JCOMS eISSN:2783-3127 https://journalofcoms.com

Journal of

Current Oncology and Medical Sciences

Vol. 4, No.2

Review Free Access

Exploring the platelet and cancer cell interaction in metastasis targeting

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Abstract

Platelets are small anucleated cell fragments that ensure the stopping of bleeding. In blood metastasis of cancer, Platelets are essential. One of the most important aspects of cancer metastasis is the interaction between platelets and circulating tumor cells. Platelets are involved in cancer spread and constitute a hazardous collation with the cancer cells. There are various factors involved in hemostasis and thrombosis, which can be activated by several cancer-related stimuli, including extracellular matrix (ECM), adenosine diphosphate (ADP), and Toll-like receptors (TLRs). Furthermore, it has been previously published that platelets build up inside the main tumors, producing growth factors that encourage tumor growth and angiogenesis. Additionally, tumor cells can interact with platelets through aggregation, further protecting cancer cells. Platelets interact both functionally and physically with different types of tumor cells via integrin and other surface receptors. Platelet integrin's primary function is to maintain platelet adhesion and aggregation at vascular damage sites. Pharmacological treatments that target integrin have been shown to effectively inhibit experimental metastasis. This review paper summarized the recent advances and progress of mechanisms in platelet activation and its interaction with cancer cells in metastasis.

Keywords: Platelets, Cancer cells, Tumor, CTCs, Immune cells

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Receive: 2024.2.15, Accepted: 2024.4.18

Introduction

Platelets are small fragments that are derived from megakaryocytes in bone marrow. Circulating in the blood, platelets not only maintain hemostasis but also play a vital role in cancer progression and metastasis (1) The interaction between platelets and cancer cells promotes cancer metastasis (2). One aspect of this interaction includes Circulating Tumor Cells (CTCs) (3). CTCs are cancer cells that separate from the primary tumor and enter blood circulation (4). Platelets bind to these CTCs and form a protective shield around them (5). This protective shield protects the CTCs from immune cell detection and helps in their dispersal to distant tissues. The interaction between CTCs and Cancer metastasis is observed in different types of cancer including lung cancer, colon cancer, and breast cancer. During cancer progression, a small number of CTCs also invade nearby tissues by extravasation process thus contributing to tumor angiogenesis (6).

Platelets are disc-shaped blood cells, which consist of three types of granules, Lysosomes, Dense granules, and Alpha granules. Alpha granules are present in abundant and store various factors such as ADP/ATP, Fibrinogen, Extracellular Matrix (ECM), and coagulation factors. Platelets release these growth factors and molecules that stimulate angiogenesis, which promotes the formation of new blood vessels around tumors and provides them with essential nutrients and oxygen to grow and spread. Cancer cells also can activate platelets during Cancer metastasis. Activated platelets and the release of various growth factors enhance pro-thrombotic events. 25-30% of thrombotic events are cancer-related (7). Cancer patients encounter an increased occurrence of both arterial and deep vein thrombosis. Activated platelets also release clotting factors that lead to the formation of blood clots within the blood vessel during cancer (8).

Platelets not only contribute to cancer metastasis but can also be used to target cancer cells that are bound with the platelets, to treat cancer (9). Platelets integrin's primary role is to maintain platelets aggregation and adhesion at the vascular damage site. Targeting integrin has been shown to inhibit experimental metastasis. In this review paper, we summarize the role of platelets in different steps of cancer progression including cancer metastasis, angiogenesis, and platelets-associated thrombosis development during cancer and the development of platelets-based target therapies to treat cancer (10).

Interaction between cancer cells and platelets

The interaction between platelets and cancer cells initiates when a particular molecule such as chemokines is released by cancer cells (11). These molecules will function as a signal that will attract platelets to the tumor microenvironment (12). A type of chemical gradient is generated by these molecules that will direct platelets to the tumor site (13). Interaction of cancer cells and platelets also occurs by immediate receptor binding or by bridging of receptors by Protein (14). For instance, one platelet receptor engaged in Cancer progression is the CLEC-2 receptor that in certain cancers binds with podoplanin. Podoplanin that are present on tumor cells interact with the CLEC-2 receptors and leads to the activation of platelets that leads to tumor growth and metastasis. However, platelets can also indirectly activated by releasing several proteins and growth factors such as VEGF and PDGF that stimulates tumor growth and leads to cancer progression. Different integrins involved in cancer and platelet interaction includes αIIbβ3, αvβ3, α5β1, α6β1 and αvβ5 that bind specifically to their ligand fibrinogen, vitronectin, fibronectin, laminin and vitronectin respectively. Although, the receptor αIIbβ3 integrin plays a significant role in Cancer metastasis. It mediates the interaction between Cancer Cells and platelets by adhesive proteins (such as fibrinogen and von Willebrand Factor). The receptor αIIbβ3 goes through structural changes after activation by interaction with platelet stimulants such as ADP, collagen, thrombin, etc. (15). The receptor αIIbβ3 shows an increased binding attraction to ligands (including fibrinogen and WF) in its active form. By facilitating the cancer Cell and Platelets aggregate's arrest in the endothelium, the receptor alphaIIbbeta3 also supports the arrest of cancer cells in vessels (16). Platelets and cancer cells interaction is a very diverse process that leads to cancer metastasis.

Progression of cancer by platelets surface receptors

Platelets surface receptors are a type of proteins that are present on the membrane of platelets and promote the

interaction between the platelets and cancer cells. Various platelets surface receptors include GPIbα, GPVI, P-selectin and GPIb-IX-V. Among them GPVI and GPIb-IX-V are platelets surface receptors that participate in maintaining hemostasis, also imply the interaction among cancer cells and platelets (17). They also contribute a vital role in encouraging the Extravasation and the arrest of Circulating Tumor Cells (CTCs) which are facilitated ultimately by the progression of metastasis by adhesion proteins. GPVI is a vital receptor for fibrin and collagen so; it facilitates the adhesion of platelets at the Injury site. In vivo experiments performed on lung carcinoma and melanoma that lack GPVI receptor in mice, show a 45% visible decrease in tumor (18). The experiment performed on mice with cancer with defective GPIb-IX shows a 14% decrease in metastatic foci. Although these receptors on platelets are involved in cancer metastasis only, they are not involved in Primary tumor growth. The activation of the platelets and adhesion of platelet-cancer cells is also facilitated by the interplay among platelet and integrin. Integrin behave as a receptor that interplay with the ligands that are present on the surface of both CTCs and platelets and thus contributes to their adhesions. On the other hand, selectin can also contribute to the adhesion between CTCs and platelets by promoting the interplay among CTCs and platelets. When platelets are activated they express P-selectin upon them, that binds to its ligand present on the CTCs and thus contribute to the adhesion between CTCs and platelets. The range of interaction among cancer Cells and Platelets does not depend upon a single receptor-receptor pairing (19).

Platelets role in tumor angiogenesis

After attaining a specific size, tumor cells have to initiate angiogenesis, in which the tumor receives additional growth factors and nutrients that are necessary for tumor cells to differentiate and spread into different parts of the body. During Tumor angiogenesis, new blood vessels at the growing tumor site are formed by the lining up of epithelial cells that are attracted by various growth factors that are released in the tumor microenvironment by platelets and lead to the formation of new capillaries and arteries (20). Platelet α-granules are the main site for storing various factors that maintain angiogenesis and hemostasis at the same time in the tumor microenvironment. When platelets are activated, they release α-granules that contain various growth factors that initiate angiogenesis, such as Vascular Endothelial Growth Factor (VEGF) and Pro-angiogenic factors; epithelial cells and some anti-angiogenic factors such as endostatin and thrombospondin-1 are also released. The complex interaction among pro-angiogenic and anti-angiogenic leads to the formation of pro-angiogenic and anti-angiogenic microenvironment respectively. This interplay contributes to both the angiogenesis of tumor for progression of cancer as well as understanding of these anti-angiogenic factors can be used to inhibit cancer. Based on stimuli that platelets receive from the external environment platelets can particularly secrete various factors to initiate or prevent the development of blood vessels in the developing tumor microenvironment (21). For example, ADP-induced platelets can secrete VEGF but cannot release end statin; meanwhile, thromboxane induces platelets to secrete endostatin rather than VEGF (22). ADP secretes VEGF in tumor microenvironment that is a pro-angiogenic factor and it is released to promote tumor progression. Thromboxane releases endostatin in tumor microenvironment that is an anti-angiogenic factor and it is released to limit tumor vascularization.

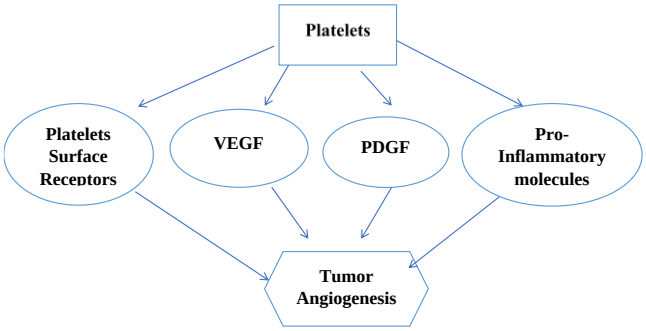

Figure 1. Demonstrates that various growth factors and receptors released by platelets induce angiogenesis.

Platelets-induced release of Angiogenic factors

Platelets are also activated by various cancer cells, these activation initiates the secretion of several substances such as Angiogenic factors (23). These are the substances that encourage the formation of new blood vessels (24). Currently, it has also been developed that Stimulated Emission Depletion (STED) imaging can also be used to demonstrate platelets-induced release of various growth factors that initiate

angiogenesis more accurately. Depending upon the external stimuli, platelets can increase or suppress the angiogenesis of tumors by particular secretion of pro or anti-angiogenic factors (25). Factors like inflammation, hypoxia and shear stress act as external stimuli and contribute to the release of pro-angiogenic and anti-angiogenic factors. For example, if inflammatory signal is released by external environment, it will promote the release of cytokines and growth factors which lead to the release of VEGF that in result encourage angiogenesis. Although factors like nutrient availability and pH can also contribute to the secretion of pro-angiogenic and anti-angiogenic factors. Platelets selectively intake and store VEGF in the α-granule that is released by a tumor in the tumor microenvironment. However, tumors can also activate the secretion of VEGF by platelet, thus maintaining the level of VEGF in the tumor microenvironment that significantly initiates angiogenesis in the tumor microenvironment (26). Various other angiogenic factors are also released by platelets including Fibroblast Growth Factor (FGF) and Platelets Derived Growth Factors (PDGF) (27). FGF promotes the migration of epithelial cells role and PDGF regulates the growth of muscle cells both of them are essential for the formation of new blood vessels in tumor angiogenesis. The Pro-angiogenic environment is established by these angiogenic factors that will encourage cancer progression (28).

Platelets encourage circulating tumor cells dispersal

Platelets not only assist the growth of the primary tumor; however, but they also play an important role in metastatic progression. They attach to the surface of Circulating Tumor Cells and act as a shield (29). This shield of platelets serves as a camouflage for CTCs, due to which CTCs are very less visible to immune cells. Platelets also make a cloak that surrounds CTCs, deterring various immune cells from identifying them as a foreign particle. This interplay prevents the CTCs from immune system detection and recognition. Platelets aid these CTCs when they encourage vasculature, which in turn assists the CTCs in the bloodstream and dissemination of CTCs to different tissues. CTCs arrest could be passive or active. During Passive arrest CTCs move in the bloodstream till they attach to the platelets without any active contribution by CTCs. Passive arrest includes the blockage of CTCs due to the formation of platelets, fibrinogen, and tumor cells in small blood vessels (30). On the other hand, active arrest includes the process in which platelets actively identify and binds to CTCs and contributes to the development of aggregate that promotes tumor cells survival. Active process refers to the transfer of tumor cells from the primary tumor into the bloodstream.

Platelets also act as a framework by covering the upper layer of circulating tumor cells that aid CTCs to move freely in the bloodstream. Thus, platelets are core regulators of tumor cells. When Platelets are activated by tumors they provide various growth factors to the CTCs. Label et al. indicated that the secretion of TGF-β (Transforming Growth Factor) by platelets and cancer cell-platelets interaction initiates metastasis by stimulating various signaling pathways (31). When these pathways are activated, they trigger Epithelial Mesenchyme Transition (EMT), which is the process in which tumor cells having epithelial phenotype lose their various features. EMT maintains the transfer of primary tumor cells into the bloodstream, which leads to the dissemination of tumor cells to distant tissues (32). Different detection methods that are used to detect CTCs include PCR, immunocytochemistry, flow cytometry and several approaches based on microfluidics.

Platelets-induced cancer cell reconfiguration

EMT (Epithelial-Mesenchymal Transition) is a vital developmental program that also takes place in cancer metastasis (33). Epithelial cancer cells create a Key Mesenchymal cell layer via the Epithelial-Mesenchymal Transition and alter their shape as they drop connection with the basement membrane. The activity of Epithelial Mesenchymal Transition can be invertible and epithelial cells can be converted into mesenchymal cells and vice versa. Epithelial Mesenchymal Transition is also assisted by components of the Extracellular Matrix, cells obtained from the microenvironment of tumor and immune cells (34). Several factors also participate in controlling Epithelial-Mesenchymal Transition including Transcription Factors, Hepatocyte Growth Factors, and Transforming Growth factors (TGF). TGF discharged by alpha granules of activated platelets transforms Tumor cells into pro-metastatic EMT (35).

TGF is activated by the interplay among platelet-cancer cells and platelets are referred as a main source for TGF-β. TGF derived from platelets in cancer cells, leading to the enhanced cancer metastasis and Epithelial-Mesenchymal Transition phenotype in vivo. Altogether, these findings show a direct linkage between EMT development and TGF released from platelets (36). However, TGF-β also activates Smad signaling pathway that promotes EMT. Interaction of TGF-β with tumor cells receptor leads to the activation of various Smad proteins that form complexes and move in to the nucleus where they promote the expression of certain genes that leads to the Epithelial Mesenchymal Transition. ECM components that are released by tumor microenvironment or tumor are recommended for being involved in Epithelial-Mesenchymal Transition. Cathepsin belongs to a group of protease enzymes that are released by various tumor cells. Cathepsin is primarily restrained in lysosomal vesicles and released as soluble enzymes that split ECM components near cancer cells. Cathepsin also triggers platelet aggregation and assists interplay of Epithelial-Mesenchymal Transition-Cancer Cells (5).

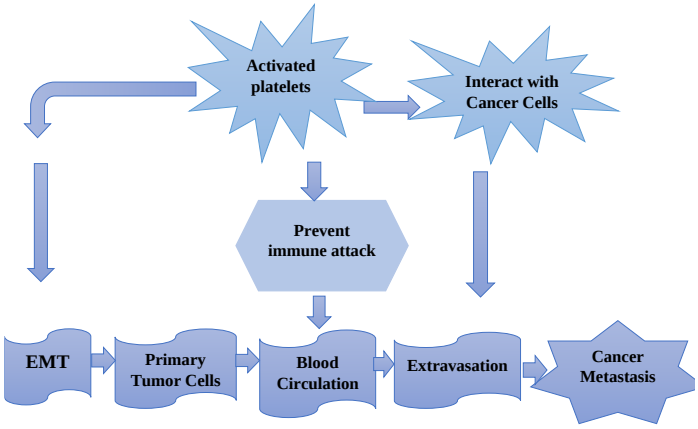

Figure 2. Schematic representation of activated platelets interaction with cancer cells as well as initiate EMT and both of them induce cancer metastasis.

Thrombosis in cancer and tumor-induced platelet activation

Patients who suffer from cancer often face blood-clotting problems in the various blood vessels that include both arteries and veins. The development of thrombosis in cancer patients is another major reason for mortality. Thrombosis elevates the possibilities of cancer metastasis and progression that have been observed in lung and breast cancers and it is associated with poor survival (37). There are more chances of the development of thrombotic complications in cancer patients in contrast to patients without cancer. Meanwhile, the accurate procedure for the development of thrombosis in cancer is not completely understood. However, more than one-fourth of the patients who suffer from cancer have been diagnosed to have relatively high levels of platelets in their blood (38).

Platelets that are activated by tumor cells can lead to the development of thrombosis (39). Tumor cell-induced platelets activation and aggregation (TCIPA) is detected in fibro-blastoma. The main controller of this pathway is cancer cell Resident Podoplanin (PDPN). High expression of Podoplanin increases the chances of thrombosis development during cancer. Podoplanin expression in epithelial cells can also increase the risk of thrombotic complications. (40). When platelets are indirectly activated by cancer cells they trigger the epithelial cells to secrete various proteins and growth factors that provide an area for platelets attachment and development of thrombosis (41). In cancer patients development of Neutrophil extracellular trap (NET) is mostly identified that as contributing to the elevated level of histone protein and other nucleosomes in the bloodstream (42). NET leads to the development of tumor-induced thrombosis and dysfunction of various organs (43). In pancreatic cancer, NET is regarded as the main contributor to the development of cancer. Elevated concentrations of TF were observed in these patients (44). These findings show that platelets lead to thrombotic complications among cancer patients (45).

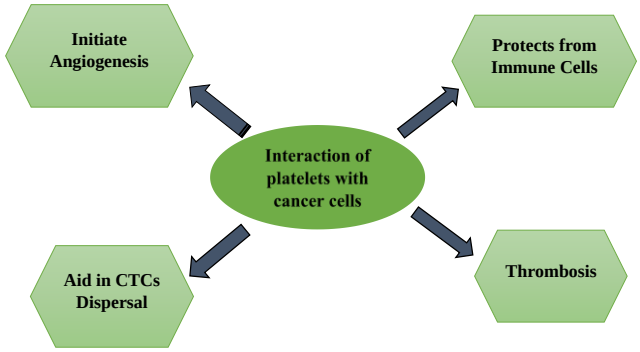

Figure 3. Diagrammatic representation of the interaction between platelets and cancer cells that induce angiogenesis,

protection from immune cells, CTCs dispersal, and thrombosis in tumor microenvironment.

Effect of platelets on anti-tumor immunity

Platelets perform very diverse roles in anti-tumor immunity activity (46). Among all cancers, only a small number of cancer cells form metastatic foci. Natural Killer (NK) cells are the immune cells that can remove cancer cells from blood circulation. Platelets are the only blood cells that interact with the cancer cells and form a protective shield around them that prevents them from immune cell detection and recognition (47). Platelets also protect tumor cells from anti-tumor immunity by the release of various molecules that are immunosuppressive in their action (48). These immunosuppressive molecules include Transforming Growth Factor Beta (TGF-β) which can suppress the anti-tumor activity of various immune cells including NK cells as well as T cells (49). TGF-β inhibits NK cells and T cells activity by inhibiting their proliferation and suppressing of cytotoxicity that leads to the immune tolerance and cancer progression. Platelets also can suppress the activity of dendritic cells that are crucial for regulating various immune responses against tumor cells (50). Platelets suppress the activity of dendritic cells through various mechanisms such as by direct physical interaction with dendritic cells that suppress their maturation and by releasing various immunosuppressive molecules such as TGF-β and PGE2 that inhibit the function of dendritic cells and their capability to activate T cells. Platelets not only play an important role in tumor angiogenesis but they also maintain the integrity of the tumor, thus preventing hemorrhage of the tumor (51). By regulating the integrity of the tumor, platelets decrease the effect of the immune system on the tumor. To survive in circulation Circulating Tumor Cells (CTCs) need to protect themselves from immune system recognition and killing mechanism (52).

Platelets protect tumor cells from NK cells

Natural Killer cells play an important role in Antitumor immunity activity (53). Platelets that are activated along with fibrinogen shield the tumor cells and protect them from Natural killer cells by the formation of a barrier that protects the tumor cells from NK cells (54). This protective shield makes it more difficult for NK cells to affect tumor cells. Moreover, various immuno-suppressive molecules released by platelets also diminish the activity of NK cells (55). A decrease in the level of Natural killer cells will enhance metastasis of cancer. It has been shown that the platelets induce metastasis of the tumor within 1 hour after the tumor has entered the blood circulation meanwhile Natural killer cells employ their antitumor immunity activity one and sixth hour after tumor extravasation. In comparison to any other blood cells, platelets can keep a large quantity of Transforming Growth Factor and secrete it into the microenvironment of the tumor during metastasis and progression of cancer. It is demonstrated that the release of this growth factor by platelets can lead to the down-regulation of Natural Killer cells, thus inhibiting their antitumor immunity (56). As platelets also promote tumor angiogenesis it is difficult for NK cells to eradicate tumor cells (57).

Drugs against tumor microenvironment

Different types of receptors and cytokines present in the tumor microenvironment take part in cancer metastasis (31). Many elements that contribute to tumor metastasis assemble in the tumor microenvironment making cancer treatment more difficult. The cancer resulting from cancer-platelets interaction explains the fact that platelet is the main factor that promote cancer by promoting angiogenesis, CTCs dispersal and protection from immune system. Thus, targeting platelets will be the best strategy to overcome the cancer progression resulting from cancer-platelet interaction. For the molecules that are over-activated in cancer, various drugs have come into being to target them (58). When it is revealed that the platelets in cancer contribute to the suppression of the immune system, an attempt to make a drug that will induce immune responses in cancer was started (59). The best strategy to inhibit cancer metastasis that is initiated by cancer-platelet interaction is to use drugs that suppress the amount of platelets in tumor site as well as use of chemotherapeutics that will use to treat cancer. The microenvironment of the tumor helps us to understand how tumors gain resistance against any antitumor drug. This concept is referred to as "*de novo* mechanisms" that show how a change in the microenvironment of a tumor can give tumor cells a new pathway to overcome the effect of antitumor drugs (60).

Table 1. Some platelets targeting drugs that can be used along chemotherapeutics in different types of cancers.

Cancer Cell type	Platelets targeting Drugs	Chemotherapeutics
Human lungs cells	Aspirin	Doxorubicin hydrochloride (Dox)
Breast cancer cells	Trastuzumab	Monomethyl auristatin E (MMAE)
Human leukemia	Hydroxyurea	Epidoxorubicin imaging Agent CY5 Carboxyfluorescein di-ester
Human lymphoma cells	Rituximab	Doxorubicin (Dox)
Human colonic carcinoma	Oxaliplatin, Bevacizumab	Tumor necrosis factor-Related apoptosis-inducing Ligand (TRAIL)
Human triple negative Breast cancer cells	Aspirin	TRAIL

Platelet is a main target to overcome cancer metastasis

Platelets and cancer cell interaction plays a major role in promoting CTCs dispersal to distant tissues, angiogenesis, suppression of anti-tumor immunity activity, and eventually cancer metastasis, so platelets are a main target to overcome cancer metastasis (61). Metastasis of cancer is the major cause of death in cancer patients. Clinical studies have shown that tumor cells that are surrounded by platelets are less affected by chemotherapy. Furthermore, platelets also encourage Epithelial-Mesenchymal Transition in tumor cells that have chemoresistance (62). These studies show that to overcome cancer metastasis effectively and completely targeting platelets will be the best strategy. Inhibition of platelets in the clinical model shows that it inhibits the metastasis of cancer. It is also demonstrated that attachment of the platelets with the cancer cells, prevents them from immune system recognition and attack, thus enhancing cancer metastasis (63). After studying the vital role of platelets in cancer metastasis, it was demonstrated that targeting platelets will be the best strategy to treat platelets-induced cancer (64). Various drugs that can suppress platelets can be used. These drugs can be transferred directly to the tumor microenvironment. Although many drugs that can target platelets also have tumor suppressive activity (65).

Platelet suppression by Aspirin and Integrin as a therapeutic target in cancer metastasis

Aspirin is a common drug that is used to overcome fever and pain. Aspirin also can suppress platelets, therefore it is used by patients with cardiac and thrombotic complications (66). Platelets-induced cancer metastasis can also be reduced by the use of aspirin. It has also been shown in clinical experiments the growth and development of cancer is reduced by aspirin. Aspirin function by suppressing the formation of various chemicals such as prostaglandins that contributes to aggregation and activation of platelets. By suppressing the amount of these chemicals, aspirin assist in preventing platelets to adhere together and form clots. Tamoxifen is another drug that is used in breast cancer as an antiestrogen (67). It is demonstrated that tamoxifen suppresses metastasis of cancer that is induced by platelets. Tamoxifen inhibit platelet activation by altering the secretion of various angiogenic factors by platelets and by suppressing the expression of various adhesion molecules on the surface of platelets. Different types of integrins are expressed by platelets, such as α6β1which facilitate the binding with collagen. Direct interplay among platelets and collagen is regulated by GPVI and α6β1 integrin. Studies have shown that the interplay among platelets and cancer cells that contribute to cancer metastasis is terminated by blocking α6β1 integrin (68). The blocking function of integrin with the help of antibodies will suppress the interaction between cancer cells and platelets. Suppression of the function of integrin by antibodies does not affect hemostasis and number of platelets in mice. This antibody does not have any effect on cancer metastasis when introduced into platelet α6β1 deficient mice. Integrin α6β1 is also found in endothelial cells and pericytes, where they impart tumorigenic effect to the microenvironment of a tumor. Inhibiting integrin α6β1 will suppress the different types of integrin-facilitated cancer metastasis,

thus inhibiting the function of this integrin is one of the best strategies against cancer (69). There are several integrin inhibitors involved in suppressing cancer metastasis in vivo models such as Cilengitide, Volociximab and ATN-161. Cilengitide is an integrin inhibitor that targets αvβ5 and αvβ3 and is a promising strategy in inhibiting clinical models by inhibiting the ability of the primary tumor cells to spread at distant tissues. Volociximab is a type of anti-angiogenic agent that inhibits the α5β1 integrin. In clinical models it inhibits metastasis by preventing the development of angiogenesis. ATN-161 is an integrin inhibitor that also inhibits α5β1. In clinical models it inhibit metastasis by effecting growth of tumors, angiogenesis and dispersal of CTCs to distant tissues.

Platelets-dependent drug delivery to target primary tumor and platelets carriers for cancer therapy

Platelets also can take chemotherapeutics to tumor cells at two sites, in the microenvironment of the tumor and blood circulation (70). For a long period, platelets were used as blood clotting agents in blood circulations. There are various ways to treat cancer but one of the best ways is to treat cancer by using platelets as a carrier for the transfer of chemotherapeutics (71). Many factors make the platelets a potential carrier to deliver the drug in the tumor microenvironment (72). Its example is Doxorubicin, which is filled with platelets by the using general incubation method. This platelets-loaded Dox has been shown to inhibit the growth of cancer in clinical models (73). The platelets-based carrier has also been shown to inhibit tumors in mouse models (74). Entirely it is demonstrated that the use of platelets as a carrier can expertly transfer chemotherapeutics to the tumor microenvironment and inhibit platelets-induced cancer (9). Additionally, Yap et al. show that there is no side effect of using platelets-based carrier on various functions of the organs. There is also research on using platelets as a carries to transfer antibodies to be used as immunotherapeutic in which antibodies are loaded into the membrane of platelets (75). In clinical models, antibody-loaded platelets have been shown to inhibit the growth of tumors (76).

Conclusion

Interaction between Platelets and cancer cells plays a very important part in cancer metastasis and progression. Platelets release various growth factors that help CTCs to grow and spread into the different parts of the body and form aggregates with them that protect them from the immune system. Cancer cell-induced activation of platelets increases the risk of developing thrombosis. Platelets also protect cancer cells from antitumor immunity activity by forming a protective layer around tumor cells that acts as a shield and prevents them from immune cell detection and killing mechanisms. Thus, targeting interaction between platelets and cancer cells is the best strategy to overcome cancer metastasis as well as cancer-induced thrombotic complications. Treating strategies include specifically targeting primary tumors, CTCs, and circulating malignancies. Among targeting strategies one of the best strategies is to use platelets as a carrier to deliver chemotherapeutics to tumor microenvironment. Meanwhile, delivery of the chemotherapeutics using platelets gives us an excellent potential to treat platelets-induced cancer but there are still many challenges that need to be controlled.

Acknowledgment

We would like to thank the Khawaja Fareed University of Engineering and Information Technology Institute of Biological Sciences students who participated in the data collection and were not listed in the author list.

Author contribution

MR, **MZ**, and **SMAB** design the study. **MR**, **MZ**, and **HMS** wrote the first draft of the manuscript. **MKI** wrote a section of the manuscript. All the authors contributed to the article and approved the submitted version

Conflict of interest

The authors report no conflict of interest.

Funding

There is no funding agency involved in this research.

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