly facilitates metastasis [17]. During intravascular transport, CTCs interact with clotting cascades and the innate immune system. Platelets help CTCs spread throughout the body by preventing the immune system from being discovered and destroyed in the circulation [18]. The discovery that CTCs are in a vulnerable phase of metastasis makes them an attractive therapeutic target [18]. Subsequently, platelets form cell-fibrin-platelet aggregates around CTCs surrounded by platelet-rich clots during their initial entry into the circulation, which provides physical protection from shear stress [19]. CTCs form clusters by interacting with platelets via transforming growth factor-β/transforming growth factor-β receptor type 1 (TGFβ/TGFβ1) [20]. Mani et al. compared the platelet content in patients with non-metastatic and metastatic tumors and found that the platelet content in non-metastatic patients was significantly lower than that in metastatic patients, and that the platelet content was inversely proportional to the survival rate [21]. Hovens et al. demonstrated that platelet levels, rather than circulating endothelial cells, are key predictors of early treatment failure in patients with prostate cancer after prostatectomy [22]. Furthermore, platelet-derived EVs have been shown to play an important role in tumorigenesis and metastasis based on the characteristics of platelet interactions with tumor cells in a variety of solid tumors (**Figure 1**), which are summarized in **Table 1**.

Tumor cells and secretions affect platelets. Tumor-induced platelets are a potential source of tumor-derived biomarkers available from blood biopsies. Noerholm et al. confirmed that tumor-derived substances are transferred from tumor cells to platelets, resulting from tumor-derived transcripts detected in platelets [23]. Previous studies have demonstrated the diagnostic value of platelet mRNA signals as noninvasive biomarkers for predicting tumorigenesis

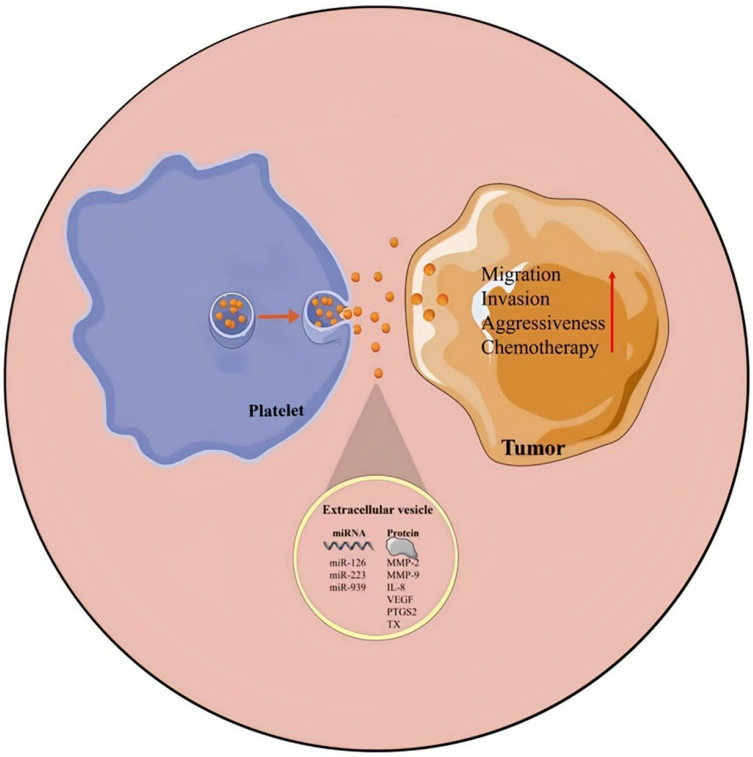

Figure 1. Effects of bioactive molecules carried by platelet-derived extracellular vesicles on tumors.

and monitoring tumor progression in a variety of solid tumors [24-28]. In a pan-cancer study, there were significant differences in platelet mRNA expression profiles between tumor patients and healthy volunteers, and platelet profiles were not only suitable for cancer diagnosis but also correctly identified the primary origin of pan-cancer [29]. Best et al. prospectively sequenced tumor-induced platelet mRNA profiles of platelets from healthy donors and cancer patients and were able to distinguish patients with local and metastatic tumors from healthy individuals with 96% accuracy [29]. Using clinical blood samples, the levels of platelets and distant metastases were found to be significantly higher in CTC-positive patients than in CTC-negative patients [30]. Therefore, CTCs predict that the incidence of distant metastases is high in patients with hypercoagulable lung cancer [30]. Panabieres et al. studied crosstalk between CTCs and platelets in vitro [31]. Both morphological and transcriptional alterations were observed in platelets after co-culture with CTC-conditioned medium, leading to platelet aggregation and activation [31]. Moreover, EMT-related gene expression decreased, but the expression of coding mesenchymal marker genes did not, and tumor invasion-related gene expression increased in CTCs co-cultured with platelets [31]. These findings support the hypothesis that CTC-platelet interactions help maintain CTC integrity in the bloodstream. Hence, platelets, as fundamental components of the tumor microenvironment, are considered significant in cancer biology because they contribute to tumor initiation, progression, and therapeutic responses.

Platelets: shelters for CTCs

Platelet-induced EMT of CTCs

Epithelial-mesenchymal transition (EMT) is a biological process in which epithelial cells are transformed into stromal cells via specific mechanisms. The main features of EMT include reduced cell adhesion molecule expression, cytoskeletal transformation from keratin to vimentin, and morphological characteristics of mesenchymal cells. Epithelial cells lose epithelial phenotypes (e.g., cell polarity and connection to the basement membrane), but gain interstitial phenotypes (e.g., higher migration and invasion, anti-apoptosis, and the ability to degrade the extracellular matrix) through EMT. However, some tumor progression models have suggested that tumor metastatic potential occurs entirely at the primary site, with few or no signaling events occurring during intravascular metastasis [32].

Given that multiple growth factors and cytokines are released into circulation, platelets are a source of cancer cells that may perceive additional signals beyond the original microenvironment [32]. The bidirectional transfer of lipids, proteins, and RNAs between platelets and tumor cells was analyzed to confirm their impact on tumor cell behavior and processes [32]. Increased expression of platelet and EMT markers acquired from CTCs was observed in blood samples [32]. This indicates that tumor

Table 1. Effects of bioactive molecules carried by platelet-derived extracellular vesicles (pEVs) on tumors

Cancer	Bioactive molecule	Main effects	Ref.
Breast cancer	miR-126 and miR-223	pEVs increased the sensitivity of BT549 cells to cisplatin chemotherapy.	[108]
	Ca^{2+}	pEVs enhance the migration through the partial remodeling of calcium handling machinery to modulate motility.	[109]
Prostate cancer	MMP-2	pEVs have been found to enhance invasion of prostate cancer cells via the upregulation of MMP-2 expression.	[110]
Lung cancer	MMP-9, IL-8, VEGF, miR-223, and scatter factor	pEVs are found to act as facilitators for the formation of new blood vessels.	[111]
Ovarian cancer	miR-939	pEVs can transport microRNAs (miRNAs) like miR-939, promoting the aggressiveness of ovarian cancer cells.	[112]
Colorectal cancer	EMT markers, cyclooxygenase (COX)-2 (PTGS2) expression, and thromboxane (TX) B2 production	pEVs could drive prometastatic and prothrombotic behaviors in cancer cells, indicating potential treatment targets.	[113]

cells and CTCs acquire highly dynamic and aggressive phenotypes, including EMT, stem-like phenotypes, and high proliferation rates, owing to platelet interactions. Moreover, TGFβ promotes metastasis by enhancing EMT and invasiveness in primary cancer, whereas platelets contain excessive growth factors and cytokines, including high concentration of TGFβ [32]. Therefore, platelet-derived factors may be involved in promoting transfer phenotypes. Hynes et al. [32] reported that platelet-derived TGFβ and direct platelet-tumor interaction synergistically activated the TGFβ/Smad and NF-kB pathways in cancer cells, which led to the transition to an aggressive mesenchymal-like phenotype and enhanced metastasis. Targeted inhibition of NF-kB signaling in cancer cells or ablation of TGFβ1 expression in platelets prevents lung metastasis [32]. Therefore, cancer cells rely on platelet-derived signals outside of the primary tumor for effective metastasis.

Matrix metalloproteinases (MMPs), a group of zinc-containing enzymes that are closely involved in angiogenesis and tumor metastasis. Specifically, MMP-2 and MMP-9 are considered the most effective for metastasis. Both enzymes cleave collagen, which is the main component of the subcutaneous matrix, thereby facilitating the transfer of tumor cells from the blood to the tissue [33]. CTCs activate by CTCs to produce microparticles and small platelet fragments that express membrane and cytoplasmic components. Co-culturing cancer cells with platelet-derived microparticles led to an increased secretion of MMP-2 in CTCs [33]. These results indicate show that platelet-related molecular channels activate EMT in CTCs.

Single-cell transcriptome analysis of CTCs provides important insights into metastatic biology. Single-CTC transcriptome analysis of gastric cancer revealed that most gastric CTCs undergo EMT, and platelet adhesion contributes to EMT progression and the acquisition of chemotherapy resistance [34]. Additionally, CTCs have prognostic value in patients with EMT-associated primary breast cancer [35]. In conclusion, EMT is an important biological process through which epithelial cell-derived malignant tumor cells acquire the ability to migrate and invade. Elucidating the molecular mechanisms of the platelet-regulated CTC EMT process, thereby exploring diagnostic and therapeutic methods based on key EMT molecules, is a key scientific issue in the study of EMT mechanisms in tumor metastasis.

Platelet-mediated CTC immune evasion

The CTCs which have been shed by primary malignancies serve as “seeds” for distant metastases. However, the mechanisms by which CTCs escape immune surveillance remain largely unclear [36]. Activated platelets gather on the surface of CTCs to form blood clots, which in turn help CTCs survive [37]. Platelets protecting CTCs from normal immune responses in the circulation may significantly

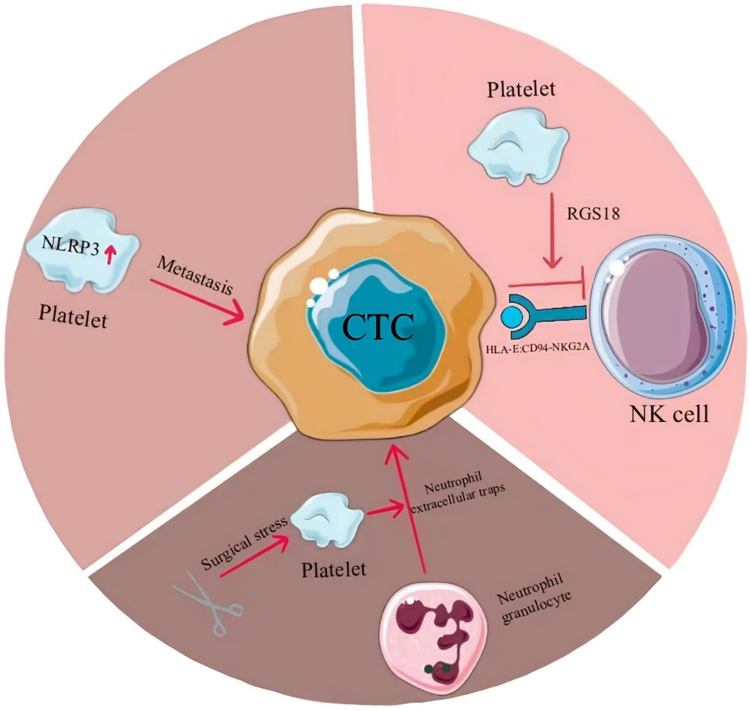

Figure 2. Platelet-mediated circulating tumor cell (CTC) immune evasion.

facilitate metastasis [19]. The nucleotide-binding domain leucine-rich repeat-containing protein 3 (NLRP3) inflammasome is a key inflammatory mechanism that was recently discovered to control platelet activation and aggregation [38]. NLRP3 inflammasome expression is upregulated in circulating platelets in a mouse model of in situ pancreatic ductal adenocarcinoma [38]. Drug inhibition or gene ablation of NLRP3 in platelets results in decreased platelet activation, platelet aggregation, and tumor progression, and interference with platelet NLRP3 signaling significantly improves the survival of tumor-bearing mice [38]. Therefore, the platelet NLRP3 inflammasome plays a key role in pancreatic ductal adenocarcinoma and may serve as a novel therapeutic target.

Most CTCs in blood circulation are eliminated by shear stress and natural killer (NK) cells [39]. NK cells are cytotoxic immune cells capable of killing target cells with low or no expression of major histocompatibility complex (MHC) class I molecules [40]. As platelets transfer their own MHC class I molecules to the surface of CTCs, NK cells ignore them when CTCs are recognized, leading to immune escape [41]. CTCs and NK cells interact with HLA-E:CD94-NKG2A through immune checkpoint molecules [36]. Shi et al. [36] characterized CTC and primary and metastatic lesions in human pancreatic ductal adenocarcinoma using single-cell transcriptomes and showed that platelet-derived *RGS18* promoted HLA-E expression through the AKT-GSK3b-CREB signaling pathway, and *RGS18* overexpression promoted hepatic metastasis in pancreatic tumors. Thus, platelet-derived *RGS18* protects CTCs from NK-mediated immune surveillance when a HLA-E immune checkpoint is involved [36].

Surgical resection is the primary treatment for most solid tumors. However, surgical injury increases the risk of tumor recurrence and metastasis [42]. Tissue trauma activates local and systemic innate immune systems, causing inflammatory responses [42]. Platelets and neutrophils play crucial roles in the early innate immune response; however, they may also contribute to the spread and distant metastasis of cancer cells [42]. Tsung et al. [42] reported that platelets activated by surgical stress enhanced platelet-tumor aggregate formation, facilitating their capture by neutrophil extracellular traps and subsequent distant metastasis. Local surgery-induced hepatic ischemia/reperfusion injury was confirmed to promote neutrophil extracellular traps to capture aggregated CTCs that eventually metastasize to the lungs, which were eliminated when platelets were depleted [42]. In summary, these results revealed that platelets help CTCs escape the immune system, and targeting the key molecular mechanisms that destroy platelets is expected to prevent tumors and postoperative distant metastasis (**Figure 2**). We could also make full use of the protective properties of platelets on CTCs and improve their capture and extraction efficiencies.

Platelet-conferred mechanical protection on CTCs

Brain metastases commonly occur in cancer patients; however, there are limited options for effective treatment. To settle in the brain, CTCs

must first become permanently lodged in brain microvessels; however, the mechanisms underlying this process are not well understood. Thrombosis often occurs in cerebral microvessels where blocked CTCs successfully extravasate and form large metastases [43]. Mechanistically, CTCs produce tissue factor-mediated thrombin that activates local plasma clotting [43]. In contrast, CTCs cannot activate platelets directly, and antiplatelet therapy reduces platelet configuration in intravascular CTC clusters but does not reduce metastatic encephaloma formation [43]. These results suggest that plasma coagulation is activated early by intravascular tumor cells in the brain and subsequently forms blood clots, leading to the discovery of a new specific mechanism that is critical for brain colonization. The pro-metastasis effect of platelets has been attributed to their ability to promote adhesion or prevent cell death in the circulation by forming a physical barrier around CTCs [32]. Platelets form cell-fibrin-platelet aggregates around CTCs to provide mechanical protection [19]. This barrier protects CTCs from NK-mediated lysis, limits their exposure to shear stress, and promotes their adhesion to endothelial cells [32]. Maftoon et al. [44] elucidated the role of platelets in CTC deformation, adhesion, and survival using highly detailed computational models. Their results illustrated that activated platelets adhered to CTCs, exacerbating metastatic spread [44]. Platelets play a vital role in thrombosis and are key factors in hemostasis and coagulation. Konstantopoulos et al. [45] described colorectal adenocarcinoma cell adhesion to tumor necrosis factor-α (TNF-α)-stimulated human umbilical vein endothelial cells (HUVECs) in the presence or absence of platelets and red blood cells. The total number of tumor cells attached to HUVECs and the percentage of secondary adhesion to total cell adhesion depended on the platelet concentration and cell wall shear stress [45]. With enhanced platelet induction, the total number of cell tethers was almost twice that observed in the absence of platelet perfusion [45]. Together, these results revealed a novel role for platelets in promoting the binding of tumor cells to endothelial cells through secondary tether mechanisms.

Other platelet-derived biomacromolecules

Dynamic crosstalk between tumors and their microenvironment is increasingly recognized as a key regulator of malignant progression. Tumor cells secrete various cytokines that activate stromal fibroblasts and induce immune cell recruitment. Signals derived from the local microenvironment promote the invasion and metastasis of tumor cells. Mucin-4 (Muc4) is a large cell surface glycoprotein involved in the protection and lubrication of epithelial structures [46]. The abnormal expression of Muc4 affected the adhesion, proliferation, and invasiveness of tumor cells, as well as the growth rate and metastasis efficiency of xenograft tumors [46]. Reduced association of tumor cells with platelets and leukocytes using histological analysis of lung lesions suggests that Muc4 may promote metastasis by promoting the association of CTCs with blood cells, thereby increasing CTC survival in circulation [46].

Platelets contain excess growth factors and cytokines; therefore, platelet-derived factors may be involved in promoting the metastatic phenotype. Platelet-derived growth factor B has been shown to promotes and maintains vascular integrity in the tumor microenvironment by promoting pericellular recruitment [47]. Nasopharyngeal carcinoma (NPC) is a highly metastatic and aggressive malignant tumor. Distant metastases are the primary cause of treatment failure and mortality. Distant metastasis in NPC patients was positively correlated with the expression level of integrin β3 (ITGβ3) in platelet-derived extracellular vesicles in NPC patients [48]. EVs transferred from platelets to NPC cells mediate intercellular communication and induce NPC metastasis by upregulating ITGβ3 expression [48]. Mechanistically, up-regulated ITGβ3 activates the MAPK/ERK/ATF4/Nrf2 axis, inhibits ferroptosis, and promotes NPC metastasis [48]. Therefore, these findings elucidate the novel role of platelet-derived EVs in metastasis, which not only improves our understanding of platelet-mediated distant tumor metastasis but also has important implications for the diagnosis and treatment of nasopharyngeal carcinoma.

In summary, platelets are involved in the complete process of tumor metastasis (**Figure 3**). Metastasis is a characteristic of tumors that limits their therapeutic effects and prognosis. Platelets are key targets for inhibiting tumor metastasis, improving tumor-targeted therapy efficacy, and improving the quality of life of

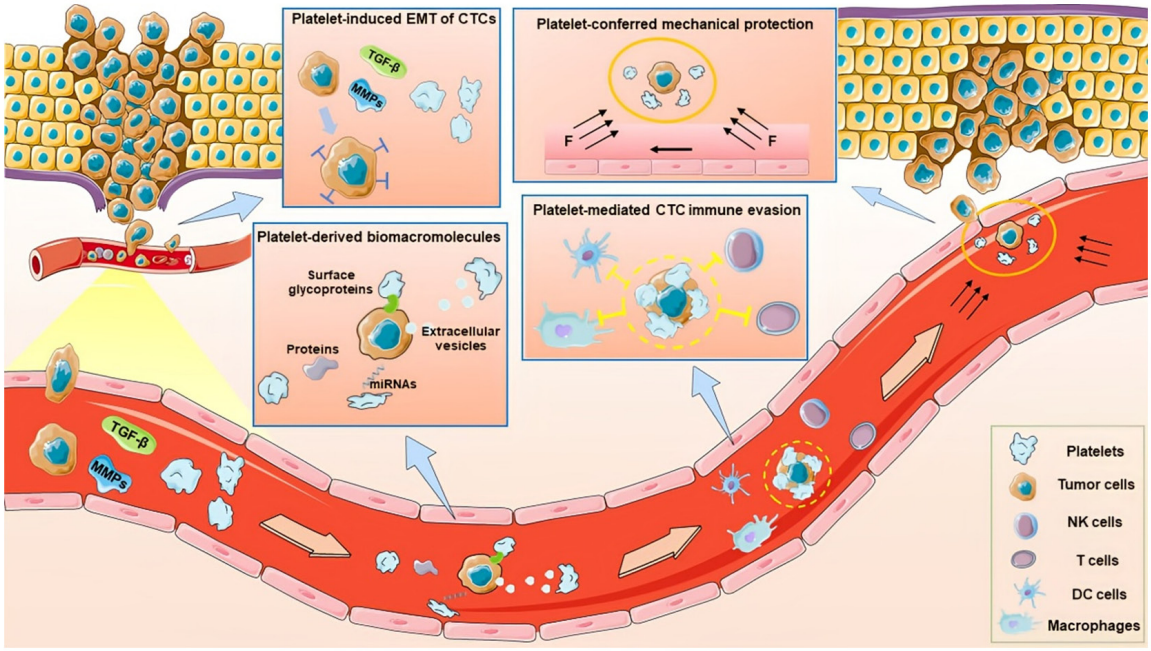

Figure 3. Platelets involve in tumor metastasis as shelters for CTCs.

patients with tumors. Platelets can be potential targets for diagnosis and treatment and achieve clinical transformation by exploring the mechanism of platelets in the occurrence and progression of tumors.

Clinical relevance of CTCs combined with platelets

CTC detection will help understand tumor development as CTCs are tumor cells present in blood circulation [1]. Numerous studies on multiple solid tumors have shown that the number of detectable CTCs is inversely associated with early- and late-stage survival [1]. Platelets are a major contributor to miRNA release into the circulation [49] and may have an impact on various components of the blood. Therefore, understanding the clinical correlation between circulating CTCs and platelets is crucial for evaluating tumor development and patient prognosis.

Clinical immunology laboratory diagnostics

Platelets are shed from mature megakaryocytes in bone marrow as small pieces of cytoplasm, and megakaryocytes combined with CTCs are associated with disease progression in tumor patients [50]. In the current study on patients with metastatic breast cancer, an association was observed between a higher number of CTCs and a higher probability of megakaryocytes [51]. Platelets act as a shelter for CTCs to evade the immune system. Therefore, the mechanism of platelet-CTC interactions in tumor immune regulation must be explored to understand their clinical relevance. Preoperative platelet assessment, alone and in combination with CTCs, has prognostic potential for nonmetastatic breast cancer [52]. Żaczek et al. [52] compared preoperative platelet counts, CTCs, 65 serum cytokines, and 770 immune-associated transcripts using the NanoString technology. A high-normal platelet count was associated with lymph node metastasis and an increasing number of mesenchymal CTCs in 70 patients with operable breast cancer [52]. Patients with high platelet and CTCs counts had the shortest overall survival [52]. Similar results have been obtained in patients with renal cell cancer [53]. Mechanistically, a high platelet count was associated with high intratumoral stromal content, specifically the phenotypes associated with CD8+ T cells [52]. Increased cytokine concentrations in the bone marrow are associated with platelet activation and production [52]. Antiplatelet therapy may have good therapeutic potential in patients who have been identified as having the highest risk of disease progression.

Kimmig et al. [54] confirmed that proinflammatory markers in the blood are strongly associated with CTCs, which are precursors to metastasis, by retrospectively analyzing the clinical data, CTC, and blood count results from 171 patients with early stage breast cancer. Inflammatory indicators included the neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), monocyte-neutrophil ratio (MNR), and systemic immunoinflammatory index (SII). Their combination with CTCs has important research value for tumor prognosis and classification. The potential prognostic roles of CTCs, NLR, and PLR in patients with colorectal cancer were evaluated to identify more accurate predictors in colorectal cancer. NLR and CTC counts serve as reliable prognostic factors in patients with colorectal cancer, and CTCs and PLR analyses may be clinically useful for colon cancer management and risk stratification [55, 56]. Similarly, Yang et al. [57] combined CTCs and NLR to identify patients at high risk of metastatic castration-resistant prostate cancer. NLR can further classify patients into different risk groups with detectable CTCs, suggesting that NLR play a complementary role in CTC-based prognostic stratification in patients with castration-resistant prostate cancer patients [57]. Additionally, Reuben et al. [58] conducted a multivariate analysis of triple-negative tumors and found that CTCs with inflammatory indicators could predict overall survival in metastatic breast cancer; however, only CTCs and MLR remained independent prognostic factors, and the two were combined to form a prognostic score. The risk of postoperative metastasis in patients with renal cell carcinoma can be predicted using mesenchymal CTCs, MNR, or staging [53]. As a combined prognostic factor, staging and MNR may provide convenient and accurate status monitoring [53]. In summary, CTCs are of great value in tumor-related liquid biopsies. Different inflammatory cells in the blood affect CTC growth and physiological functions. Therefore, extensive and in-depth exploration of the role of blood cells, including platelets, in CTCs and the detection of the clinical correlation between the two have important translational value.

Platelets combined with CTCs to evaluate therapeutic effect and prognosis

In addition to immune regulation, platelets influence the clinical relevance of CTCs from other physiological aspects. CTCs are masked by platelets, and a positive association has been found between increased CTC aggregation and rapid disease progression during follow-up [59]. CTC clusters, along with their interstitial features and platelet marker expression, are highly associated with poor prognosis in patients with unresectable pancreatic cancer [59]. Abnormalities in blood coagulation and the “leukemia” stage with high CTC counts are common in patients with advanced and progressive breast cancer. Absolute CTC counts were significantly correlated with D-dimer levels and negatively correlated with platelet counts [60]. Therefore, there was a significant correlation among increasing CTC number, increasing D-dimer number, and decreasing platelet count, indicating that CTCs may be a direct contributor to intravascular coagulation activation. Tan et al. [30] reached the same conclusion and confirmed that CTCs predicted distant metastasis in lung cancer and that the incidence of distant metastasis was high in patients in a hypercoagulable state. Additionally, Finn et al. [61] examined the effectiveness of exercise in modulating CTC and occult platelet levels in patients with metastatic prostate cancer through the ExPeCT trial, confirming that CTCs have great potential to effectively reflect treatment effects. Preoperative chemotherapy improved short-term progression-free survival when the CTC test results were positive in patients with stage II or III esophageal squamous cell carcinoma [62]. Therefore, CTC detection can be used as an indicator to guide individualized decision making regarding preoperative chemotherapy. Velasco et al. [63] used CTCs as predictive biomarkers and further stratified an aggressive variant prostate cancer subpopulation with the worst prognosis to inform treatment decisions in metastatic castration-resistant prostate cancer patients treated with carbacasel-carboplatin combined with carbacasel alone.

Monoclonal antibodies are widely used in cancer drug therapies. Aceto et al. [64] found that high CA 15-3 tumor markers, high mean red blood cell volume, high white blood cell count, and high mean platelet volume were specifically associated with CTC clusters in patients with breast cancer treated with denosumab. Therefore, prospective studies need to validate the role of mAbs in preventing CTC production. The expression of CTCs, platelet-derived growth

Table 2. Circulating tumor cells (CTCs) combined with platelets in clinical relevance

Cancer types	Consequences	Ref.
Breast cancer	Assess prognostic potential and identify patients at highest risk for disease progression	[52]
	Predicting metastasis	[54]
	Predicting intravascular coagulation activation	[60]
Colorectal cancer	Prognosis	[55]
	Patient management and risk stratification	[56]
Lung cancer	Predictive biomarkers of chemoradiotherapy combined with durvalumab	[67]
	Predicting metastasis	[30]
Pancreatic cancer	Highly associated with poor prognosis of patients	[59]
	Evaluating treatment outcomes	[61]
Prostatic cancer	Stratifying subgroups and evaluating chemotherapy effects	[63]
	Shorter overall survival	[57]
Renal cell carcinoma	Evaluating disease progression and metastasis prognosis	[53]
Soft-Tissue Sarcoma	Evaluating olaratumab monotherapy outcome	[65]

factor receptor (PDGFR), and PDGF ligands in soft tissue sarcoma was detected before and after olaratumab monotherapy [65]. An increase in CTC was observed on day 8 of cycle 1, and a significant decrease was observed on days 1 and 30 of cycle 3 [65]. CTCs can be used as predictors of non-small-cell lung cancer using monoclonal antibodies combined with chemotherapy as a common treatment strategy. Subjects with increased platelet endothelial cell adhesion molecule 1-negative CTCs showed significant reductions in median progression-free survival and overall survival when treated with bevacizumab combined with chemotherapy [66]. Another report demonstrated the feasibility of using CTCs and peripheral blood cells, particularly platelets, as predictive biomarkers for unresectable stage III cell lung cancer in patients treated with chemoradiotherapy and duvacizumab [67].

In summary, the detection and counting of CTCs are clinically useful non-invasive diagnostic biomarkers that can be helpful in clinical management and strategies. Thus, CTCs are potential markers for assessing disease profiles, in which CTCs can be detected in multiple cancer types (**Table 2**). However, CTCs represent a more diverse cell population, which limits their detection. This phenotypic diversity presents significant challenges for clinicians and researchers in enumerating, characterizing, and developing a fundamental understanding of the underlying oncology.

Platelet-associated CTC capture techniques

CTCs are known as tumor "seeds" in the blood and play a critical role in tumor progression and metastasis. In 2002, Braylan et al. [68] detected hairy cell leukemia in patients with low levels of circulating malignant cells in the peripheral blood using flow cytometry. With continuous progress in medical science and technology, liquid biopsy of CTCs has become an important tool to explore disease progression in patients with tumors and evaluate the treatment effect and prognosis. However, the number of CTCs, which is approximately 1-10 cells per 10 ml blood, is the biggest obstacle to their widespread clinical use. Currently, mainstream CTC capture methods are divided into two categories: membrane surface antigens and cell size [69]. Therefore, clarifying CTC characteristics and developing efficient and specific CTC capture technologies will become a developmental direction for tumor liquid biopsies in the future.

Membrane surface antigen

Epithelial cell adhesion molecule (EpCAM) is the most commonly used membrane surface antigen, and many studies have focused on EpCAM. Liu et al. first established a method to graft carboxybetaine methacrylate with 3-aminopropyl triethoxysilane as a coupling agent, immobilized anti-EpCAM antibodies on nylon, and successfully demonstrated CTC-trapping ability in nude mouse tumor models [70]. Subsequently, the device effectively reduced

protein adsorption and platelet adhesion and prolonged the plasma recalcification time, demonstrating the extraordinary biocompatibility and blood compatibility of the modified surface [71]. However, a single approach targeting EpCAM is not sufficient to achieve specific CTC capture from different tumor sources. Alpaugh et al. [72] compared the standard EpCAM CellSearch kit with EpCAM plus HER2, EGFR, and MUC-1 specific combined ferrofluid capture. The four-trapping ferrofluid reagent did not significantly improve the trapping effect [72]. Although commercial CTC detection kits mainly use the EpCAM antibody, the detection effect is very different for different tumors. Therefore, approaches using tumor-specific markers have significant limitations, such as the detection of free circulating tumor DNA in the plasma of patients with gastrointestinal stromal tumors harboring CKIT or PDGFRA activation mutations [73].

Size and morphology

CTCs have larger volumes, smaller mass density fluctuations, and shorter spatial density correlations than normal blood cell subpopulations [74]. These biophysical parameters provided a theoretical basis for specific CTC capture. Lackner et al. [75] investigated a novel hemofiltration technique for cell morphological classification, immunocytochemistry, and molecular characterization of filtered circulating non-hematological cells in patients with renal cell cancer. Furthermore, the unbiased, fast, and automated separation of CTCs using a single CTC chip enables detailed measurement of the physicochemical and biological properties of CTCs and their role in metastasis [76]. Therefore, CTCs may have different sizes and shapes than other blood components, making it possible to capture them specifically.

With the rapid development of microfluidic technology, the clinical transformation of liquid biopsies has become possible and has great potential for CTC capture. High-throughput concentration and isolation of CTC clusters from large blood volumes using microfluidic technology enables tumor cell population-specific diagnosis [77]. Zhai et al. [78] considered the influences of aspect ratio, dielectrophoretic force, channel size, flow rate, separation efficiency, and shape on cell separation, and proposed a novel two-stage, label-free, fast-continuous CTC capture device based on hydrodynamic inertial focusing and dielectrophoretic separation. In contrast, the integrated system of microfluidic combined with CTC analysis has been reported. Xiong et al. [79] developed a new wedge microfluidic chip that enriched CTCs of different sizes and identified CTCs using a three-color immunocytochemical method. The device demonstrated high performance in detecting CTCs in small blood samples from tumor patients and, combined with the advantages of low cost and mass production, has great potential for clinical applications in cancer treatment guidance and prognostic monitoring [79]. Side-based microfluidic techniques have been used to isolate CTCs from patients with metastatic breast cancer and to correlate their presence with clinicopathological data and overall survival [51]. These results make this a reality for the clinical application of microfluidic technology in CTC liquid biopsy.

Platelet-related techniques

CTCs interact with platelets to promote metastasis in circulation. Therefore, this characteristic of platelet-CTC interactions provides a theoretical basis for improving CTC capture efficiency. Two-dimensional fluid-solid interaction models have been used to study the critical conditions for CTCs to pass through narrow capillaries when platelets are attached to the capillary walls [80]. The computational framework combined with the accompanying results is a powerful tool for studying the biomechanical conditions in CTC-platelet interactions, providing a prognosis for disease progression [80]. The principles of platelet-induced CTC capture are divided into: inhibition of platelet adhesion [81], and CTC complexes that directly capture platelet interactions [82]. However, platelet-covered CTCs are extremely difficult to isolate because of masking or downregulation of surface epitopes. Toner et al. [83] developed a platelet-targeted microfluidic platform for the isolation of epithelial and mesenchymal phenotypes of lung cancer, breast cancer, and melanoma. This method first depletes unbound free platelets by sorting based on hydrodynamic size and then captures platelet-covered CTCs based on immune affinity using a chevron micromixer device [83]. Furthermore, CTC liquid biopsies require the whole blood samples

to be immediately processed. Reliable blood specimen stabilization for CTC preservation provides wider geographic sharing for precise rare-cell techniques but remains challenging due to the fragility and rarity of CTCs. Toner et al. [84] also described a method that combined cryopreservation with a targeted strategy against cooling-induced platelet activation to achieve long-term preservation of CTC blood samples, and the same effect was achieved by establishing a zwitterionic magnetic microgel platform [85]. These findings are of great significance for the clinical development of CTC humoral biopsies.

In summary, despite the increasing number of studies reporting on CTC capture, there is still a long way to go to solve practical clinical problems. As blood cells are usually plastic, multistep screening may be required to ensure accurate results, depending on the cell size or morphology for CTC capture. For membrane surface antigens, finding proteins that are expressed in all tumors and are specific to non-tumor cells is nearly impossible. However, there may be an opportunity to achieve a breakthrough by exploring CTC origin and identifying CTC-associated specific gene expression, such as the EMT-associated protein [86, 87].

Platelet-associated CTC treatment

Targeting CTC is believed to be effective in inhibiting tumor recurrence and metastasis. For example, immunotherapeutic fibrin gels can “wake up” the innate immune system, thereby inhibiting the potential for local recurrence and metastasis after melanoma surgery [88]. The interaction of CTCs with platelets and other immune cells in the blood is thought to contribute to the immune escape and spread of CTCs, which greatly increases the difficulty in clearing CTCs. A metastatic complex composed of CTC clusters, platelets, and neutrophils, known as circulating tumor microemboli (CTM), is highly upregulated by hypoxia-inducing factor-1 α, and hypoxia is also thought to be an important factor promoting the colonization of CTM in the lung [89]. Therefore, the types of CTC present in the blood and the effects of different blood components on CTCs need to be explored.

Antiplatelet to inhibit CTCs

Platelet-CTC interactions promote malignant tumor progression by protecting CTCs from shear stress and immunity, helping to retain CTCs in capillary beds, allowing CTCs to successfully exit the blood and enter tissues, inducing EMT, and assisting in the establishment of metastatic sites. Platelet-mimicking modified submicron human serum albumin particles have been used to track metastatic cancers [90]. Weilbaecher et al. [91] conducted a randomized Phase II study to determine whether clopidogrel and aspirin disrupted platelet function and reduced the number of CTCs in patients with metastatic breast cancer. Baseline CTCs were lower than expected, reducing the ability to detect the effect of platelet inhibition on CTCs [91]. Therefore, antiplatelet therapy, which blocks platelet activation and aggregation, inhibits metastasis and is associated with cancer prevention. Hydroxyethyl starch (HES) inhibits platelet function, and HES 200/0.5 significantly reduces CTCs in patients undergoing radical colorectal cancer surgery and to reduce the metastatic potential of platelet-activated colon cell lines by inhibiting platelet activation [92]. The modulation of platelet activity may be a new strategy for reducing the risk of surgical metastasis. Jia et al. [93] found that multifunctional S-nitrosocaptopril (CapNO) acts on both CTCs and platelets, blocking platelet-CTC interactions and endothelial adhesion, thereby inhibiting CTC pulmonary metastasis in vivo. Furthermore, CapNO affects vasodilation, anticoagulation, the inhibition of MMP2 expression in tumor cells, and the inhibition of vascular endothelial cell adhesion molecule expression [93]. These new findings provide a basis for the use of CapNO in cancer metastatic chemoprophylaxis and suggest that modulating the CTC microenvironment is a new way to prevent cancer metastasis. Biological nanomaterials designed for platelets have the same effects as anti-CTC drugs. Lys-leu-val-ph-phe peptide motifs target tumors via hyaluronic acid-functionalized liposomes and spontaneously self-assemble to form nanofibers with a mesh structure that wraps around the tumor cells [94]. The tumor cell nanofibril coating significantly blocked tumor cell-induced platelet aggregation in vitro and prevented platelet adhesion around CTCs in vivo, thereby limiting

Table 3. Platelet-associated circulating tumor cell (CTC) capture and treatment techniques

Rationales	Techniques	Ref.
Platelet adhesion inhibition	Crosslinked polymer films prepared using bifunctional monomers	[81]
Heterotypic CTC capture	Fabrication of Channeled and Three-Dimensional Electrodes	[82]
	Microfluidic platform isolation of platelet-covered circulating tumor cells	[83]
Platelet-associated CTC stabilization	Combining hypothermic preservation with targeted strategies that counter cooling-induced platelet activation	[84]
	Zwitterionic microgel preservation platform	[85]
Antiplatelet to inhibit CTCs	Platelet-based and platelet-mimicking modified human serum albumin submicron particles	[90]
	Multifunctional S-nitrosocaptopril	[93]
	Lys-Leu-Val-Phe-Phe peptide motifs	[94]
Platelet derivatives treat CTCs	Platelets genetically modified to express surface-bound tumor necrosis factor-related apoptosis-inducing ligand	[95]
	Platelet mediated TNF-related apoptosis inducing ligand delivery system	[96]
	Nano-platesomes by fusing platelet membranes with lipid membranes	[97]

platelet prometastasis and preventing early metastasis [94]. Blocking the physiological functions of platelets effectively inhibited CTC production and survival. Platelets play a critical role in circulation, in addition to promoting CTCs. Therefore, therapeutic approaches targeting platelet-CTC interactions must be explored.

Platelet derivatives treat CTCs

The production and targeted delivery of specific drugs based on platelet characteristics can neutralize CTCs to reduce tumor metastasis, which can be likened to a “Trojan horse” strategy. Platelets genetically modified to express surface-bound tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL), a cytokine that specifically induces apoptosis in tumor cells, kills cancer cells and significantly reduces metastasis in mouse models of prostate cancer [95]. King et al. [96] developed a novel platelet-mediated TRAIL delivery system that targets CTCs and blocks metastasis via “in situ” platelet modification. The system killed over 60% of circulating CTCs from a variety of primary metastatic cancer samples [96]. Platelets protect CTCs from immune clearance and support CTC extravasation to secondary sites in circulation. When deprived, platelet baiting prevents the formation of metastatic tumors. Therefore, platelet membranes have been widely used to develop bionanomaterials that inhibit CTCs. For example, nanoplates have been developed by fusing platelets, lipid membranes, and platelet membrane-based bionic drug delivery systems [97, 98]. Platelet membrane-related nanosystems can effectively bind to CTCs, improve precise drug delivery to tumors, reduce CTC survival, and inhibit tumor metastasis. Therefore, platelet-derivated CTC-targeted therapeutic systems represent a new approach to inhibit tumor growth and metastasis.

In summary, according to the mechanism of the platelet-CTC interaction, there have been many relevant studies to develop relevant therapeutic means to kill CTCs in circulation and inhibit tumor metastasis (**Table 3**). However, a long distance exists between antiplatelet drugs and platelet-derived biological nanomaterials. Therefore, there is a long way to go to explore the mechanism of platelet-CTC interactions and to develop effective diagnostic and therapeutic technologies.

Discussion and perspective

Tumor metastasis is an extremely complex process. CTCs are the “seeds” of tumor metastasis that separate from the tumor in situ and enter blood circulation, but they need to survive and find the right “soil” to take root, sprout and grow. Therefore, CTCs survive and cooperate with other cells in the surrounding environment to cope with obstacles, including increased resistance to shear stress, diseases, immune attacks, and drugs. As the blood circulates, CTCs interact with other cells to affect their

physiological functions [99, 100], and platelets are the best partners for CTCs.

Platelets provide a good protective layer for CTCs, so that CTCs will not be monitored and cleared by the native immune system, in the same way that CTCs with armor will be protected from shear stress and survive better. Platelet adhesion can aggregate individual CTCs into clusters that generally have longer survival times and greater drug resistance. Currently, the interaction mechanism between CTCs and platelets has been extensively studies and the TGF-β1 and PDGFR signaling pathways are more widely recognized [101, 102]. Although mechanistic exploration is always needed, achieving clinical transformation using the principle of mechanism is the direction we should look for next. Platelet- and CTC-related indicators are widely used in clinical studies for tumor grading and identification, therapeutic effect evaluation, and patient prognosis [103]. Although CTCs have absolute advantages and potential for use in liquid biopsy, CTC capture remains the biggest obstacle to their widespread clinical application [104]. There are only approximately 1-10 CTCs per 10 ml blood, which is insufficient to support additional testing and diagnostic techniques. Improving the capture efficiency of CTCs remains a popular research topic, and the results of flow cytometry [68], immunohistochemistry [105], and various materials science [106] studies are constantly enhancing the capture effect. Platelet-CTC interactions form a theoretical basis for the development of CTC capture technology. CTC capture technology for platelets has achieved promising results in terms of detection specificity and accuracy; however, there is still a long way to go before clinical conversion. Platelets are potential therapeutic targets and delivery platforms for CTCs. Antiplatelet drugs clear CTCs with good results; however, their side effects are unavoidable. Platelets not only act on CTCs, but also play an important role in the body's blood system. Platelet-modified derivatives and bionanomaterials have shown good efficacy in the treatment of CTCs and are highly biocompatibility and safe [107]. Similarly, related products need to have more sophisticated designs and rigorous safety studies to achieve clinical translation.

In summary, we reviewed the principles and mechanisms of platelet-CTC interactions and listed current technologies for platelet-related CTC capture, detection, diagnosis, and treatment. Although the mechanism of platelet-CTC interaction still needs to be further explored, and the development of related technologies to achieve clinical translation is still a long way away, using platelets to understand and treat tumors provides a novel perspective. The role of platelets in tumor diagnosis and treatment will become increasingly important, and clinical applications will be more extensive in the future.

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing. This work was supported by the National Natural Science Foundation of China (grant No. 82303854), and Natural Science Foundation of Sichuan Province (grant No. 22NSFSC1284).

Disclosure of conflict of interest

None.

Address correspondence to: Lichun Wu, Department of Clinical Laboratory, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital and Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Renmin South Road 55#, Chengdu 610041, Sichuan, The People's Republic of China. E-mail: wulichun@scszlyy.org.cn

References

[1] Pereira-Veiga T, Schneegans S, Pantel K and Wikman H. Circulating tumor cell-blood cell crosstalk: biology and clinical relevance. Cell Rep 2022; 40: 111298.

[2] Aceto N, Bardia A, Miyamoto DT, Donaldson MC, Wittner BS, Spencer JA, Yu M, Pely A, Engstrom A, Zhu H, Brannigan BW, Kapur R, Stott SL, Shioda T, Ramaswamy S, Ting DT, Lin CP, Toner M, Haber DA and Maheswaran S. Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. Cell 2014; 158: 1110-1122.

[3] Bates M, Mohamed BM, Ward MP, Kelly TE, O'Connor R, Malone V, Brooks R, Brooks D, Selemidis S, Martin C, O'Toole S and O'Leary JJ. Circulating tumour cells: the good, the bad and the ugly. Biochim Biophys Acta Rev Cancer 2013; 1878: 188863.

[4] Micalizzi DS, Maheswaran S and Haber DA. A conduit to metastasis: circulating tumor cell biology. Genes Dev 2017; 31: 1827-1840.

[5] Ward MP, E Kane L, A Norris L, Mohamed BM, Kelly T, Bates M, Clarke A, Brady N, Martin CM, Brooks RD, Brooks DA, Selemidis S, Hanniffy S, Dixon EP, A O'Toole S and J O'Leary J. Platelets, immune cells and the coagulation cascade; friend or foe of the circulating tumour cell? Mol Cancer 2021; 20: 59.

[6] Labelle M, Begum S and Hynes RO. Platelets guide the formation of early metastatic niches. Proc Natl Acad Sci U S A 2014; 111: E3053-3061.

[7] Foy BH, Sundt TM, Carlson JCT, Aguirre AD and Higgins JM. Human acute inflammatory recovery is defined by co-regulatory dynamics of white blood cell and platelet populations. Nat Commun 2022; 13: 4705.

[8] Menter DG, Kopetz S, Hawk E, Sood AK, Loree JM, Gresele P and Honn KV. Platelet "first responders" in wound response, cancer, and metastasis. Cancer Metastasis Rev 2017; 36: 199-213.

[9] Xu K, Al-Ani MK, Sun Y, Xu W, Pan L, Song Y, Xu Z, Pan X and Yang L. Platelet-rich plasma activates tendon-derived stem cells to promote regeneration of Achilles tendon rupture in rats. J Tissue Eng Regen Med 2017; 11: 1173-1184.

[10] Kazianka L, Drucker C, Skrabs C, Thomas W, Melchardt T, Struve S, Bergmann M, Staber PB, Porpaczy E, Einberger C, Heinz M, Hauswirth A, Raderer M, Pabinger I, Thalhammer R, Egle A, Wendtner CM, Follows G, Hoermann G, Quehenberger P, Jilma B and Jaeger U. Ristocetin-induced platelet aggregation for monitoring of bleeding tendency in CLL treated with ibrutinib. Leukemia 2017; 31: 1117-1122.

[11] Liu Y, Zhang Y, Ding Y and Zhuang R. Platelet-mediated tumor metastasis mechanism and the role of cell adhesion molecules. Crit Rev Oncol Hematol 2021; 167: 103502.

[12] Gasic GJ, Gasic TB and Stewart CC. Antimetastatic effects associated with platelet reduction. Proc Natl Acad Sci U S A 1968; 61: 46-52.

[13] In 't Veld SGJG and Wurdinger T. Tumor-educated platelets. Blood 2019; 133: 2359-2364.

[14] Janowska-Wieczorek A, Wysoczynski M, Kijowski J, Marquez-Curtis L, Machalinski B, Ratajczak J and Ratajczak MZ. Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer. Int J Cancer 2005; 113: 752-760.

[15] Kusumanto YH, Dam WA, Hospers GA, Meijer C and Mulder NH. Platelets and granulocytes, in particular the neutrophils, form important compartments for circulating vascular endothelial growth factor. Angiogenesis 2003; 6: 283-287.

[16] Ichikawa J, Ando T, Kawasaki T, Sasaki T, Shirai T, Tsukiji N, Kimura Y, Aoki K, Hayakawa K, Suzuki-Inoue K, Saitoh M and Haro H. Role of platelet C-Type lectin-like receptor 2 in promoting lung metastasis in osteosarcoma. J Bone Miner Res 2020; 35: 1738-1750.

[17] McAllister SS and Weinberg RA. The tumour-induced systemic environment as a critical regulator of cancer progression and metastasis. Nat Cell Biol 2014; 16: 717-727.

[18] Hayes B, Brady L, Sheill G, Baird AM, Guinan E, Stanfill B, Dunne J, Holden D, Vlajnic T, Casey O, Murphy V, Greene J, Allott EH, Hussey J, Cahill F, Van Hemelrijck M, Peat N, Mucci LA, Cunningham M, Grogan L, Lynch T, Manecksha RP, McCaffrey J, O'Donnell DM, Sheils O, O'Leary JJ, Rudman S, McDermott R and Finn S. Circulating tumour cell numbers correlate with platelet count and circulating lymphocyte subsets in men with advanced prostate cancer: data from the ExPeCT clinical trial (CTRIAL-IE 15-21). Cancers (Basel) 2021; 13: 4690.

[19] Best MG, Wesseling P and Wurdinger T. Tumor-educated platelets as a noninvasive biomarker source for cancer detection and progression monitoring. Cancer Res 2018; 78: 3407-3412.

[20] Torres JA, Brito ABC, Silva VSE, Messias IM, Braun AC, Ruano APC, Buim MEC, Carraro DM and Chinen LTD. CD47 expression in circulating tumor cells and circulating tumor microemboli from non-small cell lung cancer patients is a poor prognosis factor. Int J Mol Sci 2023; 24: 11958.

[21] Joseph R, Soundararajan R, Vasaikar S, Yang F, Allton KL, Tian L, den Hollander P, Isgandarova S, Haemmerle M, Mino B, Zhou T, Shin C, Martinez-Paniagua M, Sahin AA, Rodriguez-Canales J, Gelovani J, Chang JT, Acharya G, Sood AK, Wistuba II, Gibbons DL, Solis LM, Barton MC, Varadarajan N, Rosen JM, Zhang XH and Mani SA. CD8+ T cells inhibit metastasis and CXCL4 regulates its function. Br J Cancer 2021; 125: 176-189.

[22] Wong CK, Namdarian B, Chua J, Chin X, Speirs R, Nguyen T, Fankhauser M, Pedersen J, Costello AJ, Corcoran NM and Hovens CM. Levels of a subpopulation of platelets, but not circulating endothelial cells, predict early treatment failure in prostate cancer patients after prostatectomy. Br J Cancer 2012; 107: 1564-1573.

[23] Brinkman K, Meyer L, Bickel A, Enderle D, Berking C, Skog J and Noerholm M. Extracellular vesicles from plasma have higher tumour RNA fraction than platelets. J Extracell Vesicles 2020; 9: 1741176.

[24] Yang L, Jiang Q, Li DZ, Zhou X, Yu DS and Zhong J. TIMP1 mRNA in tumor-educated platelets is diagnostic biomarker for colorectal cancer. Aging (Albany NY) 2019; 11: 8998-9012.

[25] Liu L, Lin F, Ma X, Chen Z and Yu J. Tumor-educated platelet as liquid biopsy in lung cancer patients. Crit Rev Oncol Hematol 2020; 146: 102863.

[26] Best MG, Sol N, In 't Veld SGJG, Vancura A, Muller M, Niemeijer AN, Fejes AV, Tjon Kon Fat LA, Huis In 't Veld AE, Leurs C, Le Large TY, Meijer LL, Kooi IE, Rustenburg F, Schellen P, Verschueren H, Post E, Wedekind LE, Bracht J, Esenkbrink M, Wils L, Favaro F, Schoonhoven JD, Tannous J, Meijers-Heijboer H, Kazemier G, Giovannetti E, Reijneveld JC, Idema S, Killestein J, Heger M, de Jager SC, Urbanus RT, Hoefer IE, Pasterkamp G, Mannhalter C, Gomez-Arroyo J, Bogaard HJ, Noske DP, Vandertop WP, van den Broek D, Ylstra B, Nilsson RJA, Wesseling P, Karachaliou N, Rosell R, Lee-Lewandrowski E, Lewandrowski KB, Tannous BA, de Langen AJ, Smit EF, van den Heuvel MM and Wurdinger T. Swarm intelligence-enhanced detection of non-small-cell lung cancer using tumor-educated platelets. Cancer Cell 2017; 32: 238-252, e9.

[27] Tjon-Kon-Fat LA, Lundholm M, Schröder M, Wurdinger T, Thellenberg-Karlsson C, Widmark A, Wikström P and Nilsson RJA. Platelets harbor prostate cancer biomarkers and the ability to predict therapeutic response to abiraterone in castration resistant patients. Prostate 2018; 78: 48-53.

[28] Best MG and Wurdinger T. Tumor-educated platelets for the earlier detection of hepatocellular carcinoma. Clin Res Hepatol Gastroenterol 2020; 44: 794-795.

[29] Best MG, Sol N, Kooi I, Tannous J, Westerman BA, Rustenburg F, Schellen P, Verschueren H, Post E, Koster J, Ylstra B, Ameziane N, Dorsman J, Smit EF, Verheul HM, Noske DP, Reijneveld JC, Nilsson RJA, Tannous BA, Wesseling P and Wurdinger T. RNA-Seq of tumor-educated platelets enables blood-based pan-cancer, multiclass, and molecular pathway cancer diagnostics. Cancer Cell 2015; 28: 666-676.

[30] Yang L, Dong H, Li Z, Pan Y, Qu L and Tan Z. Correlation between circulating tumor cells and D-D and platelet in patients with pulmonary malignancies. Oncol Lett 2018; 15: 2169-2172.

[31] Eslami-S Z, Cortés-Hernández LE, Glogovitis I, Antunes-Ferreira M, D'Ambrosi S, Kurma K, Garima F, Cayrefourcq L, Best MG, Koppers-Lalic D, Wurdinger T and Alix-Panabières C. *In vitro* cross-talk between metastasis-competent circulating tumor cells and platelets in colon cancer: a malicious association during the harsh journey in the blood. Front Cell Dev Biol 2013; 11: 1209846.

[32] Labelle M, Begum S and Hynes RO. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer cell 2011; 20: 576-590.

[33] Dashevsky O, Varon D and Brill A. Platelet-derived microparticles promote invasiveness of prostate cancer cells via upregulation of MMP-2 production. Int J Cancer 2009; 124: 1773-1777.

[34] Negishi R, Yamakawa H, Kobayashi T, Horikawa M, Shimoyama T, Koizumi F, Sawada T, Oboki K, Omuro Y, Funasaka C, Kageyama A, Kanemasa Y, Tanaka T, Matsunaga T and Yoshino T. Transcriptomic profiling of single circulating tumor cells provides insight into human metastatic gastric cancer. Commun Biol 2022; 5: 20.

[35] Miklikova S, Minarik G, Sedlackova T, Plava J, Cihova M, Jurisova S, Kalavska K, Karaba M, Benca J, Smolkova B and Mego M. Inflammation-based scores increase the prognostic value of circulating tumor cells in primary breast cancer. Cancers (Basel) 2020; 12: 1134.

[36] Liu X, Song J, Zhang H, Liu X, Zuo F, Zhao Y, Zhao Y, Yin X, Guo X, Wu X, Zhang H, Xu J, Hu J, Jing J, Ma X and Shi H. Immune checkpoint HLA-E:CD94-NKG2A mediates evasion of circulating tumor cells from NK cell surveillance. Cancer Cell 2023; 41: 272-287.e279.

[37] Liu Y, Zhang Y, Ding Y and Zhuang R. Platelet-mediated tumor metastasis mechanism and the role of cell adhesion molecules. Crit Rev Oncol Hematol 2021; 167: 103502.

[38] Boone BA, Murthy P, Miller-Ocuin JL, Liang X, Russell KL, Loughran P, Gawaz M, Lotze MT, Zeh HJ 3rd and Vogel S. The platelet NLRP3 inflammasome is upregulated in a murine model of pancreatic cancer and promotes platelet aggregation and tumor growth. Ann Hematol 2019; 98: 1603-1610.

[39] Leblanc R and Peyruchaud O. Metastasis: new functional implications of platelets and megakaryocytes. Blood 2016; 128: 24-31.

[40] Lorenzo-Herrero S, López-Soto A, Sordo-Bahamonde C, Gonzalez-Rodriguez AP, Vitale M and Gonzalez S. NK cell-based immunotherapy in cancer metastasis. Cancers (Basel) 2018; 11: 29.

[41] Placke T, Örgel M, Schaller M, Jung G, Rammensee HG, Kopp HG and Salih HR. Platelet-derived MHC class I confers a pseudonormal phenotype to cancer cells that subverts the antitumor reactivity of natural killer immune cells. Cancer Res 2012; 72: 440-448.

[42] Ren J, He J, Zhang H, Xia Y, Hu Z, Loughran P, Billiar T, Huang H and Tsung A. Platelet TLR4-ERK5 axis facilitates NET-mediated capturing of circulating tumor cells and distant metasta-

sis after surgical stress. Cancer Res 2021; 81: 2373-2385.
[43] Feinauer MJ, Schneider SW, Berghoff AS, Robador JR, Tehranian C, Karreman MA, Venkataramani V, Solecki G, Grosch JK, Gunkel K, Kovalchuk B, Mayer FT, Fischer M, Breckwoldt MO, Brune M, Schwab Y, Wick W, Bauer AT and Winkler F. Local blood coagulation drives cancer cell arrest and brain metastasis in a mouse model. Blood 2021; 137: 1219-1232.
[44] Anvari S, Osei E and Maftoon N. Interactions of platelets with circulating tumor cells contribute to cancer metastasis. Sci Rep 2021; 11: 15477.
[45] Burdick MM and Konstantopoulos K. Platelet-induced enhancement of LS174T colon carcinoma and THP-1 monocytoid cell adhesion to vascular endothelium under flow. Am J Physiol Cell Physiol 2004; 287: C539-547.
[46] Rowson-Hodel AR, Wald JH, Hatakeyama J, O'Neal WK, Stonebraker JR, VanderVorst K, Saldana MJ, Borowsky AD, Sweeney C and Carraway KL 3rd. Membrane Mucin Muc4 promotes blood cell association with tumor cells and mediates efficient metastasis in a mouse model of breast cancer. Oncogene 2018; 37: 197-207.
[47] Zhang Y, Cedervall J, Hamidi A, Herre M, Viitaniemi K, D'Amico G, Miao Z, Unnithan RVM, Vaccaro A, van Hooren L, Georganaki M, Thulin Å, Qiao Q, Andrae J, Siegbahn A, Heldin CH, Alitalo K, Betsholtz C, Dimberg A and Olsson AK. Platelet-specific PDGFB ablation impairs tumor vessel integrity and promotes metastasis. Cancer Res 2020; 80: 3345-3358.
[48] Li F, Xu T, Chen P, Sun R, Li C, Zhao X, Ou J, Li J, Liu T, Zeng M, Zheng W, Lin Y, Yang L, Li Z, Chen H and Zhang Q. Platelet-derived extracellular vesicles inhibit ferroptosis and promote distant metastasis of nasopharyngeal carcinoma by upregulating ITGB3. Int J Biol Sci 2022; 18: 5858-5872.
[49] Fortunato O, Borzi C, Milione M, Centonze G, Conte D, Boeri M, Verri C, Moro M, Facchinetti F, Andriani F, Roz L, Caleca L, Huber V, Cova A, Camisaschi C, Castelli C, Cancila V, Tripodo C, Pastorino U and Sozzi G. Circulating mir-320a promotes immunosuppressive macrophages M2 phenotype associated with lung cancer risk. Int J Cancer 2019; 144: 2746-2761.
[50] Xu L, Mao X, Guo T, Chan PY, Shaw G, Hines J, Stankiewicz E, Wang Y, Oliver RTD, Ahmad AS, Berney D, Shamash J and Lu YJ. The novel association of circulating tumor cells and circulating megakaryocytes with prostate cancer prognosis. Clin Cancer Res 2017; 23: 5112-5122.
[51] Grašič Kuhar C, Silvester J, Mencinger M, Ovčariček T, Čemažar M, Miceska S, Modic Ž, Kuhar A, Jesenko T and Kloboves Prevodnik V. Association of circulating tumor cells, megakaryocytes and a high immune-inflammatory environment in metastatic breast cancer. Cancers (Basel) 2023; 15: 3397.
[52] Bednarz-Knoll N, Popęda M, Kryczka T, Kozakiewicz B, Pogoda K, Szade J, Markiewicz A, Strzemecki D, Kalinowski L, Skokowski J, Liu J and Żaczek AJ. Higher platelet counts correlate to tumour progression and can be induced by intratumoural stroma in non-metastatic breast carcinomas. Br J Cancer 2022; 126: 464-471.
[53] Guan Y, Xu F, Tian J, Wang Y, Guo N, Wan Z, He M, Gao M, Gao K and Chong T. Prognostic value of circulating tumor cells and immune-inflammatory cells in patients with renal cell carcinoma. Urol Oncol 2022; 40: 167.e121-167.e132.
[54] Kasimir-Bauer S, Karaaslan E, Hars O, Hoffmann O and Kimmig R. In early breast cancer, the ratios of neutrophils, platelets and monocytes to lymphocytes significantly correlate with the presence of subsets of circulating tumor cells but not with disseminated tumor cells. Cancers (Basel) 2022; 14: 3299.
[55] Li H, Liu Q, Liang S, Yao P, Lv J, Wang G, Tang R, Zhao T, Li J, Xu L, Ma L and Wang R. Circulating tumor cells and neutrophil-lymphocyte ratio are predictive markers for metastatic colorectal cancer patients. Transl Cancer Res 2021; 10: 288-297.
[56] Abdallah EA, Souza E Silva V, Braun AC, Gasparini VA, Kupper BEC, Tariki MS, Tarazona JGR, Takahashi RM, Aguiar Júnior S and Chinen LTD. A higher platelet-to-lymphocyte ratio is prevalent in the presence of circulating tumor microemboli and is a potential prognostic factor for non-metastatic colon cancer. Transl Oncol 2021; 14: 100932.
[57] Chong W, Zhang Z, Luo R, Gu J, Lin J, Wei Q, Li B, Myers R, Lu-Yao G, Kelly WK, Wang C and Yang H. Integration of circulating tumor cell and neutrophil-lymphocyte ratio to identify high-risk metastatic castration-resistant prostate cancer patients. BMC cancer 2021; 21: 655.
[58] De Giorgi U, Mego M, Scarpi E, Giordano A, Giuliano M, Valero V, Alvarez RH, Ueno NT, Cristofanilli M and Reuben JM. Association between circulating tumor cells and peripheral blood monocytes in metastatic breast cancer. Ther Adv Med Oncol 2019; 11: 1758835919866065.
[59] Lim M, Park S, Jeong HO, Park SH, Kumar S, Jang A, Lee S, Kim DU and Cho YK. Circulating tumor cell clusters are cloaked with platelets and correlate with poor prognosis in unresectable pancreatic cancer. Cancers (Basel) 2021; 13: 5272.

[60] Dirix LY, Oeyen S, Buys A, Liégois V, Prové A, Van De Mooter T, Van Laere S and Vermeulen PB. Coagulation/fibrinolysis and circulating tumor cells in patients with advanced breast cancer. Breast Cancer Res Treat 2022; 192: 583-591.

[61] Brady L, Hayes B, Sheill G, Baird AM, Guinan E, Stanfill B, Vlajnic T, Casey O, Murphy V, Greene J, Allott EH, Hussey J, Cahill F, Van Hemelrijck M, Peat N, Mucci L, Cunningham M, Grogan L, Lynch T, Manecksha RP, McCaffrey J, O'Donnell D, Sheils O, O'Leary J, Rudman S, McDermott R and Finn S. Platelet cloaking of circulating tumour cells in patients with metastatic prostate cancer: results from ExPeCT, a randomised controlled trial. PLoS One 2020; 15: e0243928.

[62] Zhao Y, Han L, Zhang W, Shan L, Wang Y, Song P, Peng C and Zhao X. Preoperative chemotherapy compared with postoperative adjuvant chemotherapy for squamous cell carcinoma of the thoracic oesophagus with the detection of circulating tumour cells randomized controlled trial. Int J Surg 2020; 73: 1-8.

[63] Chai S, Matsumoto N, Storgard R, Peng CC, Aparicio A, Ormseth B, Rappard K, Cunningham K, Kolatkar A, Nevarez R, Tu KH, Hsu CJ, Malihi P, Corn P, Zurita A, Hicks J, Kuhn P and Ruiz-Velasco C. Platelet-coated circulating tumor cells are a predictive biomarker in patients with metastatic castrate-resistant prostate cancer. Mol Cancer Res 2021; 19: 2036-2045.

[64] Vetter M, Landin J, Szczerba BM, Castro-Giner F, Gkountela S, Donato C, Krol I, Scherrer R, Balmelli C, Malinovska A, Zippelius A, Kurzeder C, Heinzelmann-Schwarz V, Weber WP, Rochlitz C and Aceto N. Denosumab treatment is associated with the absence of circulating tumor cells in patients with breast cancer. Breast Cancer Res 2018; 20: 141.

[65] Martín-Broto J, Pousa AL, Brohl AS, Van Tine BA, Powers B, Stacchiotti S, Blay JY, Hu JS, Oakley GJ 3rd, Wang H, Szpurka AM, Levy DE, Mo G, Ceccarelli M and Jones RL. Circulating tumor cells and biomarker modulation with olaratumab monotherapy followed by olaratumab plus doxorubicin: phase Ib study in patients with soft-tissue sarcoma. Mol Cancer Ther 2021; 20: 132-141.

[66] Zhang T, Zhang L, Gao Y, Wang Y, Liu Y, Zhang H, Wang Q, Hu F, Li J, Tan J, Wang DD, Gires O, Lin PP and Li B. Role of aneuploid circulating tumor cells and $CD31^+$ circulating tumor endothelial cells in predicting and monitoring anti-angiogenic therapy efficacy in advanced NSCLC. Mol Oncol 2021; 15: 2891-2909.

[67] Park CK, Lee SW, Cho HJ, Oh HJ, Kim YC, Kim YH, Ahn SJ, Cho JH and Oh IJ. Blood-based biomarker analysis for predicting efficacy of chemoradiotherapy and durvalumab in patients with unresectable stage III non-small cell lung cancer. Cancers (Basel) 2023; 15: 1151.

[68] Cornfield DB, Mitchell Nelson DM, Rimsza LM, Moller-Patti D and Braylan RC. The diagnosis of hairy cell leukemia can be established by flow cytometric analysis of peripheral blood, even in patients with low levels of circulating malignant cells. Am J Hematol 2001; 67: 223-226.

[69] Li H, Song P, Zou B, Liu M, Cui K, Zhou P, Li S and Zhang B. Circulating tumor cell analyses in patients with esophageal squamous cell carcinoma using epithelial marker-dependent and -independent approaches. Medicine (Baltimore) 2015; 94: e1565.

[70] Wang H, Yue G, Dong C, Wu F, Wei J, Yang Y, Zou Z, Wang L, Qian X, Zhang T and Liu B. Carboxybetaine methacrylate-modified nylon surface for circulating tumor cell capture. ACS Appl Mater Interfaces 2014; 6: 4550-4559.

[71] Dong C, Wang H, Zhang Z, Zhang T and Liu B. Carboxybetaine methacrylate oligomer modified nylon for circulating tumor cells capture. J Colloid Interface Sci 2014; 432: 135-143.

[72] Beck TN, Boumber YA, Aggarwal C, Pei J, Thrash-Bingham C, Fittipaldi P, Vlasenkova R, Rao C, Borghaei H, Cristofanilli M, Mehra R, Serebriiskii I and Alpaugh RK. Circulating tumor cell and cell-free RNA capture and expression analysis identify platelet-associated genes in metastatic lung cancer. BMC Cancer 2019; 19: 603.

[73] Maier J, Lange T, Kerle I, Specht K, Bruegel M, Wickenhauser C, Jost P, Niederwieser D, Peschel C, Duyster J and von Bubnoff N. Detection of mutant free circulating tumor DNA in the plasma of patients with gastrointestinal stromal tumor harboring activating mutations of CKIT or PDGFRA. Clin Cancer Res 2013; 19: 4854-4867.

[74] Phillips KG, Kolatkar A, Rees KJ, Rigg R, Marrinucci D, Luttgen M, Bethel K, Kuhn P and McCarty OJ. Quantification of cellular volume and sub-cellular density fluctuations: comparison of normal peripheral blood cells and circulating tumor cells identified in a breast cancer patient. Front Oncol 2012; 2: 96.

[75] El-Heliebi A, Kroneis T, Zöhrer E, Haybaeck J, Fischereder K, Kampel-Kettner K, Zigeuner R, Pock H, Riedl R, Stauber R, Geigl JB, Huppertz B, Sedlmayr P and Lackner C. Are morphological criteria sufficient for the identification of circulating tumor cells in renal cancer? J Transl Med 2013; 11: 214.

[76] Fachin F, Spuhler P, Martel-Foley JM, Edd JF, Barber TA, Walsh J, Karabacak M, Pai V, Yu M, Smith K, Hwang H, Yang J, Shah S, Yarmush R,

Sequist LV, Stott SL, Maheswaran S, Haber DA, Kapur R and Toner M. Monolithic chip for high-throughput blood cell depletion to sort rare circulating tumor cells. Sci Rep 2017; 7: 10936.
[77] Edd JF, Mishra A, Dubash TD, Herrera S, Mohammad R, Williams EK, Hong X, Mutlu BR, Walsh JR, Machado de Carvalho F, Aldikacti B, Nieman LT, Stott SL, Kapur R, Maheswaran S, Haber DA and Toner M. Microfluidic concentration and separation of circulating tumor cell clusters from large blood volumes. Lab Chip 2020; 20: 558-567.
[78] Bakhshi MS, Rizwan M, Khan GJ, Duan H and Zhai K. Design of a novel integrated microfluidic chip for continuous separation of circulating tumor cells from peripheral blood cells. Sci Rep 2022; 12: 17016.
[79] Yang C, Zhang N, Wang S, Shi D, Zhang C, Liu K and Xiong B. Wedge-shaped microfluidic chip for circulating tumor cells isolation and its clinical significance in gastric cancer. J Transl Med 2018; 16: 139.
[80] Milosevic M, Simic V, Nikolic A, Shao N, Kawamura Hashimoto C, Godin B, Leonard F, Liu X and Kojic M. Modeling critical interaction for metastasis between circulating tumor cells (CTCs) and platelets adhered to the capillary wall. Comput Methods Programs Biomed 2023; 242: 107810.
[81] Kobayashi S, Sugasaki A, Yamamoto Y, Shigenoi Y, Udaka A, Yamamoto A and Tanaka M. Enrichment of cancer cells based on antibody-free selective cell adhesion. ACS Biomater Sci Eng 2022; 8: 4547-4556.
[82] Wang X, Gao T, Zhu J, Long S, Zhao S, Yuan L and Wang Z. Fabrication of channeled and three-dimensional electrodes for the integrated capture and detection of invasive circulating tumor cells during hematogenous metastasis. Anal Chem 2023; 95: 2496-2503.
[83] Jiang X, Wong KHK, Khankhel AH, Zeinali M, Reategui E, Phillips MJ, Luo X, Aceto N, Fachin F, Hoang AN, Kim W, Jensen AE, Sequist LV, Maheswaran S, Haber DA, Stott SL and Toner M. Microfluidic isolation of platelet-covered circulating tumor cells. Lab Chip 2017; 17: 3498-3503.
[84] Wong KHK, Tessier SN, Miyamoto DT, Miller KL, Bookstaver LD, Carey TR, Stannard CJ, Thapar V, Tai EC, Vo KD, Emmons ES, Pleskow HM, Sandlin RD, Sequist LV, Ting DT, Haber DA, Maheswaran S, Stott SL and Toner M. Whole blood stabilization for the microfluidic isolation and molecular characterization of circulating tumor cells. Nat Commun 2017; 8: 1733.
[85] Ma Y, Zhang J, Tian Y, Fu Y, Tian S, Li Q, Yang J and Zhang L. Zwitterionic microgel preservation platform for circulating tumor cells in whole blood specimen. Nat Commun 2023; 14: 4958.
[86] Aktas B, Tewes M, Fehm T, Hauch S, Kimmig R and Kasimir-Bauer S. Stem cell and epithelial-mesenchymal transition markers are frequently overexpressed in circulating tumor cells of metastatic breast cancer patients. Breast Cancer Res 2009; 11: R46.
[87] Kasimir-Bauer S, Hoffmann O, Wallwiener D, Kimmig R and Fehm T. Expression of stem cell and epithelial-mesenchymal transition markers in primary breast cancer patients with circulating tumor cells. Breast Cancer Res 2012; 14: R15.
[88] Zhao J, Ye H, Lu Q, Wang K, Chen X, Song J, Wang H, Lu Y, Cheng M, He Z, Zhai Y, Zhang H and Sun J. Inhibition of post-surgery tumour recurrence via a sprayable chemo-immunotherapy gel releasing PD-L1 antibody and platelet-derived small EVs. J Nanobiotechnology 2022; 20: 62.
[89] Du J, Wang C, Chen Y, Zhong L, Liu X, Xue L, Zhang Y, Li Y, Li X, Tang C, Su Z and Zhang C. Targeted downregulation of HIF-1α for restraining circulating tumor microemboli mediated metastasis. J Control Release 2022; 343: 457-468.
[90] Zhao X, Georgieva R, Rerkshanandana P, Hackmann M, Heil Olaizola LE, Müller-de Ahna M and Bäumler H. Tumor cell capture using platelet-based and platelet-mimicking modified human serum albumin submicron particles. Int J Mol Sci 2022; 23: 14277.
[91] Roop RP, Naughton MJ, Van Poznak C, Schneider JG, Lammers PE, Pluard TJ, Johnson F, Eby CS and Weilbaecher KN. A randomized phase II trial investigating the effect of platelet function inhibition on circulating tumor cells in patients with metastatic breast cancer. Clin Breast Cancer 2013; 13: 409-415.
[92] Liang H, Yang C, Zhang B, Wang H, Liu H, Zhao Z, Zhang Z, Wen X and Lai X. Hydroxyethyl starch 200/0.5 decreases circulating tumor cells of colorectal cancer patients and reduces metastatic potential of colon cancer cell line through inhibiting platelets activation. Med Oncol 2015; 32: 151.
[93] Lu Y, Lian S, Ye Y, Yu T, Liang H, Cheng Y, Xie J, Zhu Y, Xie X, Yu S, Gao Y and Jia L. S-Nitrosocaptopril prevents cancer metastasis in vivo by creating the hostile bloodstream microenvironment against circulating tumor cells. Pharmacol Res 2019; 139: 535-549.
[94] Luo S, Feng J, Xiao L, Guo L, Deng L, Du Z, Xue Y, Song X, Sun X, Zhang Z, Fu Y and Gong T. Targeting self-assembly peptide for inhibiting breast tumor progression and metastasis. Biomaterials 2020; 249: 120055.
[95] Li J, Sharkey CC, Wun B, Liesveld JL and King MR. Genetic engineering of platelets to neutralize circulating tumor cells. J Control Release 2016; 228: 38-47.

[96] Ortiz-Otero N, Marshall JR, Lash BW and King MR. Platelet mediated TRAIL delivery for efficiently targeting circulating tumor cells. Nanoscale Adv 2020; 2: 3942-3953.
[97] Zhang L, Zhu Y, Wei X, Chen X, Li Y, Zhu Y, Xia J, Huang Y, Huang Y, Wang J and Pang Z. Nanoplateletsomes restrain metastatic tumor formation through decoy and active targeting in a preclinical mouse model. Acta Pharm Sin B 2022; 12: 3427-3447.
[98] Da X, Mo J, Li Q, Cao B, Huang J, Lu Y, Lu L, Fan M and Lu H. Targeted co-delivery of PD-L1 monoclonal antibody and sorafenib to circulating tumor cells via platelet-functionalized nanocarriers. Biochem Biophys Res Commun 2023; 671: 335-342.
[99] Lemoli RM, Fortuna A, Motta MR, Rizzi S, Giudice V, Nannetti A, Martinelli G, Cavo M, Amabile M, Mangianti S, Fogli M, Conte R and Tura S. Concomitant mobilization of plasma cells and hematopoietic progenitors into peripheral blood of multiple myeloma patients: positive selection and transplantation of enriched CD34+ cells to remove circulating tumor cells. Blood 1996; 87: 1625-1634.
[100] Hamilton G, Rath B, Klameth L and Hochmair MJ. Small cell lung cancer: recruitment of macrophages by circulating tumor cells. Oncoimmunology 2015; 5: e1093277.
[101] Naidu S, Shi L, Magee P, Middleton JD, Laganá A, Sahoo S, Leong HS, Galvin M, Frese K, Dive C, Guzzardo V, Fassan M and Garofalo M. PDGFR-modulated miR-23b cluster and miR-125a-5p suppress lung tumorigenesis by targeting multiple components of KRAS and NF-kB pathways. Sci Rep 2017; 7: 15441.
[102] Hapeman JD, Carneiro CS and Nedelcu AM. A model for the dissemination of circulating tumour cell clusters involving platelet recruitment and a plastic switch between cooperative and individual behaviours. BMC Ecol Evol 2023; 23: 39.
[103] Hotte SJ, Chi KN, Joshua AM, Tu D, Macfarlane RJ, Gregg RW, Ruether JD, Basappa NS, Finch D, Salim M, Winquist EW, Torri V, North S, Kollmannsberger C, Ellard SL, Eigl BJ, Tinker A, Allan AL, Beja K, Annala M, Powers J, Wyatt AW and Seymour L; Canadian Cancer Trials Group (formerly NCIC Clinical Trials Group). A phase II study of PX-866 in patients with recurrent or metastatic castration-resistant prostate cancer: Canadian cancer trials group study IND205. Clin Genitourin Cancer 2019; 17: 201-208, e201.
[104] Müller C, Petermann D, Pfeffel F, Oesterreicher C and Függer R. Lack of specificity of albumin-mRNA-positive cells as a marker of circulating hepatoma cells. Hepatology 1997; 25: 896-899.
[105] Mayall FG, Pepperell J, Bodger I, Higbee D, Stevanato L, Hustler A and Mumford KM. Cytology and cell-block immunohistochemistry of circulating tumour cells. Cytopathology 2019; 30: 620-627.
[106] Wang Y, Guo L, Feng L, Zhang W, Xiao T, Di X, Chen G and Zhang K. Single nucleotide variant profiles of viable single circulating tumour cells reveal CTC behaviours in breast cancer. Oncol Rep 2018; 39: 2147-2159.
[107] Humphries MJ, Yamada KM and Olden K. Investigation of the biological effects of anti-cell adhesive synthetic peptides that inhibit experimental metastasis of B16-F10 murine melanoma cells. J Clin Invest 1988; 81: 782-790.
[108] Gasperi V, Vangapandu C, Savini I, Ventimiglia G, Adorno G and Catani MV. Polyunsaturated fatty acids modulate the delivery of platelet microvesicle-derived microRNAs into human breast cancer cell lines. J Nutr Biochem 2019; 74: 108242.
[109] Cai Z, Feng J, Dong N, Zhou P, Huang Y and Zhang H. Platelet-derived extracellular vesicles play an important role in platelet transfusion therapy. Platelets 2023; 34: 2242708.
[110] Vismara M, Negri S, Scolari F, Brunetti V, Trivigno SMG, Faris P, Galgano L, Soda T, Berra-Romani R, Canobbio I, Torti M, Guidetti GF and Moccia F. Platelet-derived extracellular vesicles stimulate migration through partial remodelling of the $Ca2^{+}$ handling machinery in MDA-MB-231 breast cancer cells. Cells 2022; 11: 3120.
[111] Liang H, Yan X, Pan Y, Wang Y, Wang N, Li L, Liu Y, Chen X, Zhang CY, Gu H and Zen K. MicroRNA-223 delivered by platelet-derived microvesicles promotes lung cancer cell invasion via targeting tumor suppressor EPB41L3. Mol Cancer 2015; 14: 58.
[112] Ying X, Li-ya Q, Feng Z, Yin W and Ji-hong L. MiR-939 promotes the proliferation of human ovarian cancer cells by repressing APC2 expression. Biomed Pharmacother 2015; 71: 64-69.
[113] Contursi A, Fullone R, Szklanna-Koszalinska P, Marcone S, Lanuti P, Taus F, Meneguzzi A, Turri G, Dovizio M, Bruno A, Pedrazzani C, Tacconelli S, Marchisio M, Ballerini P, Minuz P, Maguire P and Patrignani P. Tumor-educated platelet extracellular vesicles: proteomic profiling and crosstalk with colorectal cancer cells. Cancers (Basel) 2023; 15: 350.