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PLATELETS AND OTHER CELLS INTERACTIONS IN THE ATHEROSCLEROSIS DEVELOPMENT

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Atherosclerosis of the blood vessels is one of the main causes of severe chronic vascular pathologies, which quite often lead to the fatal end. It is well known that the development of atherosclerosis is an inflammatory process going through several stages until the formation of an atherosclerotic plaque. The latter, due to increased instability, would come off and cause thromboembolism. Low density lipoproteins, endothelium, platelets, neutrophils, monocytes / macrophages and smooth muscle cells of the vessel wall are all active participants in the development of atherosclerosis. Thus, they trigger and carry out the process by forming a platelet thrombus on the surface of the ulcerated calcified atherosclerotic plaque. In the recent time interest in the role of platelets in inflammatory processes has grown immensely, first of all due to their ability to interact with cells participating in different stages of atherosclerosis development through adhesion, formation of aggregations, the exchange of exovesicles and microparticles, as well as through the mutually increasing secretion of cytokines, chemokines, growth factors and other chemical mediators. This review is devoted to the role of platelets in the formation and regulation of the multicellular ensemble and also local cell modules specific for each stage of atherosclerosis development.

Keywords: atherosclerosis; platelets; endotheliocytes; neutrophils; monocytes/macrophages; vessel smooth muscle cells.

ВЗАИМОДЕЙСТВИЕ ТРОМБОЦИТОВ С ДРУГИМИ КЛЕТКАМИ И ЕГО РОЛЬ В РАЗВИТИИ АТЕРОСКЛЕРОЗА

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Атеросклероз кровеносных сосудов — одна из основных причин тяжелых хронических сосудистых патологий, нередко протекающих с летальным исходом. Известно, что атеросклероз как воспалительный процесс развивается в несколько этапов и завершается образованием атеросклеротической бляшки, которая при повышенной нестабильности может отрываться и быть причиной тромбоэмболии. Активными участниками процесса атеросклероза являются липопротеины низкой плотности, эндотелий, тромбоциты, нейтрофилы, моноциты/макрофаги и гладкомышечные клетки стенки сосуда. При этом тромбоциты начинают процесс и завершают его, образуя на поверхности изъязвленной кальцинированной атеросклеротической бляшки тромбоцитарный тромб. Интерес к роли тромбоцитов в воспалительных процессах в настоящее время чрезвычайно вырос, особенно это относится к их способности взаимодействовать с клетками-участниками на разных этапах развития атеросклероза через адгезию, образование агрегаций, обмен экзовезикулами и микрочастицами и посредством взаимно усиливающейся секреции цитокинов, хемокинов, факторов роста и других химических медиаторов. Настоящий обзор посвящен роли тромбоцитов в формировании в стенке сосуда и регуляции мультиклеточного ансамбля в целом и локальных клеточных модулей, специфичных для каждой стадии развития атеросклероза.

Ключевые слова: атеросклероз; тромбоциты; эндотелий; нейтрофилы; моноциты/макрофаги; гладкомышечные клетки сосудов.

Background

Atherosclerosis is currently considered a vascular wall pathology, which represents chronic inflammation associated with impaired lipid metabolism and lipid deposition in the vessel wall with the formation of an atherosclerotic plaque. The development of atherosclerosis has

List of abbreviations

LDL, low-density lipoproteins; VLDL, very-low-density lipoproteins; ROM, reactive oxygen metabolites; VSMC, vascular smooth muscle cells; NET, neutrophil extracellular trap.

4–8 stages. In stage 1, damage to one endothelial cell or group of cells can be caused by several nonspecific factors, namely, hypertension, increased blood viscosity and osmotic pressure, lipid peroxidation of cell membranes, heavy metals, etc. These factors can contribute to the destruction of the extracellular matrix and increase endothelium permeability and entry into the intima of blood vessels of platelets, neutrophils, monocytes, dendrocytes, and lymphocytes [1], and low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL) [2–4]. Moreover, the involvement of the circulating blood cells, primarily monocytes, neutrophils, and preendotheliocytes, increases [5, 6], and the process of atherogenesis starts; however, it remains possible to restore the endothelial monolayer. A necessary condition for a shift in the functions of activated platelets along the path of atherogenesis is the presence of cofactor such as oxidized LDL. LDL is made up of cholesterol and its esters, triglycerides, apolipoprotein-B100 (apo-B100), and other proteins, as well as their glycated metabolites [1, 7, 8]. LDL and VLDL enter the intima through the endothelium by transcytosis through the caveolar mechanism under the control of platelets [1–4].

In stage 2, inflammation processes are triggered under the influence of substances secreted by the damaged epithelium, activated platelets, and myeloid cells continuing to enter the intima. Thus, platelets secrete large volumes of soluble CD40L and its receptors (CD40), platelets themselves, endothelial cells, neutrophils, macrophages, dendrocytes, and vascular smooth muscle cells (VSMCs) [9, 10]. Since the CD40/CD40L ligand–receptor interaction activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the membrane of target cells, superoxide anion and reactive oxygen metabolites (ROM) are formed in the mitochondria of these cells, which oxidize LDL that have entered the intima, and they begin to be modified, undergoing acetylation and glycosylation [9, 10]. This impairs the permeability of LDL, and they accumulate not only in the lumen of the vessel but also in the intima. Such oxidized LDLs are phagocytosed by macrophages using scavenger receptors without the participation of apoB-100 receptors [2]. Oxidized LDLs and additional ROMs worsened acidosis and enhanced activation of the redox-sensitive nuclear receptor Nrf2, which ensures the release of proinflammatory cytokines by macrophages, growth factors that stimulate the division of VSMCs, their differentiation [11], and synthesis of intercellular substance, and are involved in the development of atherosclerotic plaque. Moreover, lipoproteins are not metabolized in macrophages, and when they accumulate, they become foam cells, and the accumulated cells create lipid strips or spots in the final stages of the atherosclerosis process. Preendotheliocytes and VSMCs can also become foam cells [12, 13]. An increase in the concentration of oxidized LDLs and intensification of atherosclerosis can be facilitated by the insufficient activity of antioxidant systems involving vitamins E and C, catalase enzymes, glutathione peroxidase, and superoxide dismutases 1 and 2 [2]. Under the influence of growth factors secreted by platelets, neutrophils, and macrophages, VSMCs migrate from the media into the intima and begin to proliferate, turning into macrophage-like cells. They also accumulate modified LDLs [12, 13].

In stage III of atherosclerosis development, the stage of late changes, processes of the previous stage continue and intensify with the beginning of the formation of an atherosclerotic plaque, an increase in its volume, and fibrosis. This is facilitated by the proliferation of foam cells; secretion of fibroblast-like VSMCs and activated fibroblasts of collagen, elastin, and glycosaminoglycans; and the accumulation of intercellular substance. Platelets play a role in increasing the count of neutrophils, macrophages, and T-lymphocytes attracted by their chemokines to the plaque [14–18]. Subsequent apoptosis of foam cells and necrotic phenomena lead to the formation of a necrotic zone in the center of the plaque, accumulation of free or encapsulated cholesterol and its esters [1, 6], and a decrease in plaque stability. In the final stage, plaque surface calcification occurs, as well as its ulceration, in sites in which platelets adhere from the vessel lumen and a platelet–fibrin thrombus is formed with the addition of thromboembolism, which destroys the vessel.

In this general description of the stages of atherosclerosis development, the role of intercellular communications, particularly platelets, is not sufficiently represented yet. Many researchers have reported that the biochemical and morphofunctional plasticity of platelets determined their key role not only in hemostasis and thrombosis but also in the reactions of innate and acquired immunity and chronic inflammation [1, 6, 15–16, 19, 20]. Some authors pay special attention to

the analysis of conditions for switching the effects of platelets from thrombopoiesis to atherosclerosis. As a summary of their efforts, we can state the following. The triggering of hemostasis or immune responses and atherosclerosis by platelets depends on several factors, including the most significant ones: (1) size of damage to the vessel wall, larger in the first case and microdamages in the second case (e.g., as a result of the destruction of proteins of intercellular contacts or individual endotheliocytes); (2) complexes of adhesion proteins that attach platelets to subendothelial collagen or integrins of endothelial cells; (3) formation of platelet aggregates in the lumen of the vessel at the locus of damage to its wall during hemostasis and accumulation of platelet aggregates with neutrophils or with monocytes/macrophages in the intima during atherosclerosis development; and (4) presence of oxidized LDLs in the intima, which is necessary to trigger the atherosclerosis process and increase the permeability of endothelial cells to which and their transcytosis itself are regulated by platelets in the caveolar pathway [1–4].

At present, the interest of researchers in intercellular interactions has shifted to the issue of the functional specificity of intercellular modules. An example is the growing number of studies on neurovasal and neuroimmune units. The study of intercellular interactions during atherosclerosis development leads gradually to the formation of local multicellular complexes in the intima of the vessel wall, like hubs, with a dynamically changing composition, but the constant participation of platelets.

Thrombocytopoiesis: Platelet characterization

Platelets are formed from megakaryocytes in the red bone marrow, and up to 50% of the total are formed in the capillary perialveolar plexus of the lungs. Subsequently, platelets can divide into smaller ones [20–22]. In the niches of the bone marrow, megakaryocytes can absorb neutrophils (mechanism of emperipolesis), which makes it possible for the intracellular exchange of membrane fragments and molecular complexes between the neutrophils and intensively formed platelets [21, 22]. A similar mechanism is possible in the lungs, where the perialveolar capillary network contains many megakaryocytes, platelets formed from them, and neutrophils. A study revealed [23] that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), penetrating megakaryocytes of pulmonary capillaries, disrupts the formation of small platelets. Macroplatelets then form aggregations and interfere with capillary blood flow, causing local microbleeding. In the context of the SARS-CoV-2 pandemic, clarifying the mechanisms for the implementation of proinflammatory and pro-atherogenic functions of platelets is important. An increase in the count and size of megakaryocytes and platelets can also cause microvascular thromboembolism in the heart, lungs, and kidneys in patients who died from coronavirus disease 2019 (COVID-19) [23–25]. However, many researchers have noted thrombocytopenia in the blood plasma in patients with COVID-19, leading to local hemorrhage [25]. The inconsistency of data on changes in the platelet count may reflect their hematopoiesis at different periods of COVID-19 development, namely, initial thrombocytopenia, causing microbleeding, and a compensatory increase in thrombocytopoiesis due to this pathology. Moreover, no atherosclerotic changes were found in the vessels of the heart, which should be investigated [25].

Normally, a resting platelet represents a small, biconvex, nuclear-free cell 2–6 μm in size, containing some molecules and organelles of the original megakaryocyte, mitochondria, and densely packed tubules of the smooth endoplasmic reticulum. When platelets are activated, deep invaginations of the membrane are connected to the endoplasmic reticulum and form an open tubular system connected to the cell surface, through which platelet biologically active substances can be diffusely released as microparticles or exovesicles [26]. This can also be facilitated by the ongoing process of microfragmentation of the marginal platelet surface during its activation [20–21]. Molecules that are part of various granules, exovesicles, and microparticles can be synthesized based on mRNA obtained from a megakaryocyte, mitochondria, and endoplasmic reticulum.

The main pool consists of platelet granules α, δ, γ, and λ. The first of them, α-granules, in addition to the adhesion proteins P-selectin and von Willebrand factor, contain hemostasis factors, namely, platelet factor 4, B-thromboglobulin, fibronectin, fibrinogen, factors V and XIII, and other platelet factors of the coagulation cascade, and proteins with wide functional abilities, such as sphingosine-1-phosphate, transforming growth factor β1 (TGFβ1), and platelet-derived growth

factor (PDGF) (in humans, the PDGF-BB homodimer predominates). The sphingosine-1-phosphate receptor, SP1R1-3, is expressed by endothelial cells and VSMCs [27], transendothelially migrating neutrophils, monocytes, and dendritic cells [28], and by alveolar epithelium, where sphingosine-1-phosphate maintains the integrity of the histo-hematic barrier in the lung parenchyma [20]. TGFβ is involved in the transformation of monocytes into macrophages and transdifferentiation of VSMCs during plaque formation and vessel wall regeneration [11–13]. PDGF-BB synthesized in megakaryocytes is contained in platelet α-granules and is secreted upon its activation. It is a potent mitogen of VSMCs and vascular wall fibroblasts, activating their migration, proliferation, synthesis, and secretion of collagen and glycosaminoglycans through its receptors [26]. Together with PDGF-BB and other fibrogenic factors secreted by platelets and under the influence of fibroblasts and VSMCs, the volume of connective tissue in the plaque increases in the last stages of atherosclerosis.

Dense granules, or δ-granules, contain adenosine triphosphate or adenosine diphosphate (required for the formation of platelet aggregation), calcium (an indispensable participant in many stages of hemostasis), or serotonin, which accumulates in large amounts; therefore, platelets are considered, along with the spleen, the main depository of serotonin in the periphery [29]. When platelets are activated or the spleen contracts in the presence of thrombocytopenia, serotonin secretion helps attract neutrophils to the locus of acute inflammation and provides vasoconstriction, enhancing the hemostatic function of platelets. A similar vasomotor effect is exerted by thromboxane A2, which is formed in the endoplasmic reticulum [6, 20]. In the early stage of atherosclerosis, platelet serotonin is important for increasing endothelial permeability and recruiting leukocytes. The composition of γ-granules includes hydrolyzing enzymes similar to lysosomal ones. They can participate in the disassembly of intercellular contacts in the endothelium, which is required for the diapedesis of leukocytes into the intima. Molecules of λ-granules are involved in the resorption at the last stages of the formation of the necrotic plaque center [30]. Exovesicles and microparticles released by platelets can contain various inflammatory factors, such as proinflammatory interleukins IL-1β and IL-6, tumor necrosis factor (TNFα), granulocyte-macrophage-colony-stimulating factor, etc. Many proinflammatory cytokines and chemokines are secreted not only by platelets but also by endotheliocytes, neutrophils, and monocytes/macrophages, often when interacting in duets of platelet/endothelium, platelet/macrophage, or platelet/neutrophil or trios of endothelium/platelet/neutrophil [31, 32], platelet/macrophage/neutrophil, or platelet/macrophage/VSMCs. However, the initial launch, impetus to increase (through joint efforts of the multicellular ensemble) in the intima of the concentration of a certain proinflammatory factor up to the suprathreshold level, is implemented by activated platelets.

Mechanisms of platelet activation

Platelet activation can be induced by chemical and mechanical factors. Chemical factors include hypoxia, fibrin, fibrinogen, collagen, cytokines, and chemokines secreted by other cells in the vessel wall [6, 17]. Many platelet membrane receptors, after binding to a ligand, activate guanosine diphosphate/GTP-binding proteins of the Gs, Gq, Gi, or G12 types, followed by the activation of the corresponding intracellular signaling systems. The action of their final and/or intermediate components, owing to the absence of a platelet nucleus, is limited to targets in the cytoplasm, mitochondria, and cell membrane [2]. For example, upon the activation of the adenylyl cyclase and guanylate cyclase systems, cyclic adenosine monophosphate and cyclic guanosine monophosphate regulate the activity of membrane ion channels in different directions. In infections via Toll-like receptors (TLR4 or TLR7) of the platelets, bacterial lipopolysaccharides activate the inflammasome mechanism, followed by the activation and release of proinflammatory ILs. Moreover, the nuclear factor κB (NF-κB), known as an activator of transcription of proinflammatory cytokine genes in other nuclear cells in platelets, limits its action by suppressing the anti-apoptotic effects of Akt kinase and activation of intracellular proinflammatory pathways, particularly through p38 and thromboxane A2 [7, 33]. NF-κB in platelets also causes the secretion of cytokines with a procalcifying effect, namely, IL-1β, IL-6, and TNFα, contributing to increased inflammation and plaque calcification in the last stages of atherosclerosis development. The activation of NF-κB-dependent

inflammation in platelets has also been described upon the activation of the receptor for advanced glycation end products (RAGE), a receptor for protein glycation end products. These receptors are expressed in endotheliocytes and platelets, and their count increases in type 2 diabetes mellitus, thereby enhancing diabetic atherosclerosis [7, 8, 33]. The activation of RAGE has been described in its binding to many ligands, including AGE, high-mobility group box 1 (HMGB1), β-amyloid, and protein S100 secreted by activated macrophages [8].

In hemostasis, for mechanodependent platelet activation, first of all, adhesion through glycoproteins GP1b-IX-V is significant, which bind the platelet to subendothelial von Willebrand factor (vWF) in case of damage to the vessel wall and receptors for collagens of the vessel basement membrane, namely, glycoprotein VI (GPVI) and integrin α2β1. These receptors are associated with intracellular elements of the platelet cytoskeleton, microtubules, and actin microfilaments, and its branching is provided by actin-related protein 2/3 (Arp 2/3). It also forms protrusions and lamellipodia on the platelet surface, ensuring its migration, directed by a sequence of adhesion points (haptotaxis process), along the endothelial surface and scanning it to detect microdamages or pathogens [36, 37].

Aspects of hemodynamics and wall thickness of different parts of the vascular bed affect the shear force [2, 36–38] and platelet activation, increasing the risk of atherosclerosis in the vessels (in descending order) of the abdominal aorta; coronary, popliteal, femoral, and tibial arteries; thoracic aorta, thoracic aortic arch, and carotid arteries. In contrast to coagulation thrombosis, the involvement and activation of platelets at an early stage of atherosclerosis does not occur through the formation of platelet aggregates, but mainly due to the transient and strong adhesion of individual platelets to endothelial cells and ruptures in the endothelial lining and/or adherent leukocytes [36–38]. Moreover, the concentration of complexes of platelets with leukocytes increases not only at the point of damage to the endothelium but also in the vascular bed.

The abundance of receptors for various mediators, hormones, chemokines, and cytokines indicates the high functional plasticity of platelets and close interaction with microenvironment cells; these properties are required for participation in hemostasis, inflammation, and immune defense [20, 21, 37, 38]. As protectors of the vascular bed, platelets can perform a threefold function; i.e., they provide the formation and retraction of a platelet–fibrin thrombus, which closes damage to the vessel wall and prevents bleeding; block the penetration of pathogens into the blood through the damaged locus; and attract neutrophils and macrophages from the vascular bed to the intima of the vessel wall, promoting their migration and subsequent extravasation [37, 40]. This determines the need for the participation of platelets in the development of the inflammatory process in the vessel wall at the initial stages of atherogenesis. Recent studies have emphasized the characteristics of the implementation of these platelet functions, that is, participation in hemostasis is typical for platelet aggregation in moderate and relatively large damage to the vessel wall. Proinflammatory functions are characteristic of single platelets that scan the endothelium surface with lamellipodia in search of its microdamages (several μm^2), which are commensurate with the cell size, and spread over them, blocking the paths for microhemorrhages [19, 35, 36, 39, 40]. This explains the presence of the latter in thrombocytopenia. Such microdamages may result from transendothelial diapedesis of lymphocytes or destruction of individual endothelial cells as a result of ROM-induced apoptosis. These functions of platelets are important for suppressing microbleeding and penetration of infections into the intima and tissue surrounding the vessel. A platelet migrates along the monolayer of the endothelium through haptotaxis [37], which is a movement directed by a sequence of platelet adhesion points to the endothelium through the GPVI/α2β1/Arp2/3 receptor complex. Subsequently, the interaction with α2β1 integrin, which is a mechanosensitive receptor, and the "shear stress" of laminar blood flow [1, 38] change the biophysical properties of the membrane, such as local tension forces, which is one of the activation factors for an adhered platelet and determines its mechanosensory properties as a scavenger (mechano-scavenger) [33]. In addition, due to adhesion, the intracellular integrin signaling system is activated, which leads to an increase in the concentration of calcium ions in the platelet and Ca^{2+}-dependent rearrangements of the platelet cytoskeleton, which ensures its migration and Ca-dependent exocytosis of biologically active substances.

Stages of atherosclerosis development and platelets

An important consequence of platelet adhesion to the endothelium is the activation of the NADPH oxidase in its membrane, followed by self-enhancing production of ROM and their secretion into the surrounding microenvironment. This supports and enhances further production of ROM by the platelet mitochondria, its activation, adhesion, LDL oxidation [41, 42], and increased recruitment of preendotheliocytes, neutrophils, and monocytes/macrophages into the vessel wall. Among the substances secreted by activated platelets, angiopoietin-1 and sphingosine-1-phosphate, which regulate endothelial permeability, can influence the recruitment process at this stage, including vascular endothelial growth factor and platelet-activating factor (PAF), which can disrupt endothelial intercellular junctions. Platelet granules accumulate platelet factor 4 (PF-4), stromal cell-derived factor-1, macrophage inflammation protein 1α (MIP-1α), and chemokines RANTES (regulated upon activation, normal T cell expressed and secreted) and thymus and activation-regulated chemokine. They are involved in the recruitment of leukocytes to platelets, and some of them (serotonin, PAF, and S1P) further activate platelets by feedback and enhance their action to increase vascular permeability and attraction of leukocytes.

In the early stages of atherosclerosis, platelets contribute to the transformation of preendotheliocytes into endothelial cells, contributing to the restoration of the monolayer, and form aggregates with neutrophils or monocytes, inducing differentiation of the latter into macrophages [41]. The bilateral nature of this interaction is indicated by the results of *in vitro* experiments, which presented modulation of the reactivity and adhesive properties of platelets by neutrophils and/or macrophages [42, 43].

Platelets and macrophages

The ability of macrophages to secrete ROMs, oxidize LDLs, and exhibit phagocytic activity makes these cells a necessary component of inflammation, including atherosclerosis. In women with cardiovascular pathologies and increased cholesterol levels, the number of aggregates consisting of platelets and macrophages increases [44], which is associated with the attraction of monocytes from the vascular bed to the intima by platelets in the early stages of atherosclerosis and at the stage of increased plaque size. In aggregates, platelets activate macrophages, changing their phenotype to proinflammatory, characterized by increased secretion of proinflammatory cytokines IL-1β, IL-6, and TNFα by macrophages and under conditions of increased expression of STAT-induced suppressor of cytokine signaling-3 (SOCS3) [17, 44, 45] by impaired phagocytosis. This leads to persistent plaque growth and unresolved inflammation. In mice fed with a Western diet, reduced thrombocytopoiesis resulted in reduced plaque volume, macrophage accumulation, and reduced necrosis area. Similar results were obtained in a cohort of patients with myocardial infarction, indicating an increase in the number of platelet/macrophage aggregates, proinflammatory cytokines, and SOCS3 in plaques and a decrease in the SOCS1/SOCS3 ratio [17]. Thus, acting through macrophages, platelets have a proinflammatory effect on the vessel wall outside the mechanism of thrombosis and hemostasis [6, 44].

The study of macrophage subpopulations involved in atherogenesis [47–50] suggests that macrophages of functionally different subpopulations can be included in platelet–macrophage aggregates at different stages of the pathology development. For example, in the first stage of atherogenesis, a high LDL level as a cofactor is required to trigger the process of attracting monocytes by platelets [6], which imposes certain requirements on the macrophage phenotype. Moreover, in the stage of plaque calcification and increased necrosis area, macrophages of subpopulations with the $CD45^+$ inflammatory marker expressing osteocalcin and bone alkaline phosphatase may participate in the atherogenesis, as was revealed for patients with coronary atherosclerosis [46]. Through RNA sequencing of a single cell [47], the authors confirmed the heterogeneity of macrophage subpopulations at different stages of atherogenesis in the human aorta and lower limb arteries. The number of platelet aggregates with $CD4^+/CD6^+$ monocytes increases in myocardial infarction [50]. However, whether platelets are involved in the selection of macrophages of different subpopulations, as inflammation develops during atherosclerosis, remains to be explored.

Platelets and neutrophils

Platelets can form complexes not only with monocytes but also with neutrophils, stimulating oxidative burst and phagocytosis in them, and degranulation and netosis in neutrophils. *In vitro* experiments have revealed [51] that thrombin-activated platelets cause ROM release even in unstimulated monocytes and neutrophils. Moreover, the secretion of adenine nucleotide metabolites by platelets inhibits ROM production by neutrophils; thus, researchers draw a logical conclusion about the modulating nature of platelet control of the oxidative burst in the intima of the vessel wall with the participation of neutrophils and monocytes [35]. The activation or inhibition of ROM release by neutrophils is possible only under conditions of intercellular adhesion in the neutrophil/platelet complex. Moreover, the bilateral exchange of exovesicles and microparticles between nonadherent neutrophils and platelets promotes neutrophil activation and netosis [41]. Such microparticles may contain LDLs, thromboxane A2, and other derivatives of arachidonic acid with vasomotor and proinflammatory functions, as well as HMGB1 [41]. The latter, being a non-histone protein of chromatin, is secreted by phagocytes as a cytokine, binds to the innate immunity receptor TLR4 which intracellular signaling system activates inflammasomes, followed by the activation and secretion of proinflammatory ILs.

Depending on the context, the effect of platelets on neutrophil degranulation can be specific, as in *in vitro* experiments, in neutrophils activated by an opsonized zymogen, platelets increased lysosomal secretion and caused unstimulated neutrophils to release of myeloperoxidase and neutrophil elastase. The latter can occur during netosis, i.e., the release of neutrophil extracellular traps (NETs), which are untwisted DNA strands containing certain enzymes (myeloperoxidase and neutrophil elastase) [17, 50, 51]. Netosis is considered an apoptosis-like mechanism of neutrophil cell death [50] on the first line of the body's defense against infecting factors that are captured by the NETs and destroyed. TLR4- and integrin-dependent interaction of platelets with neutrophils can activate NET production to capture bacteria; however, endothelial damage is possible [55]. In turn, neutrophil NETs can also capture macrophages and platelets and activate them [33, 43], thus linking inflammation and thrombosis [17, 41]. This form of thrombosis triggered by the neutrophil/platelet interaction has been called immunothrombosis, which contributes to infection control. Neutrophils loaded with LDLs, and therefore having a larger volume, are prone to NET formation and, to a lesser extent, to phagocytosis [41], choosing the appropriate mechanism for regulating the cell volume. Thus, in the early stages of atherosclerosis, an activated platelet, increasing the paracellular permeability of the endothelium, "opens the door" to the subendothelial intima for neutrophils and macrophages, "closes the door" to avoid microbleeding, and activates the proinflammatory activity of these cells, enhancing the oxidative burst, netosis, and phagocytosis, and the secretion of proinflammatory mediators. The formation of the neutrophil/platelet module is facilitated by the creation of several adhesive contacts through proteins expressed by both cells, namely, the basic P-selectin/PSGL-1 and GPIbα/Mac-1. The neutrophil influences platelet function by secreting cathepsin D and elastase, whereas the platelet affects the CCL5/PF4/chemokine [41]. In addition, both cells are involved in the metabolism of arachidonic acid with TxA2 formation and the strong oxidizing agent 12-hydroeicosotetranoic acid [41].

Platelets and SMCs

Substances secreted by activated platelets, macrophages, and neutrophils in the early stages of atherosclerosis accumulate in the intima, and activate and differentiate VSMCs in a concentration-dependent manner, which migrate from the media to the intima and then to the plaque. Fibrogenic substances of platelets (PDGF-BB, PF4, B-thromboglobulin, serotonin, and TGFβ), along with oxidized LDL, contribute to VSMC transformation into myofibroblast-like VSMCs, which are characterized by lamellipodia and increased synthesis of collagens I and II and reduced synthesis of proteoglycans, which promotes greater cell mobility and their movement to the upper layers of the plaque. Here, under the influence of Kruppel-like factor 4 and oxidized LDLs (or with the addition of hydroperoxide in *in vitro* experiments), these SMCs turn into osteoblast-like ones and calcify intensively on the plaque surface due to the secretion of osteocalcin [31, 44]. This correlates with the role of calcium as an acidosis buffer. By continuing to absorb LDL, they turn into

foamy SMCs, which when accumulated increase the size of the plaque and undergo necrosis. This induces the secretion of IL-1α, which activates the phagocytic activity of VSMCs, which turn into a population of macrophage-like, cytokine-secreting cells. Aging VSMCs are seen in the final stage of transformation. They are distinguished by increased secretion of membrane metalloproteinases, cytokines, and chemokines [55, 56]. The latter, as well as biologically active substances secreted by platelets, additionally recruit macrophages and neutrophils from the vascular bed, which phagocytize old VSMCs, products of apoptosis and necrosis with the formation of a necrotic plaque center [13, 16], which gradually becomes unstable. Platelets at all stages of the development of atherosclerosis have a potentiating effect on the implementation of the functions of all participating cells and on the process as a whole.

Conclusions

An analysis of the aspects of the contact (with adhesion) and distant interaction of platelets with endotheliocytes, neutrophils, and monocytes/macrophages, as well as with VSMCs in the process of atherosclerosis development, suggests their key role in the direction of the process, possibility of switching the functions of participating cells from one protective response (hemostasis) to another, i.e., inflammation. By functioning as the "conductor" of the orchestra of all participants in the atherosclerosis process, platelets support the "soloists" of each "act" stage of the process through the formation of structural and/or functional modules. Thus, a platelet can change the phenotype of a neutrophil or macrophage and VSMCs in the appropriate stage of the process, limiting or changing the pattern of biologically active substances secreted by the cell and/or expressed receptors and implemented functions. This view of platelet function enables us to consider the level of thrombocytopoiesis as a target of therapy not only for atherosclerosis but also for other inflammation- or fibrosis-associated pathologies.

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