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Cancer Progression: Focus on Platelet

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ABSTRACT

Platelets are an important component in the process of hemostasis and coagulation. It is now known that high platelets count closely related to poor prognosis of patients with cancer, due to their role in the hematogenous spread of cancer cells. Platelets can be activated by cancer cells into tumor-educated platelets and then cause thrombosis through tumor-induced platelet aggregation. Platelets also protect cancer cells in the blood circulation from natural killer cells and help the transition of cancer cells from epithelial to mesenchymal and vice versa, resulting in the process of metastasis. In the next stage of metastasis, platelets trigger extravasation of cancer cells from primary cancer and adhesion of cancer cells to distant organs.

1. Introduction

The course of cancer (solid cancer or blood malignancy) from carcinogenesis to distant metastases is a unique series of processes involving genetic mutations, the role of the tumor microenvironment, to the role of various hematologic components such as erythrocytes, leukocytes and platelets. Currently, a new approach to cancer progression in terms of platelets is growing rapidly since there is evidence of a link between the incidence of deep vein thrombosis and cancer, as a marker of advanced cancer.

Bizzozzero (1882) was the first to discover platelets microscopically, which are the main blood components that treat vascular damage, in both *in vivo* and *in vitro* experiments. This finding triggers further research on platelets, although it is still limited

to the function of hemostasis and platelet plug formation.^{1,2} In addition to its main function of maintaining the integrity of the blood vessel barrier and hemostasis function, platelets also express surface molecules and a variety of proteins, nucleotides, and bio-active components that promote inflammation and cancer progression.^{3,4} When cancer cells released from the primary tumor into the blood circulation in the form of circulating tumor cells (CTCs), platelets are the first blood components that provide the body's natural immunological response. However, cancer cells have the ability to avoid this natural response and, instead use platelets as life support. In addition, the formation of tumor cell aggregates and platelets leads to an increased risk of thrombosis, and this is the cause of the highest

morbidity and mortality in cancer patients.⁵

2. Physiological function of platelet

Platelets are one of the special cells because they have an extraordinary capacity for morphological flexibility and the ability to secrete proteins, nucleotides, and bioactive fats that are very important to the body.⁴ Platelets come from large nucleated cells called megakaryocytes in the bone marrow. Mature platelets are in the form of small discoid cells without nuclei with a diameter of 2-5 μ m with an average volume of 6-10 fl. The median age of circulating platelets is 7-10 days with an average number of 150,000-400,000/ml. Changes in platelet count and volume are often associated with pathological conditions and markers of acute inflammation.⁵⁻⁷ In the body, the main role of platelets in circulation is to maintain primary hemostasis and normal blood flow, by taking the closest position to the walls of blood vessels so that they can respond quickly when vascular trauma occurs.⁸⁻¹¹

Another important function of platelets is their role in the immune system, both natural and adaptive. The role of platelets in the natural immune system is possible because of the release of pro-inflammatory mediators and bioactive molecules that are synthesized, stored, and matured in their granules, and only released when activated. These mediators can attract and modulate natural immune system effector cells to activate. In addition to using proinflammatory mediators, platelets can also act directly as effector cells when needed. Against bacterial, viral, fungal, and protozoan infections, it turns out that platelets also show their antimicrobial function. Platelets have also been shown to have antiviral properties, especially those associated with human immunodeficiency virus (HIV) infection, influenza, dengue, and hepatitis C.¹²⁻¹⁵

3. Thrombocytosis and thromboembolism in cancer

The close relationship between platelets (in the form of thrombocytosis) and cancer was first described by Armand Trousseau (1865), known as Trousseau syndrome. Cancer cells will trigger the release of

various cytokines and humoral factors such as granulocyte colony-stimulating factors (G-CSF), granulocyte-macrophage colony-stimulating factors (GM-CSF), basic fibroblast growth factor (b-FGF), IL-6, IL-1, and TPO. In particular, the megakaryopoiesis process is triggered by IL-6 and TPO which continue to cause an increase in thrombopoiesis, until thrombocytosis occurs. Increased platelet count is even used as a prognostic predictor for some solid cancers such as ovarian cancer, lung cancer, colorectal cancer, gastric cancer, and breast cancer.¹⁶⁻¹⁸

Thrombosis due to malignancy is one of the most frequent clinical manifestations and is closely associated with worse morbidity and mortality. The main cause of the high risk of thrombosis in cancer patients is the activation of platelets and the acceleration of platelet aggregation by cancer cells. The high tumor-cell-induced-platelet-aggregation (TCIPA) is directly related to the high rate of thrombosis and metastasis, where more than 20% of cancer patients experience vascular thromboembolism with the most clinical manifestations of pulmonary embolism and deep vein thrombosis (DVT). The risk of venous thrombosis in cancer patients is not only due to an increase in the number of platelets but also because of changes in platelet function due to the influence of cancer cells.

4. Platelet activation by cancer cells

The main reason for the high risk of thrombosis in cancer patients is cancer cells can stimulate platelet activation through various mechanisms. The majority of cancer cells release platelet activating mediators such as adenosine diphosphate (ADP), thrombin, and thromboxane A₂ (TxA₂). Cancer cells will also release high-mobility-group-box-1-chromatin-protein-1 (HMGB-1) which will also stimulate platelet activation by binding to the toll-like-receptor-4 (TLR-4) receptor. Some special cancer cells, such as squamous and germinal cancers, also produce podoplanin, which binds to the C-type lectin like-receptor-2 (CLEC-2) and promotes platelet activation. Several other types of cancer can express tissue factor (TF), which results in

the formation of thrombin and eventually also activates platelets.^{16,19}

The presence of TCIPA is characterized by aggregation, adhesion, and increase number of proangiogenesis factors released by platelets, then causes an increase in the number of CTCs which facilitate the hematogenic spread of cancer cells. The presence of platelet activation by cancer cells, coupled with exposure to subendothelial procoagulant factors, results in a continuous platelet activation cycle which makes the cancer microenvironment more fertile. Activated platelets also produce IL-1b which induces TF expression in endothelial cells and stimulates leukocyte adhesion molecules to the endothelium. Furthermore, this IL-1b will reactivate platelets through the IL-1R. Transforming growth factor- b (TGF- b) which is expressed and secreted by activated platelets in the tumor microenvironment, has immunosuppressive abilities that help cancer cells escape from immune system and assist in the transformation of neutrophils into protumorigenic phenotypes.²⁰⁻²² With good nutritional support, cancer cells will continue to grow and at the right time, some cancer cell populations will be released from the primary tumor to the circulation in the form of CTCs which facilitate metastasis to distant organs (secondary organs).

5. Platelet and cancer cell immune escape

Once cancer cells goes into circulation, it will manifest as CTC and undergo eliminating by the immune system, blood pressure, and natural apoptosis. Although most of the CTCs can be destroyed by the immune system, about 0.1% of CTCs can survive and stimulate TCIPA directly or indirectly through the release of agonist mediators (ADP, TxA2, and tumor-related proteinases). The ability of CTC to evade the natural immune system which is mediated by TCIPA causes the immune system perceive cancer cells as a variant of the normal platelet form is known as tumor-educated-platelet (TEP). Then the TEP will adhere to the CTC surface by binding to the GPIIb-IIIa-fibrinogen receptor and leading to upregulation of P-selectin. The surface CTCs covered by TCIPA causes

CTCs not to be recognized by natural killer (NK) cells so that CTCs are free from the tumoricidal effects of NK cells and lymphokine-activated-killer (LAK). Also, TEP transfers the major histocompatibility complex (MHC) to CTCs so that CTCs enter the body's cells (mimicry) and escape from body's immune system. Besides, TEP can release TGF-b which inhibits the expression of natural killer group-2-member-D (NKG2D) immunoreceptors which in turn also inhibits NK cell activity. Likewise, the release of VEGF will inhibit the maturation of dendritic cells that act as antigen-presenting-cells (APC) in the immune system.^{5,23-26} The increase in P-selectin and integrins causes the close attachment of CTCs to the vascular endothelium so that CTCs can move from the epithelium to the mesenchyme through the endothelium which undergoes permeability changes due to ADP produced by TCIPA and causes extravasation of CTC into the tissue and is a candidate for metastasis. Vice versa, by escaping cancer cells from immune escape, cancer cells can occur from the mesenchyme to the epithelium and then to the circulation in the form of CTC.^{1,5,26}

6. Platelet in cancer growth and angiogenesis

Tumor microenvironment conditions play an important role in cancer progression. Direct contact of cancer cells with vascular epithelium or the release of TGF-b by TEP will trigger the transition of normal epithelial cells to malignant. Normal cells that have the potential to become malignant must go through a transdifferentiation process, namely the epithelial-mesenchymal-transition (EMT) due to loss of E-cadherin adhesion protein and an increase in matrix metalloproteinase (MMP) so that the polarity of the epithelial cells is lost and the shape is more like mesenchymal cells. In addition, TEP also releases platelet-derived-growth-factor (PDGF) and hepatocyte growth factor (HGF) which can also trigger this transdifferentiation of EMT. Furthermore, mesenchymal cells that have changed form are intravasation into the circulation (blood and lymph) in the form of CTCs. In the blood vessels and lymph organs of the distal organ where CTCs attach,

extravasation occurs from the circulation to the tissue by transdifferentiating again in the form of a mesenchymal-epithelial-transition (MET) so that it can invade the organ. These changes cause cancer cells to have the ability to invade the surrounding tissue and release from primary cancer and then enter the blood and lymph circulation, causing hematogenic or lymphogenic metastases.^{27,28}

Platelets store proangiogenesis and antiangiogenesis mediators, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in granules-a and granules-d. Platelets act as the largest provider of proangiogenesis mediators among other blood cells making them a source of angiogenesis mediators for primary cancer and CTCs. Apart from regulating the angiogenesis process, platelets also regulate the vascular integrity of cancer, thereby preventing intratumoral bleeding. This is due to the release of ANGPT1 and serotonin which stabilizes cancer vascular by inhibiting the release of VEGF when cancer cell neovascularization has been formed. By regulating vascular integrity, platelets can also reduce tissue damage due to the infiltration of cancer cells so that they can escape the body's immune system surveillance.¹⁷ Activated platelets along with platelet microparticles (PMPs) also release various mitogenic proteins and growth factors from granules-a. These factors not only stimulate cancer growth but also stimulate cancer angiogenesis and neovascularization. Apart from these main PMPs, it turns out that platelets can also increase phosphofructokinase (PFKP) which will stimulate cell proliferation and prevent apoptosis. In patients with blood cancer, TEP can cause the release of mitochondrial cells thus causing resistance to apoptosis.²⁴

7. Platelet induced neutrophil extracellular trap (net) in cancer

Naturally, neutrophils are the body's first immune cells to work by destroying pathogens and secreting antimicrobial substances by forming neutrophil extracellular traps (NET) which begins with the release of chromatin and neutrophil granules which form a

net-like structure consisting of extracellular DNA strands and related proteins such as histones and neutrophil proteases. Primary cancer cells can express G-CSF which stimulates the formation of systemic NET. There is evidence to suggest a close association of NET with thrombosis in cancer; where NET requires platelets as regulators, as well platelets. The prothrombotic effect of NET is due to the high content of histones and negatively charged nucleic acids, which makes NET a high potential as a procoagulant with the ability to activate and aggregate platelets. Activation of platelet TLR4 can also trigger NETosis accompanied by the release of histones 3 and 4 which eventually activate platelets until they turn into TCIPA which in turn activates coagulation factors which further increases the risk of thrombosis, vascular dysfunction, and systemic inflammation. Also, P-selectin is also important in NETosis through P-selectin glycoprotein ligand-1 (PSGL-1). The high amount of NET will lead to a higher risk of vascular dysfunction and systemic inflammation in cancer patients. The metastatic process is also facilitated by the formation of NETs by releasing CTCs, promoting the release of tumor cell adhesions to the endothelium, and increasing the extravasation of cancer cells. It is known that NET can recruit CTCs thereby facilitating attachment to the epithelium and allowing distant metastases.³⁰

8. Platelet and cancer metastasis

Cancer metastasis is a continuous process involving various cytokines and inflammatory mediators. Platelets play a role ranging from changes like normal cells to release of cancer cells into the cancer microenvironment, intravasation of cancer cells into the blood or lymphatic circulation, adhesion of CTCs to the distal organ blood vessels, extravasation of CTCs from the blood or lymphatic circulation to secondary organs to form metastatic foci, to perform angiogenesis to grow. In carrying out this important role, platelets secrete various mediators and cytokines from the granules located in their cytoplasm. The platelet surface membrane contains various adhesion molecules, such as integrins,

selectins, glycoproteins high in leucine content and immunoglobulin superfamily proteins. With the presence of various adhesion molecules on these surfaces, platelets can bind not only to other platelets or to the walls of the circulation, but can also bind to other cells including cancer cells, and form TCIPA. Interaction between TCIPA and platelet-derived-microparticles (PDMPs) released from platelet granules, helping CTCs to adhere to and persist in the circulating endothelial wall and facilitate metastasis.

16,26,30

9. Conclusion

Various studies have developed showing the important role of platelets in cancer progression. Not only in the initial process of transdifferentiation into malignancy but also at each stage of cancer progression to metastasis. This is closely related to the privilege of platelets as blood cells with the highest number and short life span which may be a source of energy for cancer growth and development. Besides, platelet surface molecules have various proteins that allow the binding of cancer cells to occur, making it easier for cancer cells to escape from the body's immune system, even platelets are used as a medium for transporting cancer cells to secondary organs which then become the focus of metastases. Also, the content of granule-a and granule-d in platelets can make the cancer microenvironment fertile, thus making it easier for cancer cells to grow and make neovascularization (angiogenesis). Broadly speaking, the role of platelets in cancer progression are: (1) as a source of energy for cancer cells; (2) helping cancer cells to avoid the body's immune system (immune escape); (3) the transportation medium for cancer cells to reach distant target organs (metastasis); (4) helps the proliferation and angiogenesis of cancer cells; and (5) stimulating the formation of NET which cause chronic inflammation and endothelial dysfunction of blood vessels in cancer patients.

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