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Тромбоциты и регенерация

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РЕЗЮМЕ

Представлен анализ данных, доказывающих участие тромбоцитов в механизмах регуляции репаративной регенерации тканей. Показано их влияние на повреждение, апоптоз, пролиферацию клеток, ремоделирование экстрацеллюлярного матрикса, ангиогенез и нейрогенез. Дана оценка их взаимодействию с макрофагами в процессе восстановления структуры поврежденных тканей. Охарактеризованы некоторые тромбоцитарные регенеративные факторы.

Ключевые слова: тромбоциты, регенерация, ангиогенез, нейрогенез, макрофаги.

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Platelets and regeneration

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ABSTRACT

The review presents the analysis of data proving the role of platelets in the mechanisms of regulation of reparative tissue regeneration. The influence of platelets on damage, apoptosis, and proliferation of cells, as well as on extracellular matrix remodeling, angiogenesis, and neurogenesis is shown. Their interaction with macrophages in restoring the structure of damaged tissues is assessed. Several regenerative properties of platelets are characterized.

Key words: platelets, regeneration, angiogenesis, neurogenesis, macrophages.

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INTRODUCTION

It has long been thought that platelets are involved only in the processes of hemostasis. However, studies over the past two decades have shown the polyfunctionality of these formed blood elements, which makes them an important link in body adaptation to various extreme factors, such as hypoxia, ionizing radiation, infection, stress, etc. [1].

Platelets play a particular role in reparative processes, being the first to react to damage, along with neutrophils and macrophages. However, experimental studies showed that depletion of the neutrophil storage pool does not affect the regeneration process [2]. Platelets accumulate at the ends of damaged blood vessels, turn fibrinogen into fibrin, and form a blood clot consisting of cross-linked fibrin, fibronectin, vitronectin, thrombospondin, red blood cells, and platelets [3, 4]. In this clot, platelets are responsible for activating and releasing important biomolecules from their α-granules, including platelet-specific proteins, growth factors, clotting factors, adhesion molecules, cytokines, angiogenic factors, proteoglycans, and cytokines / chemokines [5]. Secretion of cytokines, chemokines, and growth factors, in turn, induces proliferation and activation of cells involved in wound healing, such as fibroblasts, neutrophils, monocytes, smooth muscle cells, and mesenchymal stem cells (MSCs) [6].

Antiplatelet drugs inhibit regeneration by slowing down the secretion of growth factors, such as vascular endothelial growth factor (VEGF), by platelets. So, in rats with gastric ulcer, the adenosine diphosphate (ADP) receptor inhibitor – ticlopidine – not only significantly suppresses platelet aggregation, but also disrupts gastric ulcer healing and angiogenesis. Moreover, platelet transfusions can reverse this effect [7]. In this case, platelets are present in the bloodstream but do not release their granules.

It can be assumed that the regenerative effect of platelets is due to one of three components: growth factors, chemokines, or proteins localized on the granule membrane and embedded in the platelet membrane after activation.

In trauma, the injury site is filled with a 3-dimensional polymerized fibrin clot containing plasma rich in wound healing factors, platelets, MSCs, and fibroblasts. Within several days, the cells inside the wound form a complex cocktail of wound healing, neurotrophic, and other factors. These observations served as the basis for the use of platelet-rich plasma ((PRP), platelet concentrate, platelet gel) for stimulating regeneration.

Blood plasma with a high platelet content is a complex of physiologically active substances that are defined as platelet-derived wound healing factors (PDWHF) [8–10]. They include several isotypes of platelet-derived growth factors (PDGF): ADP, adenosine triphosphate (ATP), calcium, serotonin, platelet factor 4, fibronectin, β-thromboglobulin, von Willebrand factor (vWF), fibrinogen, blood clotting factors V and XIII, transforming growth factor-β (TGFβ), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblast growth factor (β-FGF), fibroblast growth factor-2 (FGF-2), platelet factor 4 (PF4), ciliary neurotrophic factor (CNTF), insulin-like growth factor-1 (IGF-1), and platelet-derived angiogenesis factor (PDAF) [9, 11]. Some of these factors are involved in recruiting progenitor cells involved in tissue healing to the site of damage, while others are targeted by cells of the damaged tissue.

Although PRP is increasingly used for wound closure and activation of wound healing [12], specific mechanisms of platelet regulation of reparative processes have only recently attracted the attention of researchers. The accumulated clinical and experimental data allow to look at the physiology of blood plates from a new perspective.

Platelets are non-nuclear elements of blood, the cytoplasm of which can contain up to 100 membrane granules. The granules act as storage tanks for active substances. Several types of platelet granules were described, of which α-granules, dense granules, and lysosomes are of the greatest interest [13, 14].

α-granules are the most numerous (40–80%) and the largest (200–400 nm). They store more than 300 different proteins, such as blood coagulation proteins (factor V, factor IX, factor XIII, antithrombin, plasminogen, plasminogen activator inhibitor-1 (PAI-1)), adhesion molecules (fibrinogen, vWF, thrombospondin), chemokines, and growth factors (vascular

endothelial growth factor (VEGF), PDGF, FGF, EGF, hepatocyte growth factor (HGF), TGFβ). The release of these biologically active substances is not random but proceeds under the influence of an external stimulus. The contents of the granules are released after adhesion to collagen, other matrix components, or in response to soluble agonists, such as ADP or thrombin [5]. α-Granules are considered to be the key organelles with regard to platelet function.

Dense granules are smaller in size and quantity, store high concentrations of calcium, magnesium, nucleotides (ATP, ADP, cyclic adenosine monophosphate (cAMP), uridine triphosphate (UTP)), and pyrophosphates, serotonin (5-HT) and histamine. Secretion of dense platelet granules plays a major role in enhancing platelet response and thrombosis.

Platelet lysosomes, like in other cells, contain enzymes, such as cathepsin, elastase, collagenase, carboxypeptidase, glucosidase, glucuronidase, and acid phosphatase, which are associated with degradation of proteins, carbohydrates, and lipids [15–17].

In addition to protein synthesis, platelets also act as a source of active metabolites, such as eicosanoids synthesized from arachidonic acid, which are released from membrane phospholipids. Thromboxane A2 (TXA2) is a potent vasoconstrictor and is also associated with a proliferative response of damaged vessels [18]. Sphingosine-1-phosphate (S1P), which has the mitogenic action, is secreted by activated platelets at the time of clot formation and stimulates assembly of the fibronectin matrix and expression of TF (tissue factor) in endothelial cells [19]. Platelet-activating factor (PAF) is an active platelet-derived lipid that suppresses leukocyte migration and activates endothelial cells [20].

The platelet membrane contains many functional cell adhesion molecules, such as P-selectin, GPIIb/IIIa, GPIb, and integrins, which are not only involved in clot formation, but also allow platelets to interact with endothelial cells, white blood cells, including macrophages, and progenitor cells [21, 22]. P-selectin is present on the activated platelet membrane after the release of α-granules. This ensures that only activated platelets interact with immune and endothelial cells. The main leukocyte ligand for P-selectin is PSGL-1. Parallel release of cytokines and chemokines affects the interaction of platelets with leukocytes. This leads to increased regulation of leukocyte transcription factors and production of more cytokines and chemokines [5].

After damage, substances that are usually found inside cells enter the extracellular space. These endogenous molecules, which include proteins and nucleic acids, are called dampers and are a key signal for initiating immune responses and regeneration. Dampers can activate various types of receptors, including Toll-like receptors, nucleotide-binding oligomerization domain (NOD)-like receptors, retinoic acid-inducible gene 1 (RIG-1)-like receptors, C-type lectin receptors (CLR), receptors for advanced glycation end products (RAGE), G-protein-coupled receptors (GPCR), and ion channels [23], located on epithelial cells, endothelial cells, fibroblasts, neutrophils, macrophages, platelets, dendritic cells, etc.

The platelet response begins with the interaction of the P2Y1 and P2Y12 receptors located on the platelet membrane with ADP molecules emerging from damaged cells, and the G2 and Gi proteins, respectively, are secondary messengers in transmitting this signal. These receptors are known for their central role in platelet activation and aggregation [5, 23].

Platelet activation causes release of substances from dense granules through exocytosis involving Rab proteins. The released components include ADP (activating neighboring platelets in the above-described way), ATP, inorganic polyphosphate, pyrophosphate, serotonin, and calcium.

Activated platelets also release their α-granules containing biologically active substances, such as chemokine ligand 5 ((CCL5) or regulated upon activation, normal T cell expressed, and secreted (RANTES)), thrombin, transforming growth factor β (TGF-β), PDGF and VEGF, platelet factor 4, TF, IGF, FGF, CXCL12 or stromal cell-derived factor-1 (SDF-1), CD40 ligand, and EGF [3, 5, 24, 25]. Factors secreted by platelets induce and increase the activity of fibroblasts and have chemotactic effects first on neutrophils and then on macrophages, which ultimately leads to removal of dead cells and cell debris [26]. Moreover, platelets synthesize and secrete factors that induce and regulate proliferation and migration of other cell types, such as smooth muscle cells (SMCs) [27] and MSCs [28].

Cell proliferation and extracellular matrix remodeling are particularly important in early stages of regeneration. This response is modulated by the TGFβ signaling pathway in all Smads proteins. Inhibition of this pathway by the TGFβ antagonist SB-431542 leads to a decrease in cell proliferation and prevents regeneration [29]. Thus, in mice with TGF-β3 deficiency, inhibition of tissue inhibitor of metalloproteinases-2 (TIMP2) and matrix metallopeptidase-13 (MMP-13) or collagenase-3 was observed [30]. This

enzyme shows very high degrading activity against collagens of types I, II, III, IV, and XIV during endochondral and intramembranous osteogenesis. In human fibroblasts, it was shown that the addition of TGF-β1 led to an increase in the levels of mRNA and matrix metalloproteinase-2 (MMP-2) and a decrease in the level of collagenase mRNA [31]. TGF-β1 also regulated synthesis of TIMPs, which inhibit matrix metallopeptidases (MMPs) via the mitogen-activated pathway [32].

Activated platelets trigger recruitment, adhesion, and proliferation of adult stem cells, including CD34-positive progenitor cells [33], MSCs [28], SMS precursors [27, 34], and endothelial cell precursors [35]. Stromal cell-derived factor-1 (SDF-1) [36] and IGF-1 [37], which are also released by platelets, act as "homing beacons" for progenitor cells at the site of damage.

Activated platelets form extracellular vesicles by releasing their plasma membrane - platelet extracellular vesicles (PEV), through which intercellular communication with leukocytes is carried out. Although PEV can be produced in healthy individuals, their increased level is detected in injuries. The ability of PEV to bind to granulocytes, lymphocytes, and monocytes to form leukocyte vesicular complexes (LVCs) was shown [38–40].

Platelets are involved in the regulation of apoptosis and interaction of regenerating cells [41]. They secrete both proapoptotic (Fas-L [42], CD40L [43], tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) [44], TNF-like weak inducer of apoptosis (TWEAK) [45], and tumor necrosis factor superfamily element 14, also known as LIGHT [46]) and anti-apoptotic (HGF [47], SDF-1 [22], serotonin [27, 48], ADP [27] and S-1-P [49]) mediators. In addition, platelet-derived microparticles can regulate apoptosis in endothelial cells and SMCs and transmit survival signals to monocytes, endothelial cells, and neural stem cells. In the spleen and lungs, granzyme B acts as a meditator for platelet-induced apoptosis. Amphoterin, which is exported on the cell surface of platelets upon their activation, also regulates apoptosis and autophagy of tumor cells, which depends on redox processes (redox status). Therefore, platelets regulate a complex set of tissue repair mechanisms [50].

Along with matrix remodeling, proliferation, and differentiation of specific cells, restoration of microcirculation and innervation plays an essential role in reproducing the structure the damaged tissue.

There is growing evidence that platelets are a necessary condition for angiogenesis in wound healing / tissue regeneration [51, 52]. At the sites of platelet aggregation, regeneration of damaged vascular intima begins [53].

An injection of own platelets and leukocytes in a rat with hind limb ischemia initiated angiogenesis in it [54]. There was a significant decrease in neovascularization with a fall in the number of platelets *in vivo* [55, 56]

Platelets secrete various promoters of angiogenesis, such as VEGF, basic fibroblast growth factor (bFGF), EGF, and PDGFs or angiopoietin-1 [57].

VEGF is a very powerful angiogenic factor [58, 59]. Changes in the proliferative activity of the endothelium and apoptosis of endothelial cells are caused by release of VEGF and endostatin by platelets [7]. The VEGF-C and VEGF types are contained in α-granules of platelets and are released upon platelet activation [60]. Platelets not only synthesize VEGF but also act as carriers of this factor from other sources of its formation [60].

In platelets and megakaryocytes, angiopoietin-1 (which provides stabilization of proliferating endothelial cells and vessels) was found in vascularized tissues, while it was absent in these cells in non-vascular zones [61]. Angiopoietin-1 is released from platelets after their activation, for example, by thrombin [61].

Redistribution of endogenous growth factors from the cytoplasm of intact platelets to the periphery of filopodia and laminopodia in activated platelets may be associated, at least to some extent, with the regulation of angiogenesis [62, 63]. In addition to angiogenesis stimulators, platelets secrete a number of its inhibitors, such as angiostatin, endostatin, platelet factor (PF)-4, or thrombospondin (TSP)-1. Angiostatin is an example of an angiogenesis inhibitor formed by platelets, which is released during the aggregation of blood plates [64].

Endostatin specifically inhibits endothelial cell proliferation and powerfully suppresses angiogenesis and tumor growth [65]. PF-4 was the first hemostatic protein to show an angiogenesis-inhibiting effect *in vivo* [66]. At least partially, the antiangiogenic activity of PF-4 is due to interference with FGF-2, which causes inhibition of its dimerization following interaction with the FGF receptor and internalization.

Platelet thrombospondin (TSP) is also an inhibitor of angiogenesis; it destabilizes local contacts of endothelial cells and inhibits proliferation of the latter [67]. Moreover, thrombospondins, megakaryocytes, and

platelets act as the main antiangiogenic switches and determine the degree of revascularization *in vivo* [68].

Interestingly, platelet-induced angiogenesis requires the physical presence of platelets, because their secretion (supernatant) alone does not have a noticeable effect on tube formation *in vitro* [69]. Thus, the cell-cell interaction between platelets and endothelial cells appears to play an important role in neovascularization. In another study, adding platelets to a solution for infusions before injecting animals induced dose-dependent angiogenesis [70].

To initiate angiogenesis, destabilization is necessary – weakening of intercellular contacts between endothelial cells, destruction of the basement membrane, as well as local proteolysis of matrix proteins for endothelial cells or their precursors from the circulating blood to migrate and form new vessels [71, 72].

Urokinase is most often considered as a key regulator of vascular wall remodeling after mechanical damage [73]. Activated platelets release neurotransmitters, serotonin, dopamine, histamine, and glutamate, and can also alter the activity of neuronal cells [74]. The presence of platelets in the area of damage to the nervous system accelerates restoration of function and enhances not only angiogenesis but also neuronal regeneration [75].

In small experimental animals, it was shown that when the central and peripheral sections of the cut nerve are connected with a collagen tube filled with PRP, it induces axon regeneration. Thus, it is possible to compensate for the defect of the sciatic nerve in rats up to 1 cm long [76–79]. In this case, a thicker myelin sheath is formed, the rate of regeneration increases and recovery goes over a greater distance [10]. For PRP fibrin to promote more neurons to regenerate over a greater distance, it must bind and interact with neurotrophic cells. In this interaction, an important role is attributed to such factors as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3 (NT-3), and PDGF [80–85]. These factors, which, in turn, are associated with platelets and mesenchymal cells, transform matrix fibrin to actively promote axonal regeneration [86].

The noted phenomenon was shown during transection of the facial nerve in the guinea pig [87], the facial nerve in the rat [76], the sciatic nerve in the rat [77, 88–90], and the cavernous nerve in the rat [87, 91].

It is generally accepted that macrophages are an important link in the regeneration process, acting as coordinators of actions aimed at restoring the original tissue structure or scarring. Macrophages act as a source of proinflammatory cytokines in the damaged area, such as interleukin (IL) 1, IL-6, and tumor necrosis factor (TNF). They are responsible for controlling adhesion and migration of inflammatory cells, as well as proliferation of fibroblasts and keratinocytes [3].

The depletion of macrophages in axolotl by injecting clodronate encapsulated in liposomes leads to impaired regeneration of the amputated limb [92]. Clodronate is unable to penetrate into the cell membrane. However, being encapsulated in liposomes, it is phagocytosed by macrophages. This drug is metabolized by macrophages *in vitro* to adenosine-5- [B, γ-dichloromethylene] triphosphate (AppCCl2p). AppCCl2p (ATP analogue), inhibiting the mitochondrial electrogenic ADP / ATP translocase, causes depolarization of the mitochondrial membrane and subsequent cytochrome C release and caspase activation, which leads to specific apoptosis of macrophages [93]. Therefore, we can talk about a relationship between the lack of regeneration of the extremities and depletion of macrophages in this experiment.

Selective macrophage depletion using clodronate in modeling myocardial infarction leads to a serious violation of the myocardial architecture, increased collagen deposition, and increased mortality in mice [94, 95].

The use of a transgenic mouse (lysM-Cre / DTR mouse strain) containing macrophages sensitive to diphtheria toxin (DTox) showed delayed wound healing with strong morphological disturbances [96]. This is due to a decrease in TGF-β1 expression, a dysregulated VEGF pattern, and an almost complete loss of wound contraction in the absence of myofibroblast differentiation. Macrophage depletion was detected by decreased mRNA expression of EGF-like module-containing mucin-like hormone receptor-1 (Emr-1) and lysozyme of macrophages (LysM), which is a macrophage-specific marker F4/80.

All of the above-mentioned studies suggest that macrophages play a significant role in the regeneration process. Without these cells, regeneration fails, a hypertrophic scar or a non-healing wound is formed.

The macrophage population can be divided into two functional phenotypes. They are named M1 (classically activated) and M2 (alternatively activated) macrophages [3]. M1 macrophages are activated in response to damage to lipopolysaccharide (LPS), TNF-α, and interferon (INF)γ [97]. These ligands act on macrophages via LPS / IFNγ or TLR-2, -3, -4, and -9

and cause the release of IL-1B, TNFα, and IL-6, mediated by the signaling factors NF-kB, STAT1, IRF5, and AP-1 [98]. These cytokines amplify the inflammatory and antimicrobial responses [3, 99, 100].

IL-4 and IL-13 (M2a), which trigger Fcγ receptors in the presence of a Toll-like receptor (M2b) or IL-10 (M2c), can stimulate macrophages to differentiate into M2 macrophages [97, 98]. These three macrophage phenotypes are not activated, for example, M1, and exhibit properties different from them.

M1 and M2a macrophages are present together at the site of damage. Macrophages migrating to the wound on the 1st day after injury mainly (85%) show the M1 phenotype [101], but on the 5th day, the M2 phenotype is the dominant macrophage population in the wound [98]. Compared to the axolotl, the mammalian has an increase in proinflammatory cytokines over anti-inflammatory ones after injury [92], which may be a key reason for the decrease in the regenerative properties of mammalian tissues.

The activation of both Toll-like and Fcγ receptors in macrophages results in the M2b phenotype. The M2b phenotype, as compared to M2a, produces much higher levels of IL-10 along with the proinflammatory cytokines TNFα, IL-1β, and IL-6 [97]. During a later proliferative phase, the M2b-mediated release of IL-10 appears to stimulate the activation of M2c macrophages [98]. IL-10 inhibits production of proinflammatory cytokines, such as TNFα, IL-6, and IL-12, and antigen presentation by macrophages through the downregulation of major histocompatibility complex (MHC) class II molecules [97]. Activation of the STAT3 signaling pathway results in the release of TGFβ.

Since platelets and macrophages play the key role in regeneration, the mechanisms of interaction of these cells in the dynamics of repairing damaged tissues are of particular importance.

During regeneration, platelets and macrophages interact with one other both directly and indirectly through other cells (for example, endothelial cells), exerting a reciprocal effect. Platelets and platelet factors (mediators) activate and modulate apoptosis in monocytes, and platelet phagocytosis is essential in pro- and anti-inflammatory processes [102].

With the direct interaction of activated platelets with blood monocytes, platelet-monocyte complexes form. Aggregates of platelets with monocytes form more easily (i.e. at lower concentrations of platelet agonists) and faster and are more stable than platelet-neutrophil and platelet-lymphocyte complexes [103]. Sialidase treatment of platelets leads to an increase in their binding to homologous peritoneal macrophages but does not affect the rate of phagocytosis. The interaction of platelets with macrophages is mediated by a galactose-specific receptor on the surface of macrophages [104].

Infection-induced thrombocytosis is a clinically significant complication of tuberculosis, accompanied by impaired immunity. Inhibition of platelets with aspirin or treatment of the platelet-specific receptor, glycoprotein IIb / IIIa, with inhibitors leads to a decrease in platelet-macrophage interactions and restoration of macrophage-mediated immunity to mycobacterial infection [105, 106].

When interacting with activated platelets through PSGL-1 / P-selectin, as well as when binding products of activated platelets (RANTES, IL-1β, and PAF), NF-kB-dependent inflammatory genes are induced in monocytes [107]. Binding of PSGL-1 leads to the activation of the MAP kinase and the mTOR pathways [107]. A signal triggered in monocytes upon contact with platelets and binding of endogenous IL-1 induces expression of cyclooxygenase-2 (COX-2) and formation of prostaglandin E2 (PGE2) dependent on it [107]. The latter, in turn, reduces the activity of platelets [108, 109].

Upon contact with platelets, monocytes acquire an inflammatory phenotype and increase the affinity of adhesion to the endothelium [110, 111]. Platelets are captured by monocytes and macrophages, which causes an increase in the release of cytokines from monocytes [112]. Thus, activated platelets affect the survival and differentiation of monocytes, after which the complexes of monocytes with activated platelets disintegrate [113].

Platelet-macrophage communication is also carried out through PEVs, which, after binding to the monocyte and formation of a platelet-monocyte complex, is absorbed by the latter within 30–60 minutes [110]. Thus, PEVs can deliver, in particular, the RANTES chemokine (CCL5) to monocytes and endothelial cells, promoting the attraction of monocytes to the subendothelium [114]

CCL5 is one of the most important monocyte chemoattractants released by platelets after injury. CCL5 interacts with the endothelial surface in the presence of the cytokine IL-1β and acts as a cell-associated signal for monocyte adhesion and migration across the vascular endothelium. IL-1β is also released from platelets [5].

RANTES is also secreted by endothelial cells under the influence of IFNγ and TNFα [115]. TGFβ not

only stimulates the activation of macrophages M2c, but the M2c subtype itself is an important source of TGFβ, which contributes to many aspects of wound healing: inflammation, chemotaxis, wound reduction, angiogenesis, and extracellular matrix (ECM) deposition [3].

The exposure of activated platelets to monocytes causes an increase in the expression of tissue factor (TF) and binding to the coagulation factor Xa and fibrinogen. The resulting thrombin causes not only aggregation and activation of platelets, but also activation of monocytes, directing them to enhanced adhesion and production of chemokines CCL2 and RANTES [116, 117]. Binding of the platelet cytokine CXCL13 to the CXCR5 receptor on monocytes leads to inhibition of TNFα and IL-6 production [118].

Platelets eject microparticles not only upon activation but also upon aging as a result of an apoptosis-like process (apoptosis-induced platelet microparticles). With prolonged incubation with monocytes, they contribute to cell differentiation but suppress their proliferation. Analysis of monocyte membrane receptors shows increased levels of expression of CD11b (integrin aMb2), CD14, and CD31 (platelet / endothelial cell adhesion molecule-1), as well as chemokine receptors CCR5 and CXCR4, but not CCR2, which means that apoptosis-induced platelet microparticles polarize cells towards resident monocyte M2. Cells treated with apoptosis-induced platelet microparticles actively consume oxidized low-density lipoprotein (LDL) and release matrix metalloproteinases and hydrogen peroxide. One more confirmation of differentiation in direction of resident professional phagocytes is that particles stimulate expression of LDL, CD36, and CD68 receptors, as well as production of proinflammatory and immunomodulatory cytokines by monocytes [118].

Therefore, there is no doubt that in the processes of reparative regeneration, one of the leading places is occupied by platelets participating in its regulation at all stages of restoring the structure of damaged tissue. Deciphering the specific mechanisms of their reparative function will allow to develop new effective methods of targeted effect on wound healing.

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