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The Connection between Platelets and the Development of Cancer

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Abstract:

Platelets are tiny (2-4 m), anucleate, hematopoietic cells that are discharged into the circulation by bone marrow megakaryocytes. Platelets were formerly thought to be the main agents of hemostasis and thrombosis. Armand Trousseau established a strong link between thrombosis and cancer in 1865. The hypothesis that platelets play many roles in the development of malignancies and in cancer-associated thrombosis is thus supported by a wealth of clinical and experimental data.The functions of tumor-educated platelets (TEPs) in the development of cancer, from primary tumors to subsequent metastatic breakouts, will be covered in this study.

INTRODUCTION

Platelets are tiny (2-4 m) anucleate hematopoietic cells that are discharged into the circulation by bone marrow megakaryocytes. Circulating platelets in healthy people range in number from 150 to 350 109/L. It was recently shown in a mouse model that intravascular megakaryocytes originating from extrapulmonary locations may also manufacture platelets in the lung (1). Platelets were formerly thought to be the main agents of hemostasis and thrombosis. Osler, who demonstrated the existence of "blood plaques" in white thrombi, provided the first description of the hemostatic properties of platelets in 1873. Armand Trousseau established a strong link between thrombosis and cancer in 1865 (2). The hypothesis that platelets play many roles in the development of malignancies and in cancer-associated thrombosis is thus supported by a large body of experimental as well as clinical data (3). The vast majority of circulating and ingested biomolecules, as well as those that are specific to platelets, are stored in the body's platelets. Upon activation, platelets release the biomolecules in their granules that aid in the development of cancer. Cancer and platelets interact in a genuine way. In fact, platelet count and activation state, which are essential for cancer progression, can be affected by cancer itself. The ability of cancer cells to increase platelet count is not unharmful, as evidenced by the relationship between inhibition of thrombocytosis or induction of thrombocytopenia and a reduction in tumour growth and metastasis (7, 8). Yet there is disagreement over platelets' functions in the development of tumours. On the one hand, a large body of research has shown that platelets promote the growth, angiogenesis, pro-survival signalling, and invasiveness of cancer cells.In ovarian cancer cells, for instance, Egan and colleagues demonstrated that platelet adherence and degranulation increased (9). Moreover, platelet stickiness and substances secreted by platelets seem to actively contribute to the epithelial-to-mesenchymal transformation (EMT) of cancer cells, increasing their capacity for invasion and metastasis (10). Nonetheless, a few studies have shown that platelets or platelet-derived microparticles have an anti-proliferative effect on cancer cells, as shown by the activation of cell cycle arrest, inhibition of DNA synthesis, and triggering of apoptosis, respectively (11, 12). Platelets may also be "taught" by cancer cells by altering their RNA patterns and morphologies. Many cancer forms, particularly lung, prostate, glioma, and breast carcinoma, have been linked to altered platelet RNA profiles (4–6). Best et al.'s accuracy in separating cancer patients from healthy people using RNA-seq data suggests that the recently developed idea of tumour-educated platelets (TEPs) may provide useful tools for cancer diagnosis (6). The functions of platelets and tumour-educated platelets (TEPs) in the development of cancer, from primary tumours to subsequent metastatic breakouts,

will be covered in this paper(13).

Growth, angiogenesis, and metastasis-promoting angiogenic agents in tumor development

Platelet alpha granules are particularly abundant in growth factors and mitogens like TGF (transforming growth factor), EGF (epidermal growth factor), and PDGF (14). PDGFR-mediated signaling by platelet-derived growth factors (PDGF) activates a variety of cellular processes, including cell division, growth, and proliferation. Metastatic breast tumors' growth is accelerated by PDGF, and a shorter survival time and higher degree of metastasis are linked to breast cancer patients' elevated serum levels of PDGF(15). VEGF, a growth factor essential in the stimulation of angiogenesis and vasculogenesis, is also present in platelet alpha granules. In 1974, Folkman and colleagues published the first description of tumor angiogenesis, showing that tumors can only grow to a diameter of 2 mm before they must sprout new blood vessels to maintain the diffusion of nutrients and oxygen needed for tumor growth(16).

VEGF-R promotes endothelial cell migration, proliferation, and vessel creation. Platelets contain a plethora of angiogenesis-regulating proteins in their granules, including VEGF, PDGF, TGF, EGF, angiopoietin-1, IGF-1, sphingosine-1-phosphate, and MMPs(17). Rong Li and colleagues showed that intratumoral platelets have a role in controlling blood vessel development and density, mostly via the production of VEGF and TGF(18). Therapeutic VEGF monoclonal antibodies and tyrosine kinase inhibitors have been developed. TGF, a mitogen produced with platelet activation from alpha granules, has been linked to tumor development, metastasis, and a poor prognosis(19).

TGF can function as a tumor suppressor and effectively stop the growth and proliferation of tumors and cancer cells in their early stages, but it is primarily thought to promote tumor growth and metastasis because platelets release it into the microenvironment. Direct contact between platelets and cancer cells and the release of platelet-derived TGF activate TGF(20).

Procoagulant proteins, hemostatic agents, and platelet agonists in tumor angiogenesis, growth, and metastasis

ADP, TXA2, and thrombin, three platelet agonists that certain cancer cells may produce, have all been demonstrated to cause platelet activation and to aid in the development and spread of tumors (21–22). Cho et al. showed that platelets promote the growth of ovarian cancer cells in a TGF-dependent way (24). Moreover, this team recently showed that ticagrelor inhibits the platelet ADP receptor P2Y12, which reduces ovarian tumor development by 60% compared to aspirin and by 75% compared to mice receiving a placebo (25).

Our research found that clopidogrel, another P2Y12 inhibitor, decreases pancreatic tumor development and metastasis but uses an orthotopic pancreatic cancer mouse model (26). Moreover, Simon Gebremeskel and associates demonstrated that ticagrelor's reversible suppression of P2Y12 reduces metastases and increases survival in a mouse model of melanoma (27). These results offer proof of concept for the therapeutic use of P2Y12 inhibitors like clopidogrel and ticagrelor for the prevention of tumor progression and metastasis and suggest a role for P2Y12-mediated platelet activation in encouraging tumor growth and metastasis. Moreover, it has been shown that the activation of the endothelium P2Y2 receptor by platelet-tumor cell interaction-dependent ATP release increases vascular permeability, promoting tumor cell extravasation and metastatic seeding (28). Since the 1980s, thromboxane, which is produced after platelet aggregation of cancer cells, has received attention and is positively correlated with the progression of ovarian cancer. Many malignancies, including colorectal, prostate, bladder, and non-small-cell lung carcinomas, have been shown to overexpress thromboxane ligands and thromboxane synthase. The addition of TXA2 restored tumor growth when thromboxane synthase function was inhibited, and it also triggered apoptosis (29, 30). Cancer cells have a number of functions in tumor development, angiogenesis, and invasion, including the production of thrombin after platelet activation, which is controlled by cancer cells, and thrombin release by cancer cells themselves. In several cancer cell lines, including human and mouse breast carcinomas, prostate carcinomas, and melanomas, as well as primary endothelial cells, commonly known as HUVEC (human umbilical vein endothelial cells), thrombin treatment increases cathepsin D (CD) mRNA and protein expression. The improvement of cancer cell chemotaxis and migration, as well as HUVEC matrigel tube formation, was caused in these cell lines by up-regulation of CD expression and secretion. Moreover, the use of CD-knockdown cancer cells and the pharmaceutical suppression of thrombin by hirudin both significantly slow tumor growth and metastasis (31, 32). Through the induction and interaction of MMP-9 and 1-integrin on the cell surface through a PI3K-dependent mechanism, thrombin also facilitates tumor invasion (33). Moreover, thrombin may cause EMT in SKOV3 ovarian cancer cells, which enhances the cells' propensity for invasion (34). Additionally, thrombin increases the production of VEGF and tissue factor (TF) by MDA-231 breast cancer cells, which increases the cells' ability to metastasize (35). A transmembrane glycoprotein called TF helps the extrinsic route of the body's regular blood coagulation protease cascade get started. To create an active complex that is in charge of thrombin production,

fibrin deposition, and the proteolytic activation of factors IX and X, TF can bind to factor VIIa (TF/fVIIa). Coagulation factor extravasation was seen in the tumor microenvironment, mostly as a result of increased tumor vascular permeability. According to research by Liu and colleagues, the TF produced by cancer cells and the TF-activated coagulation cascade in the tumor microenvironment are crucial for the development of tumors. A TF/FVIIa inhibitor caused growth retardation in mice treated with breast tumors, whereas doxorubicin-based prodrugs that are specifically activated by the protease activity of TF, FVIIa, FXa, and thrombin completely eliminated both the primary tumor and metastasis (36). Through the ligation of endothelial integrins v3 and 61, the deposit of the non-coagulant alternatively spliced isoform of TF into the tumor stroma induced angiogenesis. Additionally, this team demonstrated that inhibiting TF-VIIa-PAR2 signaling but not TF-initiated coagulation reduced the growth and angiogenesis of breast tumors (37). These studies show that TF is essential for tumor development and angiogenesis and that the protease activity of the coagulation cascade in the tumor microenvironment may act as an enzymatic target for chemotherapeutic pro-drugs. When platelets are activated, the platelet peroxisomes contain the platelet-activating factors (PAFs), which are then released. It has been shown that certain melanoma cell lines possess a functioning platelet activating factor receptor (PAF-R), which, via its signaling, initiates a pro-survival program. Additionally, it was shown that PAFs may increase VEGF expression in immortalized vascular cells, mostly via activating the NF-kappaB pathway and reducing p53 activity (38). Furthermore, blocking PAFR signaling with antagonists seems to limit tumor development and restrict angiogenesis in breast, prostate, colitis-associated cancer, and Kaposi's sarcoma (39–40).

The functions of adhesion proteins in tumor development, metastasis, and dissemination

Cancer cells have the ability to stimulate platelets in two main ways: indirectly via a variety of secreted substances and directly through their adherence to moving platelets. The development of cancer seems to depend on direct contact between platelets and cancer cells(41). First, the survival of tumor cells in the circulation depends on the collection of platelets surrounding them. In fact, it has been shown that in the lungs of mice, platelet-coated tumor cells and fibrinogen deposition create a physical barrier that shields tumor cells from the cytotoxic action of NK cells (42). Furthermore, the activating immunoreceptor NKG2D on NK cells was down-regulated as a result of platelet activation and subsequent release of platelet-derived TGF, which reduced their anti-tumor efficacy (43). Platelet aggregation surrounding cancer cells is crucial for both shielding cancer cells from severe shear stress in the circulation and thwarting immune attack (44). Second, it seems that platelet adhesion and degranulation are required for ovarian cancer cells to produce pro-survival and pro-angiogenic signals (45). Similar to this, Labelle et al. showed that the synergistic activation of TGF/smad and NF-kB pathways in breast and colorectal cancer cells depends on direct contact between platelets and cancer cells, followed by the release of platelet-derived TGF. The stimulation of these pathways causes greater metastasis in vivo and the development of an invasive mesenchymal-like phenotype in vitro(46). Additionally, it has been shown that the capacity of cancer cells to cause platelet aggregation, also known as tumor cell-induced platelet aggregation (TCIPA), and thrombocytopenia in mice is closely connected to their capacity to spread in vivo (47). Together, these findings show that interactions between platelets and cancer cells are crucial for the development of tumors. Few studies, however, have examined the function of platelet and cancer cell adhesive proteins in the development of malignancies as well as their potential as therapies (48).

Integrins

Karpatkin et al.'s research from 1988 showed that platelet integrin IIb3 suppression by blocking antibodies decreased colorectal and melanoma cancer cell-platelet interactions in vitro and decreased metastasis in vivo. It is possible that fibronectin and the Von Willebrand factor (VWF) interact in a way that is IIb3-dependent since the addition of RGDS inhibited the contacts between platelets and cancer cells (49). Furthermore, tumor cell integrin v3 has been shown to bind platelet integrin IIb3, mediating the contact and aggregation of cancer cells with platelets as well as promoting tumor development and metastasis in vivo (50–51).Platelet integrin 61 interacts directly with colorectal MC-38 and breast cancer AT3 cell ADAM9, according to research by Mammadova-Bach et al. that was published more recently. Interactions between platelet integrin 61 and tumor cells that are reliant on ADAM9 cause platelet activation, granule release, and the encouragement of cancer cell extravasation in the lungs (52).

Selectins and mucins

P-selection is a protein that facilitates the interaction of platelets with a variety of cancer cell lines, including colorectal, lung, breast, gastric, and melanomas. It is expressed on the surface of activated platelets and is implicated in tumor development and metastasis(53). Podoplanin (PDPN) and colon, bladder, and lung carcinomas have increased expression of P-selectin. P-selectin is the first mediator of the rolling and

anchoring of platelet-cancer cell aggregates to the endothelium, which is then facilitated by the platelet adhesive proteins GP1b, IIb-3 integrin, and VWF. Additional platelet receptors that some cancer cells can express include GP1ba, IIb-3 integrin, and v-3 integrin. (54).

The role of immunosuppression, platelet chemokines, and tumor development, angiogenesis, and metastasis

It seems that platelet chemokines are essential for the development of malignancy and immunosuppression. Since the early 1990s, attention has been focused on the role of platelet factor-4 (PF4), or chemokine CXCL4, in the suppression of angiogenesis. Angiostatic chemokine PF4/CXCL4 is released from platelet alpha granules during platelet activation(55).

Recombinant PF4 has been shown by Maione et al. to limit blood vessel growth in a dose-dependent manner using experiments on chicken chorioallantoic membranes(56). In 2004, Struyf and colleagues discovered a fresh, nonallelic variation of PF4/CXCL4 called PF4var/CXCL4L1 from thrombin-activated platelets. The two secreted forms of PF4var/CXCL4L1 seem to be a more powerful inhibitor of angiogenesis than PF4/CXCL4 and other an-giostatic chemokines, while only having a three amino acid difference between them (57). Furthermore, PF4var/CXCL4L1 inhibited angiogenesis more effectively than PF4/CXCL4 or other angiostatic chemokines, such as interferon gamma (IFNgamma), in animal models of melanoma and lung tumours (58-59).

Platelets actively contribute to the persistence of cancer cells and stop them on the vessel walls during the spread of cancer cells via the blood. Additionally, Labelle and associates showed in the lungs of mice that intravascular platelet-tumor cell microthrombi release the chemokine CXCL5/7 that recruits +CD11b+MMP9 +LY6G granulocyte cells to form early metastatic niches. Inhibiting CXCR2, which blocks the CXL5/7 receptor on granulocytes, prevented granulocyte recruitment and prevented metastatic seeding, proving that platelet-mediated granulocyte recruitment is essential for the development of metastatic niches (60).

Platelet microparticles (PMPs)

Megakaryocytes and platelets continuously discharge platelet microparticles (PMPs), which are associated with aggressive tumors and unfavorable clinical outcomes. Through a variety of mechanisms, cancer cells can activate platelets, causing them to change shape, degranulate, and produce PMPs(61). PMPs have the potential to carry bioactive lipids such as sphingosine 1 phosphate (S1P) and arachidonic acids (AA). In vitro treatment of endothelial cells with PMPs increased proliferation, chemotactic migration, and the formation of capillary-like tubes in HUVECs. In vivo injection of PMPs into the rat myocardium induced angiogenesis and stimulated post-ischemic revascularization(62).

PMPs also enhance angiogenesis, invasiveness, and metastasis in breast and lung malignancies. PMPs increased the mRNA expression of angiogenic factors such as VEGF, MMP-9, interleukin-8 (Il-8), and HGF in lung cancer cell lines and improved Cancer cells have a higher propensity for metastasis when they express platelet receptors, a process known as “platelet mimicry”(63). In vitro PMP administration increased the expression and secretion of membrane type-1 MMP, which is implicated in invasion behavior, in various breast and lung cancer cell lines. Additionally, PMPs have the capacity to introduce nucleic acids into cancer cells(64). Liang et al. showed that the transport of microRNA-223 into lung cancer cells by PMPs increased the invasiveness of the cancer cells(65). Recent research found that PMPs may invade solid tumors and spread miRNAs that inhibit tumor development. PMPs may operate in a way that is either pro- or anti-tumor, depending on the situation. The potential of PMPs to control immune cell activity allows them to also have an indirect impact on the development of tumors(66). Local macrophages seem to undergo a process of differentiation known as M2 macrophage differentiation, which has pro-tumorigenic properties. Sprague and colleagues investigated the function of PMPs in the control of adaptive immunity. (67).

CONCLUSION

During the development of cancer, platelets and cancer actually interact. On the one hand, a variety of platelet agonists, including ADP, thrombin, and thromboxane, are released by cancer cells. Additionally, cancer cells have the capacity to continuously produce MPs as a result of their oncogenic transformation. These MPs are released in the bloodstream and (i) take part in platelet activation and RNA profile changes, and (ii) support pro-thrombotic states in cancer patients. However, platelet activation results in the release of the active biomolecules that are present in their granules and are all involved in the development of cancer. Numerous growth and angiogenic factors found in platelets support tumor growth and angiogenesis. Additionally, platelet aggregation around tumor cells (TCIPA) provides cancer cells with a number of benefits, including the ability to evade immune surveillance, protection from shear stress, prosurvival signals, adhesion to the endothelium, and extravasation. It seems that successful metastatic breakout and tumor development depend on platelet activation. Based on these findings, several investigations should target platelet activation, sticky proteins involved in contacts between cancer cells and platelets, and alpha granule

contents to slow the evolution of tumors.

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