D J Med Sci 2023;9(3):142-149
doi: 10.5606/fng.btd.2023.135

Review

Platelet mediated cancer modulation: A comprehensive review from biological mechanisms

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ABSTRACT

Deciphering the molecular details of platelets' interactions with cancer cells is crucial, as evidenced by their identification as active participants in the metastatic cascade. This information not only improves our understanding of the complexity of cancer biology, but it also points to possible directions for therapeutic intervention. Targeting and identifying the important molecular actors in the interactions between cancer and platelets presents a possible avenue for novel cancer therapies. Intriguing topics for more research include the effect of platelets on the immune system and their possible role in cancer cells' immunological evasion. Future approaches to cancer immunotherapy may be reshaped by the intricate interactions between platelets and the immune system. Comprehending the intricate roles played by platelets in the development of cancer is becoming more and more important as personalized treatment gains traction. Therapeutic approaches take on a new dimension with the potential to incorporate platelet regulation into cancer therapy regimens. Nevertheless, in order to further our understanding of the relationships between platelets and cancer, future research should include other factors, such as perinatal and prenatal impacts. This review highlights the importance of platelets within the framework of cancer biology, providing opportunities for more research and practical use.

Keywords: Biology, cancer, medicine, platelets, treatment.

Due to their crucial role in hemostasis and thrombosis, platelet dysfunctions can lead to various diseases. The essential processes of platelet adhesion, activation, and aggregation are integral to hemostasis, and any imbalance in these processes may give rise to bleeding disorders.[1] While rare and severe platelet diseases, like Glanzmann thrombasthenia and Bernard-Soulier syndrome, are better understood, diagnosing lesser disorders of platelet function, particularly in pediatric instances, remains challenging.[2,3] Understanding neurological illnesses has also benefited from the application of platelet research.[4] Furthermore, in cancer patients, platelet count has been linked to the incidence of symptomatic venous thromboembolism.[5] Although inherited platelet abnormalities are less common, their severity necessitates special care.[6] Particularly in patients experiencing bleeding after tonsillectomy, platelet function testing has been proposed as a valuable early indicator of inherited platelet function problems.[7] Additionally, even though it can be impacted by a number of illnesses, platelet count has been linked to the risk of significant bleeding in cases of venous thromboembolism.[8] Understanding the potential for thrombosis of ventricular assist devices requires an estimation of platelet adhesion potential, which can be used to forecast the probability of thrombus development.[9] In cerebral sinus venous thrombosis, platelet-selectin has been found to be a marker for thrombocyte aggregation.[10]

Thrombocytes, another name for platelets, are tiny, disc-shaped anucleate blood cells that are essential for thrombosis and hemostasis. The ability of platelets to preserve vascular integrity and stop excessive bleeding depends on their

Received: December 03, 2023
Accepted: October 17, 2023
Published online: December 19, 2023

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Cite this article as:
Akgeyik F, Demirezen A, Erbaş O. Platelet mediated cancer modulation: A comprehensive review from biological mechanisms. D J Med Sci 2023;9(3):142-149. doi: 10.5606/fng.btd.2023.135.

structural makeup. Megakaryocytes in the bone marrow produce platelets, which are then sent into the bloodstream and circulate for 8 to 10 days.[11] Platelet ultrastructure is distinguished by its diminutive size, measuring roughly 2-4 μm in diameter, and its distinct organelles, such as alpha-granules and dense granules, which retain a range of bioactive chemicals, including adhesion molecules, growth factors, and clotting factors.[12] Actin and microtubules in particular are essential for the cytoskeletal organization of platelets, which preserves their structural integrity and facilitates their interaction with other cells and the extracellular matrix.[13] Moreover, actin, a contractile protein, is abundant in platelets and plays a crucial role in the exocytosis of platelet secretory granules.[14]

Understanding the normal physiology of platelets and diagnosing and tracking a range of hematological diseases both depend on their morphological characterization. For example, variations in the size and morphology of platelets might offer important diagnostic details in diseases like thrombocytosis and thrombocytopenia.[15] In clinical investigations, platelet markers including mean platelet volume and platelet distribution width have been assessed as markers of platelet morphology and activation.[16]

Platelets' main job is to stop excessive bleeding by aggregating blood at the site of vascular damage. Platelets do this by a number of intricate procedures that culminate in the creation of a hemostatic, such as adhesion, activation, and aggregation.[17] Platelets have been demonstrated to play a role in the prevention of pathogen growth, such as Plasmodium falciparum, the causative agent of malaria, suggesting their involvement in the immune response. It has been discovered that platelets participate in the acute-phase response and have immunomodulatory effects, suggesting their function in controlling systemic inflammation and immunological response.[18]

Through a variety of processes, platelets significantly contribute to the spread and metastasis of cancer. It has been demonstrated that the interactions between platelets and cancer cells stimulate angiogenesis, metastasis, tumor growth, and cancer-associated thrombosis.[19] Activated platelets are involved in all stages of the development of cancer, including the growth of tumors, the enhancement of invasive potentials, and the facilitation of tumor cell survival in the bloodstream.[19,20] Moreover, it has been discovered that when platelets attach to cancer cells, they quicken the release of platelet-derived angiogenic regulators, which promote angiogenesis in the tumor.[21] By comprehending the interactions that occur between platelets and cancer cells, possible methods to prevent cancer from spreading and lower the risk of cancer-related thrombosis may be found.[22]

By directly interacting with cancer cells to promote tumor cell survival, proliferation, and invasion, platelets have also been linked to the development of tumor metastasis.[23] Platelets have been demonstrated to aid in the aggregation of platelets caused by tumor cells, which disrupts cancer cell clusters and encourages the embolization of cancer cells in the microvasculature.[24] It also has been discovered that platelets have a significant impact on the development of tumors via a variety of pathways, such as the secretion of various growth factors, shielding cancer cells from immune monitoring, and mediating cancer-cell arrest in the microvasculature.[25]

Evidence demonstrating that platelets stimulate osteosarcoma cell proliferation by activating the platelet-derived growth factor receptor (PDGFR)-Akt signaling pathway has added credence to the involvement of platelets in cancer metastasis.[24] Moreover, it has been shown that during hematogenic metastasis, platelets promote initial pulmonary retention but prevent melanoma cell proliferation later on.[26]

EFFECTS OF PLATELETS ON CANCER METASTASIS

Through a variety of processes, such as sustaining tumor cell arrest in the vasculature, boosting tumor cell extravasation, stimulating tumor cell growth, and improving tumor cell contact with the extracellular matrix, platelets play a crucial role in cancer spread.[27] It has long been known that platelets play a role in the spread of cancer and that substances generated by cancer cells also activate platelets.[28] It has been demonstrated that platelets increase cancer cell survival, stimulate plasticity in cancer cells, and encourage the extravasation of circulating

cancer cells during dissemination.[29] Research has shown a link between cancer metastasis and a high platelet count, indicating that platelets may have an unidentified function in the development of tumors.[30] Moreover, platelets have been linked to metastasis by encouraging the development of cancer spheres that express tissue factor protein and metastatic markers.[31] To bolster their involvement in cancer spread, platelets are also known to help cancer cells transmigrate through the endothelium.[32] The capacity of platelets to stimulate thrombus formation and cause death in tumor cells has further demonstrated their role in cancer spread.[33,34]

THE RELATIONSHIP BETWEEN PLATELET ACTIVATION AND CANCER

Cancer metastasizes and advances due in large part to platelet activation. Platelets and cancer cells interact to produce soluble mediators and reciprocal activation, which in turn creates a milieu that supports the progression of cancer and platelet activation.[35] Tumor cell-induced platelet aggregation, which is the term for the various ways in which the primary tumor triggers platelet formation, activation, and aggregation, provides additional evidence for this connection.[36] The importance of platelet activation and platelet-cancer cell contact in cancer spread has been shown by xenograft experiments and transgenic mouse models. Furthermore, the propensity of cancer cells to stimulate platelets *in vitro*, or tumor cell-induced platelet aggregation, is a predictor of their aggressiveness *in vivo*. Tumor cell-induced platelet activation, the initial stage of cancer-induced thrombosis, or a multitude of other mediators and cytokines impact platelets both functionally and numerically when they are present. Increased platelet reactivity in patients with late-stage metastatic cancer has also been linked to platelet activation, indicating a possible function for this process in the development of cancer. Moreover, angiogenic molecules like vascular endothelial growth factor, which may aid in tumor angiogenesis and metastasis, have been related to platelet activation.[37] Furthermore, autotaxin formed from platelets and lysophosphatidic acid produced after platelet activation encourages the spread of breast cancer to the skeleton. The correlation between intratumoral platelet presence and tumor vascular shape and metastasis, as well as the involvement of platelet activation in cancer progression, provide more evidence for this relationship. All things considered, the connection between platelet activation and cancer is complex, involving a number of pathways that support angiogenesis, metastasis, and cancer growth.[38]

EFFECTS OF PLATELETS ON CANCER TREATMENT

In cancer treatment, platelets have a complex role that affects how the cancer progresses and how it responds to therapy. It has been demonstrated that the interaction between platelets and cancer cells promotes the survival and metastasis of cancer cells, making platelets crucial targets for treatment and prevention. *In vitro*, antiplatelet therapies like aspirin and ReoPro/c7E3 have shown promise in preventing the spread and progression of cancer.[39] Additionally, platelets have been linked to drug resistance in cancer cells, underlining their role in the processes of chemotherapeutic drug failure. Though research on the precise role platelets play in cancer treatment is still underway, a greater understanding of their function is necessary to establish effective therapeutic techniques for cancer care, prevention, screening, and risk assessment protocols.[40]

The effects of some drugs on platelet count have been noted in the context of cancer treatment. Tyrosine kinase inhibitor therapy, for example, has been linked to a reduction in platelet count in cancer patients undergoing chemotherapy. Thrombosis risk has been observed to rise fourfold in cancer patients, suggesting a correlation between platelet activation and the initiation, course, and outcome of cancer.[41] Poor prognosis and a higher risk of venous thromboembolism have been associated with lower platelet reactivity in cancer patients, highlighting the possible influence of platelets on the course of cancer and patient outcomes.[42]

There has also been research on the possible therapeutic uses of platelets in the treatment of cancer. Antiplatelet drugs have been suggested as potential inhibitors of this immunoevasive

response, implying a potential role for antiplatelet drugs as adjuvant therapy to immune checkpoint inhibitors in cancer treatment. For instance, it has been demonstrated that platelets stimulate programmed death-ligand 1 (PD-L1) expression by cancer cells. The usage of antiplatelet medications has been linked to a slower rate of malignant disease progression; however, new research indicates that certain medications that restrict platelets may actually hasten a patient's cancer course.[43]

Apart from their possible medical applications, platelets have also been studied for their ability to influence the hematogenous spread of lung cancer, however, the underlying processes are yet unknown. The therapeutic significance of platelet levels in cancer therapy has been highlighted by the proposal to use platelet count as a biomarker for tracking disease recurrence and treatment response in recurrent epithelial ovarian cancer treatment.[44]

EFFECTS OF PLATELETS ON THE PROLIFERATION OF CANCER CELLS

Through a variety of ways, platelets significantly contribute to the proliferation of cancer cells, which in turn promotes the spread and metastasis of cancer. It has been demonstrated that the contact between platelets and cancer cells stimulates the proliferation of cancer cells, hence boosting tumor growth and progression. According to reports, platelets secrete several growth factors that drive the growth and spread of cancer cells. They also release different angiogenic regulators that control tumor angiogenesis. After direct co-incubation with platelets, platelets have been linked to the enhancement of cancer cells' malignant characteristics, including adhesion, migration, proliferation, and invasion.[45]

ANTI-TUMOR IMMUNE RESPONSES OF PLATELETS

The capacity of platelets to augment ovarian cancer cell invasion provides additional evidence for the function they play in fostering cancer cell proliferation. This suggests that activated platelets may be responsible for tumor cell proliferation and metastasis. Furthermore, in an orthotopic mouse model of breast cancer, platelets have been demonstrated to augment platelet activation and reactivity, resulting in improved platelet function and possible consequences for cancer cell proliferation and metastasis. The capacity of platelets to induce PD-L1 expression by cancer cells, which may aid in cancer cell evasion and proliferation, is a further indication of the role of platelets in cancer cell proliferation.[46,47] On the other hand, platelets can also activate immune cells and tumor cells, triggering anti-tumor immunological responses that may support anti-tumor immunity and immune surveillance. It has been documented that platelets engage with immune cells to elicit anti-tumor responses and that both immune cells and tumor cells can activate them to modify the immunological microenvironment. Moreover, platelets have been linked to the promotion of tumor growth and metastasis through the disruption of platelet factor 4 (PF4) binding in complexes with polyanions on the cell surface. This suggests that platelets may play a role in preventing PF4-induced cell proliferation when present in the presence of platelets.[48]

The potential of platelets to affect tumor angiogenesis, tumor cell evasion of host immunity, and the production of different growth factors and immunomodulatory chemicals further support their function in influencing the tumor microenvironment and immune responses.[49] Unraveling specific tumor-promoting actions facilitated by platelets poses challenges, given that platelets not only play a role in promoting metastasis but have also been shown to influence anti-tumor immunity through various mechanisms. Furthermore, through the release of transforming growth factor-beta in the tumor microenvironment, which has the ability to suppress the anti-tumor immune response, platelets have been linked to the promotion of tumor development and angiogenesis. Platelets have been shown to protect cancer cells from natural killer cells in the blood, improve cancer cells' attachment to blood vessel walls, disrupt endothelial junctions, and stimulate angiogenesis by selectively sequestering, transporting, and releasing a number of growth factors. These mechanisms have all been shown to enhance ovarian cancer cell proliferation and promote metastasis.[50]

CANCER BIOMARKERS OF PLATELETS

Platelets have become known as possible sources of cancer biomarkers, providing information on the onset, course, and effects of treatment. Platelet protein biomarker candidates that can be used for the early diagnosis of different forms of cancer have been found in recent investigations. Furthermore, platelet-derived microparticles have proven to be promising as cancer biomarkers, offering hope for raising the accuracy of prognostic and diagnostic tests. Moreover, pulmonary hypertension brought on by pulmonary tumor thrombotic microangiopathy has been successfully treated with imatinib, a PDGFR tyrosine kinase inhibitor. This suggests that PDGFR may be a new biomarker for refractory disease in breast cancer.[51]

Platelet-derived adenosine triphosphate (ATP) and adenosine diphosphate (ADP) have been shown to enhance pancreatic cancer cell survival and gemcitabine resistance. Platelets have also been linked to the modulation of medication resistance and cancer cell survival. It has been demonstrated that the P2Y12 inhibitor ticagrelor neutralizes the survival signals that platelet-derived ATP and ADP cause in cancer cells. This suggests that platelet-derived chemicals may be used as biomarkers for both medication resistance and cancer cell survival. Moreover, it has been hypothesized that persistent platelet inhibition may, in initially cancer-free individuals, paradoxically accelerate the development of malignant illnesses, suggesting the possibility of platelet inhibition as a biomarker for the advancement of cancer.[52]

Research has indicated that platelets may impact the growth and spread of cancer cells by acting as chemoattractants, upregulating the expression of cell markers that trigger metastasis, and promoting the development of cancer spheres. The reciprocal relationship between platelets and cancer cells offers possible approaches for cancer treatments and raises the possibility that platelet-cancer cell interactions could serve as biomarkers for how well cancer treatments work.[53]

CANCER-RELATED INFLAMMATORY RESPONSES OF PLATELETS

Platelets have a major impact on the inflammatory reactions linked to cancer, which affects the disease at different phases of its development and evolution. It has been demonstrated that the interaction between platelets and cancer cells affects inflammatory processes in cancer by changing the endothelium's activation state, attracting leukocytes to tumor sites, and adjusting the inflammatory environment at the locations of primary and metastatic tumors. Diseases including rheumatoid arthritis (RA), atherosclerosis, and cancer metastasis are caused by platelets, which actively take part in inflammatory processes. By giving tumors the blood flow they need to grow and by encouraging the spread of tumor cells, platelets have been linked to the promotion of tumor formation and metastasis.[54]

Studies have shown that the non-specific inflammatory response brought on by malignant tumors is anticipated to raise platelet counts and encourage tumor growth, which will worsen the prognosis for cancer patients. Platelets have also been linked to systemic inflammatory reactions. Furthermore, lower platelet reactivity was observed in cancer patients with a poor prognosis, most likely due to ongoing activation. It also has been hypothesized that persistent platelet inhibition may, in initially cancer-free individuals, paradoxically accelerate the development of malignant illnesses, suggesting the use of platelet inhibition as a biomarker for the advancement of cancer.[55,56]

Platelets have a major impact on how cancer metabolism is modulated, which affects many facets of cancer initiation and progression. It has been demonstrated that the interaction between platelets and cancer cells affects cancer metabolism, changes the endothelium's activation state, draws leukocytes to tumor sites, and modifies the inflammatory environment at the locations of primary and metastatic tumors. Platelets have been associated with the promotion of both tumor formation and metastasis, as they stimulate the metastasis of tumor cells and provide the necessary blood flow for tumor growth. Studies have linked platelets to systemic inflammatory responses, showing that

the non-specific inflammatory response brought on by malignant tumors is anticipated to raise platelet counts and encourage tumor growth, both of which worsen the prognosis for cancer patients.[57,58]

Studies have shown that platelet alterations allowed for the differentiation of patients with early-stage cancer from healthy individuals, suggesting the potential of platelet-derived molecules as biomarkers for cancer diagnosis and progression. Platelets have also been identified as potential sources of cancer biomarkers. It has been demonstrated that platelets transmit different proteins and RAs into the tumor cells and surrounding environment, which stimulates tumor growth and metastasis. These findings raise the possibility that platelet RA profiles could be used as diagnostic biomarkers for biological processes linked to cancer.[59,60]

In conclusion, this comprehensive exploration of the interactions between platelets and cancer cells has shed light on the intricate dynamics that govern their relationship. The findings presented herein underscore the pivotal role of platelets in various stages of cancer progression, from initiation to metastasis. The molecular insights gained from this analysis provide a foundation for understanding the underlying mechanisms of platelet-cancer interactions. The discovery that platelets are involved in the metastatic cascade emphasizes how important it is to analyze the molecular interactions between different biological components. This information not only helps us better grasp the nuances of cancer biology, but it also suggests possible targets for treatment. Novel therapy approaches may be made possible by identifying and addressing important molecular actors in the interactions between platelets and cancer. Moreover, the influence of platelets on the immune system and their possible function in immune evasion by cancerous cells provide opportunities for additional immunological research. Future studies in this fascinating field of platelets and the immune response hold great promise for novel discoveries that could revolutionize cancer immunotherapy. It is becoming more and more important to comprehend the subtle roles that platelets play in the development of cancer as we move toward a time of individualized medicine. Therapeutic approaches could take on a new dimension with the potential to incorporate platelet regulation into cancer therapy regimens. Future research must, however, go further into the intricacies of platelet-cancer relationships, examining other variables like perinatal and prenatal effects. Understanding the molecular nuances of the interactions between platelets and cancer has the potential to advance our knowledge of how cancer progresses as well as the creation of focused treatment strategies.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Provided the idea, concept, authors and extensive literature review of this comprehensive review: F.A., A.D.; Has supervised and critically reviewed this article with his pioneering ideas and opinions: O.E.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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