

REVIEW ARTICLE

Platelet biology in cancer and leukemia:
Mechanisms and therapeutic insightsGayathri Jayaraman¹, Vijay Prasad Koppineedi¹, Mounika Sarvepalli¹,
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Abstract

Acute leukemia (AL) is a hematological malignancy characterized by the uncontrolled proliferation of immature blood cells, disrupting normal hematopoiesis and leading to severe cytopenias and tissue infiltration. In acute myeloid leukemia (AML), leukemic blasts and dysfunctional megakaryocytes replace healthy bone marrow cells, severely impairing platelet production and resulting in thrombocytopenia. This profound reduction in platelet count increases the risk of life-threatening hemorrhagic events, posing a significant challenge in AML management. Beyond their well-established role in hemostasis, platelets actively participate in cancer progression through tumor cell-induced platelet aggregation, which promotes metastasis and immune evasion. By forming microthrombi and secreting a diverse range of bioactive molecules, platelets create a tumor-supportive microenvironment through interactions with endothelial cells, immune cells, fibroblasts, and epithelial cells. These interactions enhance angiogenesis, inflammation, and tumor survival, thereby influencing the pathophysiology of leukemia. Emerging evidence suggests that platelet dysfunction in AML is not merely a consequence of thrombocytopenia but also a key contributor to disease progression. Alterations in platelet signaling, granule secretion, and receptor expression may further exacerbate leukemic cell proliferation and immune evasion. Moreover, platelet-derived extracellular vesicles have been implicated in facilitating leukemic stem cell survival and chemotherapy resistance. This review provides a comprehensive analysis of platelet dysfunction in AML, emphasizing its mechanistic role in disease progression and its potential as a therapeutic target. A deeper understanding of platelet-leukemia crosstalk could reveal novel strategies for mitigating tumor growth and improving patient outcomes. Targeting platelet-mediated pathways may not only enhance conventional leukemia treatments but also pave the way for innovative anti-leukemic therapies with improved efficacy and reduced disease relapse.

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1. Introduction

Platelets are relatively small, nucleus-free blood cells with an average diameter of 1.5 – 3 μm . The megakaryocytes present in the lungs, spleen, yolk sac, and bone marrow are the source of these tiny anucleate cells.¹ Megakaryocyte maturation results in the

formation of platelets with the help of an indispensable hormone named thrombopoietin. During this process, platelets generate cytoplasmic projections that pinch off to form new platelets, which are then dislodged from the production site and enter the bloodstream, where they are involved in hemostasis, thrombosis, and procoagulant activation. Platelets have a life expectancy of 7 – 10 days and typically remain stable. However, when exposed to certain biological stimuli, the disc-shaped platelets transform into irregular spheres with spiky pseudopods. As a result, platelets can adhere to areas of vascular injury and clump together. Inappropriate platelet activation can lead to various conditions, including thrombosis, cancer, diabetes, and inflammation.²

Platelets come second to abundant red blood cells and possess a complex endocytic machinery for absorbing and storing various proteins. The processes of hemostasis and thrombosis dynamically influence their phenotype and function. Activation of platelet occurs when surface receptors on the platelets are stimulated to recognize specific signals.³ Furthermore, several translational clinical research have shown that platelets, along with their constituents, profoundly support various morbid processes, including immune responses, cancer, and inflammation. Platelets have emerged as key players in cancer progression and leukemia pathophysiology. These anucleate cell fragments, derived from megakaryocytes, interact with tumor cells, immune cells, and the vascular endothelium, thereby influencing several hallmarks of cancer, including proliferation, angiogenesis, metastasis, and immune evasion. The bidirectional crosstalk between platelets and malignant cells contributes significantly to the tumor microenvironment, which promotes cancer cell survival and dissemination.^{4,5}

In solid tumors, platelets facilitate metastasis by shielding circulating tumor cells (CTCs) from immune surveillance and aiding in their adhesion to the endothelium. Through the release of pro-tumorigenic factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF- β), and vascular endothelial growth factor (VEGF), platelets enhance cancer cell invasion and angiogenesis.^{6,7} Moreover, tumor-induced platelet activation leads to a hypercoagulable state, thereby increasing the risk of cancer-associated thrombosis, which is a major cause of morbidity and mortality in cancer patients. Leukemia, a hematologic malignancy affecting the blood and bone marrow, is also influenced by platelet biology. Thrombocytopenia (low platelet count [PLT]) is a hallmark of leukemia, often resulting from bone marrow suppression or platelet destruction. However, beyond their quantitative alterations, platelets contribute

to leukemogenesis through abnormal interactions with leukemic stem cells (LSCs), inflammatory cytokines, and the bone marrow microenvironment.^{8,9} Furthermore, emerging evidence suggests that platelets can either support or suppress leukemia progression, depending on the disease subtype and the molecular mechanisms involved.

Given the integral role of platelets in cancer and leukemia, targeting platelet-tumor interactions has gained attention as a potential therapeutic strategy. Anti-platelet agents such as aspirin, P2Y₁₂ inhibitors, and integrin antagonists have shown promise in preclinical and clinical studies for reducing tumor progression and metastasis.¹⁰ In addition, novel therapeutic approaches, including platelet engineering and nanotechnology-based drug delivery systems, offer innovative avenues for cancer treatment. Therefore, this review explores the multifaceted roles of platelets in cancer and leukemia, delving into their underlying mechanisms and therapeutic implications. By understanding how platelets contribute to tumor biology and leukemic pathology, researchers can develop more effective strategies to mitigate cancer progression, improve patient outcomes, and refine current therapeutic interventions. Given their foundational role in hemostasis, platelets also engage in bidirectional crosstalk with tumor cells, a topic further explored in the following sections.

2. Composition and receptors of platelets

Giant cells differ in their composition, comprising a mixture of proteins, granules, lipids derived from triglycerides, and carbohydrates, along with trace elements. In contrast, platelets lack genetic material due to the absence of a nucleus. However, some retain RNA transcripts and mitochondria. Platelets possess granules, including dense granules, α -granules, and lysosomes. The plasma membrane contains several glycoproteins, such as GPIb and GPIIb/IIIa, which play crucial roles in platelet aggregation and adhesion.^{2,3} In addition, platelets have receptors for thrombin, adenosine diphosphate (ADP), collagen, and other factors related to coagulation and platelet activation. The α -granules are rich in fibrinogen, von Willebrand factor, factor V, PDGF, and TGF- β .² Meanwhile, the dense granules, also known as delta granules, contain adenosine triphosphate (ATP), ADP, and calcium ions (Ca²⁺).¹¹

Platelet receptors play a significant role in platelet function (Figure 1). These receptors either activate platelets or serve as attachment molecules, allowing them to bind to damaged endothelium, other platelets, and leukocytes.¹² Platelets are involved not only in hemostasis

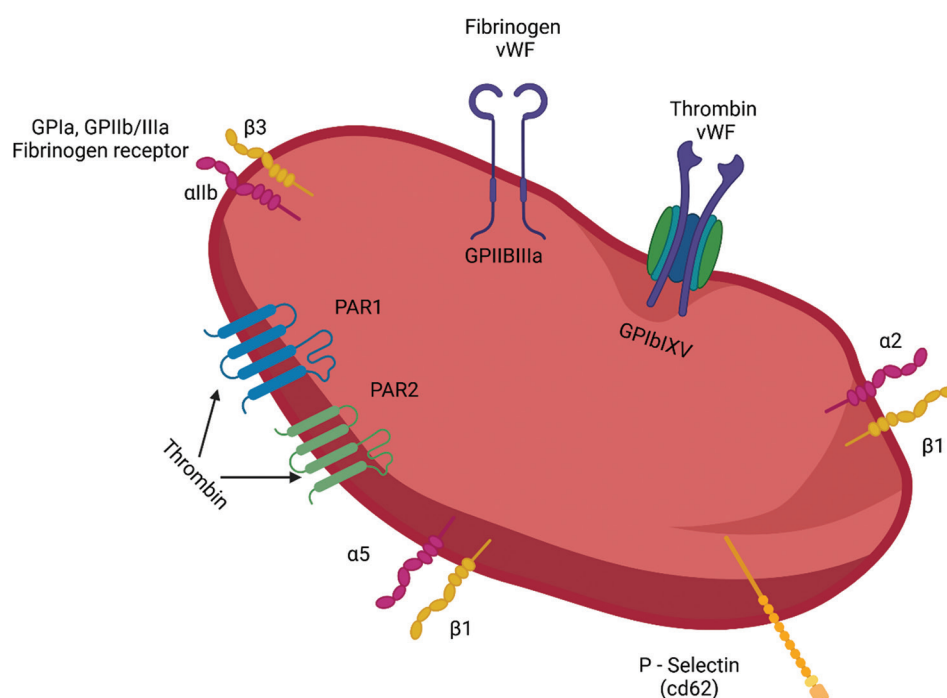


Figure 1. Platelet membrane receptors and their roles in hemostasis and thrombosis. The schematic representation illustrates key receptors on the platelet membrane, including glycoprotein complexes (GPIIb/IIIa and GPIb/X/V) and protease-activated receptors (PAR1 and PAR2). GPIIb/IIIa plays a critical role in platelet aggregation by binding fibrinogen, while GPIb/X/V is essential for platelet adhesion through vWF. PAR1 and PAR2 mediate platelet activation in response to thrombin signaling. Collectively, these receptors regulate platelet adhesion, activation, and aggregation, which are crucial for maintaining vascular integrity and facilitating thrombus formation. Created using BioRender.com.

Abbreviations: PAR1: Protease-activated receptor-1; PAR2: Protease-activated receptor-2; vWF: von Willebrand factor.

but also in inflammation, anti-microbial activity, angiogenesis, tumor formation, and metastasis. Platelet receptors include integrins, selectins, transmembrane receptors, leucine-rich repeats, tetraspanins, prostaglandin receptors, immunoglobulin superfamily receptors, lipid receptors, tyrosine kinase receptors, and various others that mediate the platelets to adhere to leukemic cells.² Moreover, platelets are among the many cell types containing integrins, which function as both signaling molecules and adhesion structures. Integrins are composed of non-covalently bound heterodimers made up of α and β subunits.¹³ In platelets, three types of integrins are found: $\beta 1$, $\beta 2$, and $\beta 3$. The GPIa-IIa complex, part of the $\beta 1$ family, is a crucial platelet receptor for collagen, whereas the GPIb-IX-V complex is the most predominant platelet receptor.¹³ Furthermore, platelets also express receptors that interact with cancer cells, and this coordinated communication enhances metastasis by triggering an epithelial–mesenchymal transition (EMT).¹⁴ As a result, the activation of platelets plays a crucial role in cancer development. In addition, elevated levels of coagulation and thrombosis parameters are observed in cancer patients.

2.1. Platelet and cancer

As specified by current research, platelets play a vital role in the advancement of cancer progression. To explore this relationship, researchers have designed many experimental models to investigate the potential interaction between platelet activity and cancer development.¹⁵ These models aim to fully understand the specific contributions of platelet roles to this process (Figure 2).

In experimental animal models, where platelet functions are selectively modified using pharmacological interventions or targeted genetic deletions, findings have demonstrated that platelets play a crucial role in shielding tumor cells from immune attack within the bloodstream.¹ In addition, platelets can promote the arrest of tumor cells within the blood vessels and influence their survival, thereby supporting the formation of secondary lesions.¹ In addition, platelets possess ligands and receptors that promote the growth and metastasis of transformed cells in the body. They bind to leukocytes through various receptors, the most notable being P-selectin, which interacts with P-selectin glycoprotein ligand 1 on leukocytes.¹⁶ This binding initiates a downstream

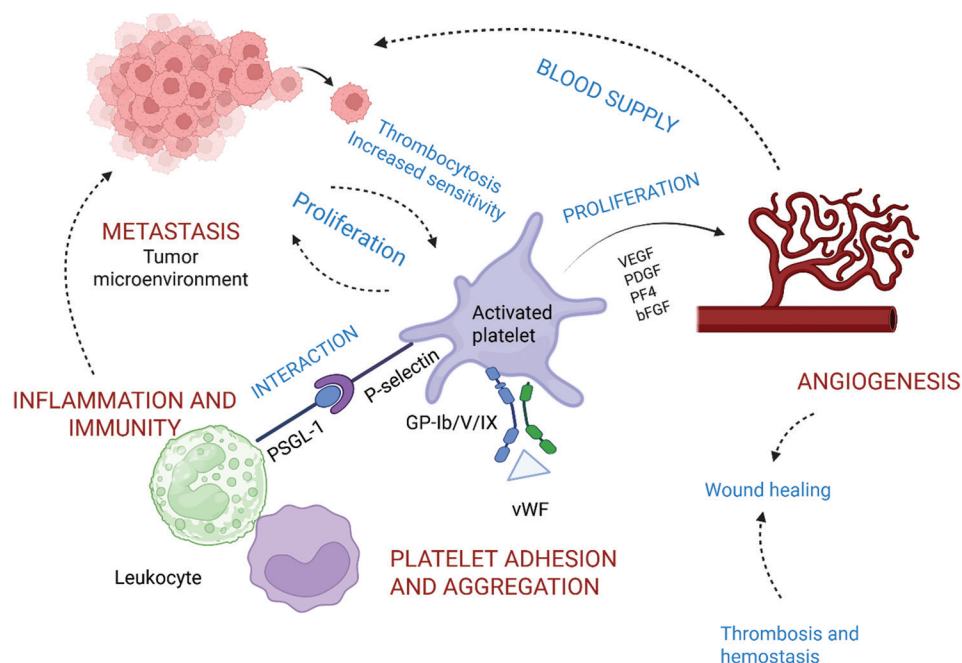


Figure 2. The role of platelets in tumor metastasis, angiogenesis, and immunity. Created using BioRender.com.

Abbreviations: bFGF: Basic fibroblast growth factor; PDGF: Platelet-derived growth factor; PF4: Platelet factor 4; PSGL-1: P-selectin glycoprotein ligand-1; VEGF: Vascular endothelial growth factor; vWF: von Willebrand factor.

singling pathway which results in integrin activation on leukocytes.¹⁶ Upon activation, P-selectin appears on the surface of the platelet plasma membrane, enabling the formation of α -granules and aggregation with other circulating platelets and leukocytes.^{17,18} These interactions are essential for metastasis.

P-selectin binds to MC-38 colon carcinoma cells, resulting in a reduction of experimental metastasis in syngeneic *in vivo* models.^{3,17} In experimental models, both the growth of subcutaneously implanted tumors and the extent of metastasis were significantly reduced in P-selectin-deficient mice. This inhibitory effect was observed in immunocompetent models using MC-38 colon carcinoma cells and B16 melanoma cells.¹⁷

2.2. Platelet-cancer cell interactions and mechanisms

2.2.1. Platelet activation and tumor cell protection

Platelets are activated by tumor cells through various mechanisms, including the release of procoagulant factors and extracellular vesicles (EVs). Upon activation, platelets form a protective shield around CTCs, thereby safeguarding them from immune surveillance and mechanical shear stress.^{5,19} This protection facilitates the survival and dissemination of CTCs, which are critical for metastasis.

2.2.2. Role of PDGF

PDGF, released by platelets, plays a pivotal role in carcinogenesis and metastasis. It promotes tumor cell proliferation, angiogenesis, and EMT, all of which enhance cancer cell invasiveness.²⁰ Moreover, PDGF signaling modulates the tumor microenvironment and creates a niche that is conducive to tumor growth and metastasis.

2.2.3. Platelet-released bioactive molecules

Platelets release a variety of bioactive molecules, including TGF- β 1, which induces drug resistance in leukemia cells by activating the TGF- β signaling pathway.²¹ In addition, platelet-derived microparticles enhance the cytotoxic effects of chemotherapeutic agents such as cytarabine (Ara-C) in acute lymphoblastic leukemia (ALL) by modulating apoptosis-related genes, including B-cell lymphoma-2 (BCL-2) associated X and BCL-2.²²

2.2.4. Platelets and the tumor

Platelets influence the tumor microenvironment by recruiting immune cells and promoting angiogenesis. They release pro-angiogenic factors, such as VEGF, which enhance tumor cell dissemination and metastasis.^{23,24} Furthermore, platelets modulate immune responses by delivering immunomodulatory factors that suppress anti-tumor immunity and promote tumor growth.^{19,25}

2.3. Platelet and angiogenesis

Angiogenesis is the process where new blood vessels form to supply oxygen and remove waste products, which leads to the growth and survival of altered cells. This process contributes to the establishment of a specific tumor microenvironment that plays a crucial role in promoting the progression of tumor cells.² Important factors released from tumor cells favor the emergence of new blood vessels from previously existing one, which supports the proliferation of transformed cells. These factors influence tumor maturation and development by either inducing or obstructing angiogenesis. Notably, platelets contain a variety of biological molecules that can regulate angiogenesis.²⁶ For example, dopamine and serotonin are neurotransmitters produced in the central nervous system that play a role in various neurological and psychological processes (Table 1).² Angiogenesis-associated expression of VEGF, platelet factor 4 (PF4), PDGF-subunit B, and TGF- β 1 differs in the platelet pellet samples of cancer and control subjects.⁷ Moreover, dopamine and serotonin are primarily stored in the dense granules of platelets and are released on platelet activation, with dopamine acting to inhibit angiogenesis.^{27,28} In an *in vivo* mouse model, injecting dopamine into the peritoneum blocked both angiogenesis and tumor growth.¹¹ This effect was associated with the inhibition of VEGF and vascular permeability factor-mediated proliferation and migration of human umbilical vein endothelial cells.¹¹ In contrast, serotonin can promote angiogenesis by stimulating the proliferation of endothelial cells. This occurs by activating various downstream signaling kinases, including Src, phosphoinositide 3-kinase, protein kinase B, extracellular signal-regulated kinase, and mammalian target of rapamycin. These serotonin-mediated signaling pathways are associated with VEGF.^{11,26}

2.4. Tumor growth and metastasis

Platelets contain a wealth of biologically active molecules, and research indicates that various platelet agonists can

trigger distinct release patterns.²⁹ It has been proposed that platelets may play a dual role in cancer development: they contribute to the metastatic spread of cancer cells that are resistant to platelet-mediated cytotoxicity, while exerting cytotoxic effects on those that remain sensitive. On the surface of the endothelium, platelets form hetero-aggregates with resistant tumor cells and release cytotoxic substances that harm the endothelium. This injury creates openings in the vasculature, allowing resistant cancer cells to infiltrate and metastasize.² Among the immune defense molecules present within platelets are tumor necrosis factor- α (TNF- α), CD154, Fas ligand, tumor necrosis factor-related apoptosis-inducing ligand, and other proapoptotic members of the TNF family.¹⁴ Metastasis refers to the process of the movement of tumor cells away from the original site to different organs within the body's system. Steps in this process include cell invasion into the surrounding tissue, intravasation, survival while in circulation, micrometastasis formation, and final colonization in new sites.³⁰ The interaction between tumor cells and platelets is critical in nearly every step of cancer metastasis.¹⁷ For tumor cells to metastasize, they often undergo a phenotypic change called EMT. This process increases the expression of various molecular markers, such as SNAIL, vimentin, cadherin, and matrix metalloproteinases.³¹ In addition, platelet-derived TGF- β can significantly enhance the expression of these markers in cancer cells.^{12,31} Moreover, the migration of tumor cells from the tissue into the bloodstream is facilitated by platelet-derived ADP, which activates P2Y2 receptors on endothelial cells.³² After entering the bloodstream, the efficacy of cancer cell dissemination depends on interactions with platelets. Numerous studies have shown that platelets facilitate the metastatic process through hematogenous dissemination.^{31,33} Cancer cells can mimic platelets by activating genes associated with megakaryocytes and displaying platelet surface markers, including adhesion molecules such as integrins and selectins.^{34,35} Finally, the extravasation of tumor cells from the bloodstream is facilitated by platelets and appears to depend on their interaction with integrin $\alpha v \beta 3$ expressed on tumor cells.³⁶

2.5. Platelet and acute myeloid leukemia (AML)

AML is a type of cancer that targets both the bloodstream and bone marrow. This condition may occur as a result of errors during the differentiation process of hematopoietic stem cells, leading to the excessive production of inefficiently formed white blood cells in the body that do not function properly.² These tumor cells suppress the formation of healthy cells, leading to various symptoms and complications. This always leads to uncontrollable

Table 1. Range of platelet-derived angiogenic factors in physiological condition

Platelet-derived angiogenic factors	The normal range (10 ⁶ platelets/L)	References
VEGF	0.9 (0.1 – 2.3) pg	7
PF4	10.2 (4.2 – 20.5) ng	7
bFGF	0.42 (0.15 – 0.75) pg	2
PDGF	21 (12 – 33) pg	2

Abbreviations: bFGF: Basic fibroblast growth factor; PDGF: Platelet-derived growth factor; PF4: Platelet factor 4; VEGF: Vascular endothelial growth factor.

bleeding and ultimately results in death.¹⁸ However, leukemia patients often receive thrombocyte transfusions to halt excess hemorrhage. Although medical advances have improved this process, not all patients benefit from it. Increasingly ineffective transfusions present a serious concern for clinical researchers and clinicians, and may, on occasion, lead to fatal outcomes.³⁷ Acute leukemia (AL) is classified into AML and ALL.³⁸ Most AML patients are adults, whereas ALL patients are children.¹⁸ The majority of AML patients receive chemotherapy to achieve a normal level of PLT in the body. However, some develop resistance to anti-cancer medications, which results in relapse and refractory leukemia.³⁹ The mechanism of bleeding in leukemia is intricate and includes infiltration of leukemic cells into the vessel walls, decreased platelet production, and disruptions in coagulation and anti-coagulation processes.⁴⁰ The primary causes of bleeding in AL are quantitative decrease and qualitative dysfunction of platelets.³⁸ Under normal physiological conditions, platelets flow through the bloodstream in a laminar pattern, staying near the endothelium without adhering to one another or to endothelial cells. The activation of platelets results in three phases, which include adhesion, secretion, and aggregation.⁴⁰ Platelet limiting factors can be recognized as clinically relevant in the early diagnosis, follow up of disease progression, and analysis of treatment responses, as they are not only measurable noninvasively in clinical settings but also can accurately reflect their *in vivo* dynamics for proliferation.³⁸ Moreover, platelet parameters include PLT, mean platelet volume (MPV), and platelet distribution width (PDW).⁴⁰ ALL patients with a PLT count of $\geq 100 \times 10^9/\text{L}$ exhibit fewer immature cells in bone marrow smears, lower rates of *KMT2A* gene rearrangement, and a more favorable prognosis compared to those with a PLT count of $< 100 \times 10^9/\text{L}$.^{40,41} Similarly, AML patients (except the M3 subtype) with pretreatment PLT levels ranging between 50 and $120 \times 10^9/\text{L}$ have higher survival and lower relapse rates than those with PLT levels < 50 or $> 120 \times 10^9/\text{L}$.⁴² It was reported that AML patients with PLT levels below $25 \times 10^9/\text{L}$ at the time of initial diagnosis show an improved response to chemotherapy and a more favorable prognosis.⁴³ MPV is used to measure the average size of platelets in the body. An elevated MPV suggests that the circulating platelets are larger, immature, and possess higher levels of active substances, along with more active metabolism and functionality.^{44,45} Zhang *et al.*⁴⁵ stated that MPV serves as a reference value for determining the cause of thrombocytopenia and assessing platelet function. They also indicated that, in general, thrombocytopenia caused by increased destruction of peripheral platelets may increase MPV owing to the production of larger platelets stimulated by thrombopoietin. Conversely, MPV is lower

in individuals with thrombocytopenia caused by bone marrow abnormalities.^{46,47} Elevated MPV levels at the time of diagnosis with AML have been associated with poorer prognoses, while such levels have been associated not only with higher rates of complete remission but also with extended median overall survival and longer progression-free survival after chemotherapy.⁴⁸ However, because MPV measurement is affected by various factors, it cannot be used as a reliable indicator for predicting the prognosis of AML patients.⁴⁹ As a result, further research is needed to determine the utility of MPV in diagnosing or predicting AL.⁴⁵ Plateletcrit, calculated by multiplying PLT and MPV, is influenced by both the number and size of platelets and generally mirrors changes in PLT levels.⁵⁰ The coefficient of variation in measured platelet size, or PDW, is a parameter that indicates variation in platelet volume. In the case of normal bone marrow function, PDW is positively correlated with MPV.⁴⁵ An increase in the number of new platelets in peripheral circulation reduces the uniformity of platelet volume, leading to a rise in PDW.⁴⁷

2.5.1. Platelet dysfunction in ALL

2.5.1.1. Clinical correlations

PLT $\geq 100 \times 10^9/\text{L}$ serves as a prognostic marker for lower bone marrow blasts and *KMT2A* gene rearrangement, suggesting a less aggressive disease subtype with better treatment response. Conversely, thrombocytopenia (PLT $< 50 \times 10^9/\text{L}$) at diagnosis correlates with higher relapse rates and poorer overall survival, particularly in pediatric ALL. Abnormal platelet indices may reflect disease burden, with elevated MPV linked to minimal residual disease positivity. Increased levels of soluble P-selectin and PF4 indicate hyperactivated platelets, contributing to thromboembolic complications in ALL. Leukemia-derived procoagulant microparticles trigger thrombin generation, thereby exacerbating disseminated intravascular coagulation-like coagulopathy.^{38,41}

2.5.1.2. Mechanistic insights

Platelet-derived microparticles enhance cytarabine (Ara-C) cytotoxicity by facilitating drug delivery and modulating leukemia cell metabolism.²² In addition, activated platelets express immune checkpoint ligands, such as programmed death-ligand 1 (PD-L1) and galectin-9, which promote T-cell exhaustion and immune evasion in ALL. Platelet-secreted TGF- β and VEGF support leukemia cell survival and bone marrow vascular remodeling, which together foster chemoresistance.⁵¹

2.5.1.3. Therapeutic implications

Aspirin is under investigation in clinical trials for its potential to reduce thrombosis and disrupt platelet-leukemia

interactions. P2Y₁₂ inhibitors, including clopidogrel and ticagrelor, may synergize with chemotherapy by inhibiting platelet-mediated immune suppression. Protease-activated receptor-1 (PAR-1) antagonists, such as vorapaxar, could mitigate thromboinflammation in high-risk ALL. Combination immunotherapy involving anti-programmed cell death protein-1 (anti-PD-1) and anti-platelet agents may overcome platelet-driven immune evasion. Thrombopoietin receptor agonists, such as romiplostim, eltrombopag, show promise in managing persistent chemotherapy-induced thrombocytopenia.¹⁰

2.6. Platelet and immune system

Platelets are vitally necessary for several immune processes, regardless of their traditional roles in hemostasis and thrombosis.⁵² Immune complexes attach to the Fc receptor of human platelets, commonly known as FcγRIIIa or CD32, and activate the platelet.⁵³ FcγRIIIa is one of the three tyrosine kinase signaling receptors in human platelets, which falls under the category of the immunoreceptor tyrosine-based activation motif (ITAM) family.⁵⁴ With the activation of ITAMs, platelets start to aggregate and then degranulate, transforming into procoagulant platelets, and EVs are released.⁵⁵ Moreover, it has been shown that the 12(S)-lipoxygenase (12-LOX) enzyme is also involved in platelet activation through FcγRIIIa.⁵⁶

Contursi *et al.*⁵¹ stated that tumor cells encounter substantial obstacles to survive in the bloodstream due to immune surveillance.⁵¹ Furthermore, for this reason, metastasis and subsequent extravasation involve complex mechanisms that support cancer cell survival in the systemic circulation.⁵¹ The recruitment of monocyte, neutrophils, and platelets is central to this process, as these cells protect tumor cells from immune surveillance and promote the development of metastases.⁵⁷ Platelets are essential in regulating both innate and adaptive immunity, especially T cells. Moreover, platelets can act as antigen-presenting cells, since they express major histocompatibility complex (MHC) class I proteins on their surface, which activates the adaptive immune response.⁵² It has been reported that platelets can transfer MHC class I proteins to tumor cells, leading to a tumor cell phenotype known as the “phenotype of false pretenses.”⁵¹ Platelet-derived MHC class I transfer to tumor cells, masking them from natural killer (NK) cell surveillance.⁵⁸ This enables platelets to disrupt the ability of NK cells to recognize between self and non-self, ultimately hindering the host's immune defense and preventing the production of interferon. New evidence suggests that platelets may express the immune checkpoint molecule PD-L1, and the binding of PD-L1 to PD-1 on T cells, ultimately leads to T-cell exhaustion.⁵¹ Platelets activated by AL cells attach to the surface of

these cells and encase them, shielding them from cellular components of the immune system and protecting them from the impact of chemotherapy drugs.⁵⁹ The main source of TGF-β in the tumor microenvironment and systemic circulation is platelets. The expression of glycoprotein-A repetitions predominant and the release of TGF-β itself are responsible for the synthesis and secretion of platelet-derived TGF-β.^{51,60}

3. Platelet as therapeutics

The preceding sections delineate platelet-tumor interactions; we now translate these insights into therapeutic strategies. Platelets are essential for blood clot formation and can significantly benefit patients with blood disorders by reducing bleeding caused by either dysfunction or a decreased number of platelets. Their transfusion is therefore considered the most efficacious therapeutic approaches.⁶¹ The effectiveness of a platelet transfusion can be evaluated by assessing determinants of platelet quality, such as platelet recovery, survival, and function.⁴² Foss *et al.*⁴² states that the risk of hemorrhage is high in patients with AML due to systemic coagulopathy, platelet dysfunction, and platelet deficiency. Interventional treatment has involved the transfusion of platelets for hemostatic purposes, traditionally performed below the 20,000 μL threshold, but now performed at a lower threshold in non-febrile patients without active bleeding. However, transfusion effects are complex because of variability, as well as factors including platelets production methods, transfusion refractoriness from alloimmunization, altered platelet function during storage, and the limited studies on the potential effects of transfused platelets on leukemic cells, including their possible effects on chemotherapy.

Platelets play a crucial role in cancer growth and metastasis by modulating the tumor microenvironment. Targeting platelets therapeutically offers potential for novel cancer diagnostics and treatments, thereby highlighting their significance beyond hemostasis in both cancer and leukemia contexts.⁴ Therapeutic strategies include targeting platelet receptors and using anti-platelet agents, such as aspirin, which may improve cancer outcomes while managing thrombotic complications.²³ Moreover, platelets enhance tumorigenesis through angiogenesis and metastasis by releasing bioactive contents that stimulate cancer progression. They also serve as biomarkers for therapeutic response and can be targeted for drug delivery systems, offering insights into overcoming drug resistance in cancer and leukemia treatments.²² In addition, platelets protect CTCs from immune attacks and apoptosis, enhance intravasation, and promote EMT via cytokines such as TGF-β and PDGF. Therefore, targeting platelet interactions may offer therapeutic strategies to reduce metastasis

in both cancer and leukemia.⁵ Major mechanisms and therapeutic strategies in platelet-cancer interactions are presented in Table 2.

3.1. Targeting platelet-cancer cell interactions

Blocking the interaction between platelets and cancer cells has emerged as a promising therapeutic strategy. Biomimetic delivery system using platelet membrane-hybridized liposomes have been developed to inhibit platelet activation and glycolysis, thereby suppressing tumor metastasis without affecting normal platelet functions.⁶ Similarly, anti-platelet agents, such as aspirin and clopidogrel, have shown potential in reducing cancer progression and metastasis by inhibiting platelet activation and aggregation.⁶²

3.1.1. Inhibiting PDGF signaling

Pharmacological targeting of the PDGF/PDGFR signaling axis has shown promise in inhibiting cancer progression. Kinase inhibitors targeting this pathway have shown efficacy in preclinical models, thereby highlighting their potential as adjuvant therapies for cancer treatment.²⁰

3.1.2. Engineered platelets for cancer therapy

Engineered platelets, modified through surface modification, gene editing, or membrane coating, have been explored for their potential in targeted cancer therapy. These platelets can deliver anti-tumor drugs or generate particles that specifically target tumor cells, thereby offering a novel approach to tumor therapy.^{6,63}

3.1.3. Platelet-derived miRNAs as diagnostic and therapeutic targets

Platelet-enriched miRNAs have been identified as potential biomarkers for tumor diagnosis and treatment. These miRNAs regulate tumor proliferation, metastasis, and

immune evasion, thereby making them attractive targets for therapeutic intervention.⁶⁴

3.1.4. PF4 as a therapeutic agent

PF4, a chemokine stored in platelet α -granules, has been shown to inhibit the proliferation of LSCs by signaling through the low-density lipoprotein receptor. Recombinant PF4 has been proposed as an adjuvant therapy to prevent AML relapse by targeting chemotherapeutic-resistant LSCs.^{24,65}

3.2. Managing thrombotic complications in leukemia-associated thrombocytopenia

3.2.1. Risk stratification

Thrombocytopenia ($PLT < 50 \times 10^9/L$) complicates the use of anti-coagulants; yet, leukemia patients remain at high thrombotic risk due to tissue factor, expressing blasts, hypercoagulable microparticles, and cytokine-driven endothelial activation. Low-molecular-weight heparin is preferred for prophylaxis; however, dose reduction or interruption may be needed when PLT falls below $30 - 50 \times 10^9/L$. Moreover, risk assessment models, such as Khorana Score and CATS score, help in identifying high-risk patients who may still benefit from prophylactic anti-coagulation despite thrombocytopenia.^{42,43}

3.2.2. Individualized therapy

For active bleeding, prophylactic platelet transfusions (goal $PLT \geq 20 - 30 \times 10^9/L$) are prioritized, while therapeutic anti-coagulation is reserved for confirmed thrombosis. Direct oral anti-coagulants, such as apixaban, are increasingly used in stable thrombocytopenic patients ($PLT \geq 30 - 50 \times 10^9/L$) due to a lower bleeding risk compared to warfarin. Catheter-related thrombosis may require line removal and a short-course anti-coagulation if PLT falls below $20 \times 10^9/L$.⁶¹

Table 2. Key mechanisms and therapeutic strategies in platelet-cancer interactions

Mechanism/Strategy	Description	References
Platelet activation and tumor cell protection	Platelets form a protective shield around CTCs, facilitating metastasis.	5
PDGF signaling	PDGF promotes tumor proliferation, angiogenesis, and EMT.	20
Platelet-derived bioactive molecules	TGF- β 1 induces drug resistance in AML, while PMPs enhance Ara-C cytotoxicity.	20,21
Targeting platelet-cancer interactions	Biomimetic liposomes and anti-platelet agents inhibit platelet-tumor crosstalk.	6,58
Engineered platelets	Engineered platelets deliver anti-tumor drugs or target tumor cells.	63
Platelet-derived miRNAs	miRNAs regulate tumor proliferation and metastasis, serving as therapeutic targets.	64
PF4	PF4 inhibits LSC proliferation by targeting LDLR, preventing AML relapse.	65

Abbreviations: AML: Acute myeloid leukemia; CTCs: Circulating tumor cells; EMT: Epithelial-mesenchymal transition; LDLR: Low-density lipoprotein receptor; LSC: Leukemic stem cell; PDGF: Platelet-derived growth factor; PF4: Platelet factor 4; PMPs: Platelet-derived microparticles; TGF- β 1: Transforming growth factor-beta 1.

3.2.3. Emerging strategies

PF4 shows promise in neutralizing heparin-like molecules on leukemia cells, thereby reducing thrombosis without worsening thrombocytopenia. In addition, PAR-1 antagonists, such as vorapaxar, may inhibit thrombin-mediated platelet activation while preserving hemostasis. PF4/heparin antibody testing may help in identifying heparin-induced thrombocytopenia-like thrombosis in leukemia patients following chemotherapy.⁶⁵

4. Conclusion

Platelets play a multifaceted role in cancer and leukemia, influencing tumor growth, metastasis, and drug resistance. This review summarizes the changes of different platelet parameters in patients with AML. Recent advances in understanding these mechanisms have opened new avenues for therapeutic intervention. Targeting platelet-cancer cell interactions, inhibiting PDGF signaling, and leveraging engineered platelets or platelet-derived miRNAs represent promising strategies for cancer treatment. The use of anti-platelet therapies in patients is both detrimental and beneficial, necessitating careful consideration of side effects and possible drug-drug interactions. Balancing platelets efficacy with bleeding risk is crucial, especially when using engineered platelets for drug delivery or as biomarkers of therapeutic response. Cancer-related biomarkers may provide predictive insights into leukemic patient's response and need for such therapy. Combination therapy using anti-platelet agents and chemotherapy may enhance therapeutic efficacy by minimizing resistance. Existing evidence indicates that therapeutically targeting platelets in cancer offers benefits but also carries an increased risk of thrombotic events. Further research is needed to translate these insights into clinical applications, offering hope for improved patient outcomes in the future.

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Conflict of interest

The authors declare that they have no competing interests.

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