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Education Article

Platelets (thrombocytes) - the other recognized functions

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SUMMARY

Introduction: Platelets are smallest blood cells of discoid or round shape and are cytoplasmic fragments of megakaryocytes.Platelets consist of 3 types of granules: alpha granules, dense granules and lysosomes. Granule secretion releases coagulation factors, growth factors, cytokines, and a number of proteolytic enzymes.Platelets contain a number of receptors known as platelet agonists. Basic and most studied role of platelets is in hemostasis process. The aim of this paper is to point on platelet function unrelated to hemostasis.

Matherials and methoods: Papers on other recognized functions of platelets were searched for in biomedical journals idexed in MEDLINE form 2004 to 2016.

Topic: This paper studies less known platelet functions becoming subject of interest with the development of applied science. Platelets participate in inflammation by releasing proinflammatory mediators (CD154, CD40L). Complement activation via P-selectin, platelet-generates immunomodulatory effect. CD40L accelerates releasing RANTES protein leading to intensified activation of T-lymphocytes. During embryonic development, platelets allow blood and lymph vessels separation by activating CLE-2 receptor and ligand PDPN. Platelets alleviate migration and invasiveness of tumor cells, contribute to disease progression and development of metastases. Platelets affect maturation of follicles and oocytes and have important role in embryo implantation process and placentation.

Conclusion: Based on these findings, conclusion imposes platelets as not only active participants in the hemostasis process but as having significant role in inflammation, unspecified and specified body defending, tumor biology, embryonic development and in female reproductive system regulation. Numerous roles of platelets open wide range for the new drugs' operation.

Their specific characteristic is the basis for the personalized Clinical pharmacology development and possibility of applying specific drug as polyindicative therapeutic agent.

Keywords: platelets, Inflammation, tumor, reproduction

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INTRODUCTION

Platelets are the smallest blood cells of discoid or round shape and are cytoplasmic fragments of megakaryocytes. Average size of a mature platelets is about 6 μm^3 with a diameter of about 2.3 μm. Proportion of platelets in a total volume of blood is 3%. In adults circulate around 1012 platelets and their life span is 7-11 days. In order for body to sustain the platelet count daily, more than 1011 platelets is produced, and in the case of hemorrhaging that number significantly increases [1,2,3].

Platelets contain 3 types of granules:

- α-granules containing adhesion proteins (fibrinogen, GPllblla, P-selectin (CD62P), vWF, coagulation factors, fibrinolitic factors, cytokine, growth factors-PDGF, TGF-β, IL-1β, sCD40L, RANTES β-thromboglobulin/NAP2, TF4/CXCL4, adhesion receptores)
- thick granules containing nucleotide (ADP, ATP, GTP), catecholamines, serotonin, glutamate, histamine, pyrophosphate and divalent cations
- lysosomes containing multiple proteolytic enzymes

Secretion or discharge of granulate content, has the key role in the platelet activation, amplification of platelet activation, in the formation of aggregates and stabilizing the thrombus. The enzyme system of plateletssynthesizes prostaglandins from phospholipids platelet membrane. Glycogen granules are the main source of energy [4,5].

Moreover, secretion of granules have the important role in inflammation, the process of atherosclerosis, unspecific defense of body, wound healing, angiogenesis, and malignancy [6]. Consequently, platelets participate in many physiological and pathophysiological processes.

Basic and top- studied role of platelets is in hemostasis process [7,8]. Platelets engage in the processes of inflammation, unspecific body's defense, reproduction and tumor biology shown in (Figure No. 1) [9,10].

Platelet receptors

Platelet membrane receptors have always represented scientific focus. Platelet receptors are known as platelet agonists, each representing its own specific activity [2]. Platelet receptors

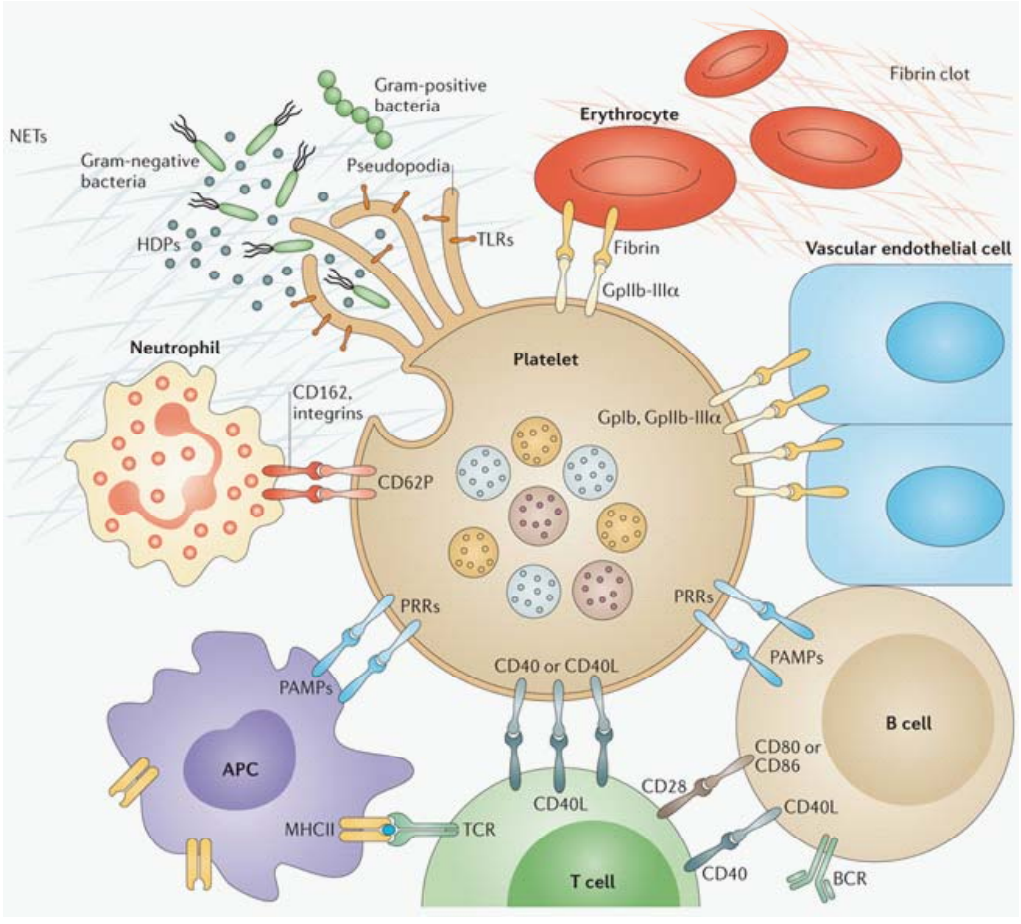

Figure 1. Multifunctionality of platelets chart;

available at http://www. nature.com / nrmicro / journal

are divided in receptors that participate in the activation, in the amplification and stabilization.

The receptors participating in the activation, adhesion and aggregation of platelets can be found at surface of platelets or in the plasma membrane.

Best known receptors at surface of platelets are as following:

• GPIb-IX-V complex, represents the receptor for: the von Willebrand factor (vWF), thrombin, FXI, FXII, P-selectin, HK, Mac-1, and TSP-1. Its absence is known as Bernard-Soulier syndrome.

• GPVI receptor for collagen and laminin, belonging to superfamily of immunoglobulin CD148

Receptors found in the membrane of platelets:

• α2β1 – receptor for collagen

• αIIbβ3 – receptor for fibrinogen, fibrin, vWF, TSP-1, fibronectin, vitronectin.Its deficiency leads to Glanzmann thrombasthenia

• α5β1 – receptor for fibronectin

• α6β1 – receptor for laminin

• αVβ3 – receptor for, fibronectin, fibrinogen, vWF, osteopontin

Receptors active in the amplification phase of platelet activities are found in platelet membranes. The most famous of them are:

• Receptor for ADP – $P2Y_1$

• Thrombin receptor PAR1

• The receptor for platelet activating factor (PAF) – PAF receptor

• Thromboxane receptor – tPA

• ATP receptor – P_2X_1

• TPO receptor – c-Mp1

• PDGF receptor

Platelet receptors active in the stabilization phase of platelet activity can be found in the membrane or reach platelet membrane from α granules during activation phrases like P-selectin, CD36, PEAR1, PECAM-1 and PGI_2 receptor [2, 11, 12, 9].

METHODOLOGY

Papers about OTHER RECOGNIZED FUNCTIONS of platelets were searched for in biomedical journals indexed in MEDLINE from 2004 to 2016.

TOPIC

This work processes other, less studied platelet functions, becoming the subject of interest to the development of applied sciences in the field of tumor biology, the development of diagnostic tumor biomarker leading to the development of personalized medicine and to special personalized Clinical pharmacology.

1.The role of platelets in inflammation

Platelets have an important role in inflammation due to the strengthening of proinflammatory mediator releases: CD154, CD40 ligand (CD40L) and thromboxanes (TXS). α-granules contain RANTES and inflammatory signaling molecules. Among them, CD154 holds a peculiar position, as platelets represent a major source of CD154 and as CD154 contributes to most of these new platelet attributes. CD154, the CD40 ligand, a member of the Tumor Necrosis Factor (TNF) family, is central to the immune response [2, 13].

Membrane chemokine fractalkine is expressed on endothelial cells as response to pro-inflammatory agents, otherwise not present on the endothelium of blood vessels of healthy individuals. Fractalkine, in turn, through the G-protein is inducing exposure of P-selectin on platelets and further improves platelet adhesion to fibrinogen, one of the proteins in the acute phase, by means of GPIIbIIIa [14].

2. The role of platelets in unspecific and specific body defense

One way of operating modes of platelets, in addition to the hemostasis is an immunomodulatory complement activation via P-selectin mediated by the receptor Par4 [15]. P-selectin,located in the alpha granules activates neutrophils. Modern researches show that endothelial cells of human umbilical vein,stimulated by tumor necrosis factor-α and interferon - γ express, to a large extent, the membrane chemokine fractalkine (CX3CL1) that leads to the significant exchange rate of accumulation of leukocytes in the blood circulation. Researches on animal model have shown that the role of platelets expressing the receptor for fractalkine (CX3CR1) is essential for adhesion of leukocytes to the endothelium. Fractalkine released from endothelial cells leads to the activation of adhered platelets which, consequently leads to platelet degranulation and expression of P-selectin on the membrane of platelets essential for the adhesion of leukocytes to the inflamed endothelium.

Soluble and membrane-fractalkine can induce degranulation and expression of P-selectin on platelet surface. In this way, formed P-selectin directly leads to an interaction of leukocytes and platelets [14, 16, 17].

Besides the role in the activation of platelets αIIbβ3 and CD40L platelets also have a role in elimination of a pathogen. Receptor for CD40L, CD40 expresses a large number of immune cells including monocytes,dendritic cells, B lymphocytes and thus influences the development of acquired immune response.

In a similar way, CD40L bound for T-lymphocytes activates platelets and improves releases of Regulated on Activation, Normal T Expressed and secreted (RANTES) proteins after which follows amplified activation of T-lymphocytes enabling pro inflammatory response [14, 18, 19].

3. The role of platelets in the regulation of blood and lymph vessels

Various groups of researchers have received genetic confirmation of the role of platelets in the mechanism of regulation of vascular development. Researches have shown that platelets are responsible for the separation of blood and lymph vessels by activating CLE-2 receptor via Podoplanin ligand (PDPN), which is located on the lymphatic endothelial cells (LECs). PDPN and CLEC-2 are both transmembrane proteins and their expression in membranes of belonging cells is essential for the direct contact of platelets and endothelial cells [20].

It is known that the alpha granules of platelets contain a number of angiogenic growth regulators.This theory supports hypothesis that degranulation means the activation mechanism of platelets controlling growth of lymphatic vessels [20].

The interaction between platelets and LEC can be noticed in the main veins during LEC changes in expression of PDPN. However, this interaction is not detected in the intestine, where also exists communication between blood and lymph vessels. The use of platelets as a means for marking a contact to the blood vessels with lyphatic endothelial cells is justified, given that platelets are one of the few blood cells where even after trauma there is no process of extravasation or entering in the lymphatic vessels. In what way platelet activation mediated by LEC prevents connection of blood vessels and LEC, remains unclear. Importance of these studies is in the discovery that platelets have an important role in embryogenesis of vascular system which is not related to hemostasis [2, 20].

4. The role of platelets in tumor biology

Platelets have a multiple role in the progression of cancer. Procoagulant surrounding provided by platelets, allows building up cancer cells and thus, guarding them from the immune system, leads to tumor growth. Platelets alleviate migration and invasiveness of tumor cells leading to the formation of metastases. Researches show that in breast cancer and ovarian cancer platelets thus increase invasiveness of cancer cells further inducing disease progression. In addition, the same tumor cells demonstrate the ability of platelet aggregation that increases the opportunities for the development of metastases. Platelet activation and regulation of other cells is controlled by the thrombin via active protease receptors related to the G protein. Researches have shown that thrombin and its signaling pathways contribute greatly to the progression of tumorigenesis and neo angiogenesis. Due to this fact, the routine use of anticoagulant therapy for malignant diseases is part of the daily clinical job with particular caution because of the unstable procoagulability characteristic of both occult and overt type of malignant disease [2,7,8,21,22,23].

5.1 Role of platelets in the regulation of the female reproductive system

Clinical and experimental researches have shown that platelets influence the regulation of the hypothalamic-pituitary-ovarian system (axles). Hypothalamic gonadotrophin-releasing hormone (GnRH) releases follicle stimulating hormone (FSH) from the anterior pituitary inducing and stimulating maturation of follicles and oocytes, as well as the secretion of ovarian steroid hormones. In this period, follicular cells thus increase the production of PAF. In this way stimulated platelets accumulate in follicular vessels surrounding follicle and due to releases of soluble molecules (growth factors, mediators, chemokines, cytokines, and neurotransmitters) locally lead to hormone secretion and maturation of oocytes.

Based on these findings, the conclusion imposes that platelets are not just tiny participants but that they have a leading influence on the complex regulatory systems having several unclear mechanisms. Hence, platelets are corpuscular transmitters much more than

participants in the process of hemostasis [24, 25]

5.2 Role of platelets in pregnancy (implantation, placentation)

Platelets have a major role in the formation of spiral arteries and trophoblast. Process is still unknown. It is assumed that the platelets are activated in contact with thrombomodulin and protein C receptor on trophoblast. Trophoblastic cells demonstrate the ability of activating coagulation in the vascular bed of the placenta. Another way of platelet reaction is immunomodulatory platelet-type complement activation via P-selectin receptor Par4 [15, 24]. Immunohistochemical staining with antibodies to P-seletin demonstrated the presence of activated platelets in the decidua, in the area of maternal origin between the trophoblastic cells of the placenta and in spiral arteries [15, 24].

Conditions and disorder of increased platelet activity lead to the trophoblast disorder particularly visible in preeclampsia and Hemolysis Elevated Liver Enzymes Low platelet (HELLP) syndrome. Fetal prothrombogenic gens may also locally activate platelets of a mother leading to the disorder of placental development [15, 24].

CONCLUSION

Platelet function unrelated to hemostasis is becoming the subject of research along with the development of applied science.

Platelets are actively involved in the inflammatory process by its proinflammatory mediators release. Platelets by its immunomodulatory effects and activation of leukocytes are actively involved in non-sctecific and specific host defense. Platelets have an important role in embryonic development and in the separation of blood and lymph vessels. Activated platelets accelerate cancer progress and development of metastases in many different ways.

Platelets influence hormonal discharge and oocyte maturing by releasing growth factors,cytokine and neurotransmitters in blood vessels around ovarian follicle. Therefore, Platelets are directly involved in female reproductive system regulation.

Thus, new range of therapeutic effects linking many immunological diseases, unspecific and specific defense of the body, neoangiogenesis, female fertile functioning and maintaining pregnancy are opening as fields of research. In addition, platelets have important role in tumor biology.This role represents new and significant field for the function of new drugs.

The receptors on platelets are the target for applying many drugs with poly therapeutic effects.Their specific individual effect is the base for the development of personalized Clinical pharmacology and good understanding of the receptors on platelets enables application of single drug as poly-indicative agent.

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Trombociti – ostale prepoznate funkcije

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KRATAK SADRŽAJ

Uvod: Trombociti su najmanje ćelije krvi diskoidnog ili okruglog oblika i predstavljaju fragmente citoplazme megakariocita. Trombociti sadrže 3 tipa granula: alfa granule, guste granule i lizozome. Sekrecijom se iz granula oslobađaju faktori koagulacije, faktori rasta, citokini i mnoštvo proteolitičkih enzima. Trombociti sadrže brojne receptore koji su poznati kao trombocitni agonisti. Osnovna i najviše proučavana uloga trombocita je u procesu hemostaze.
Cilj: Cilj ovog rada je da ukaže na funkcije trombocita koje nisu vezane za hemostazu.
Materijal i metode: Pretraživani su radovi objavljeni u biomedicinskim časopisima indeksirani na Medline od 2004. do 2016. godine koji obrađuju ostale prepoznate funckije trombocita.
Tema: Ovaj rad pročava manje proučavane funkcije trombocita koje postaju predmet interesovanja razvojem primenjene nauke. Trombociti učestvuju u inflamaciji oslobađanjem proinflamatornih medijatora (CD154, CD40L). Aktivacijom komplementa preko P-selektina trombociti ostvaruju imunomodulatorni efekat. CD40L pospešuje oslobađanje RANTES proteina nakon čega dolazi do pojačane aktivacije T-limfocita. U toku embrionalnog razvoja trombociti omogućavaju odvajanje krvnih i limfnih sudova aktivacijom CLE-2 receptora i PDPN liganda. Trombociti olakšavaju migraciju i invazivnost tumorskih ćelija čime doprinose progresiju bolesti i razvoj metastaza. Trombociti deluju na maturaciju folikula i oocita i imaju važnu ulogu u procesu implantacije i placentacije.
Zaključak: Na osnovu ovih saznanja nameće se zaključak da trombociti nisu samo učesnici u procesu hemostaze već imaju značajnu ulogu u inflamaciji, nespecifičnoj i specifičnoj odbrani organizma, u tumorskoj biologiji, u embrionalnom razvoju, u regulaciji ženskog reproduktivnog sistema. Mnogobrojne uloge trombocita otvaraju široka područja za delovanje novih lekova. Njihova specifičnost predstavlja osnovu za razvoj personalizovane kliničke farmakologije i mogućnost primene jednog leka kao poliindikaciono sredtsvo.

Ključne reči: trombociti, inflamacija, tumor, reprodukcija

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