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REVIEW
ОБЗОР

Programmed neutrophil death in immunothrombosis

Natalya G. Plekhova ✉, Alexander O. Mikhailov, Nikolay V. Tsvetov, Anastasia N. Voronova

Pacific State Medical University, *Vladivostok, Russian Federation*
✉ plekhova.ng@tgmu.ru

Abstract. *Relevance.* Understanding the fundamental mechanisms of immunothrombosis is essential for developing effective treatments and prevention of thrombotic disorders. This review aims to summarize the current knowledge on the role of programmed neutrophil death in the molecular and cellular mechanisms underlying immunothrombosis, as well as to demonstrate how dysregulation of hemostasis initiated by neutrophil death is associated with various pathological conditions. Based on a search of the electronic scientific databases Google Scholar, PubMed (MEDLINE), Scopus, and Web of Science using keywords and their combinations, with the methodological quality assessed using the AMSTAR 2 software, the role of neutrophil death in the development of immunothrombosis is presented. The review describes the types of programmed neutrophil cell death, namely apoptosis, pyroptosis, necroptosis, ferroptosis, and neutrophil extracellular traps (NETs), along with their molecular triggers and mechanisms. A modern concept of immunothrombosis pathogenesis is presented, demonstrating the involvement of hemostatic proteins, platelets, and proinflammatory cells in its pathogenesis and taking into account the complex relationship between hemostasis and inflammation. Each type of programmed neutrophil death is shown to be involved in the development of immunothrombosis. In addition, the review presents data on therapeutic strategies employing immunometabolic regulators and NET inhibitors, which potentially can attenuate immunothrombotic activity without affecting hemostasis. Such treatment approaches offer advantages for managing patients with various thrombo-inflammatory conditions. *Conclusion.* Overall, the data demonstrate that neutrophil apoptosis has an antithrombotic effect, whereas other types of programmed cell death promote thrombus formation and vascular events. The latter differ in that they require specific triggers: a cytokine storm for pyroptosis, the release of death-associated molecular patterns (DAMPs) for necroptosis, and oxidative stress for ferroptosis. These types of cell death are unified by their capacity to initiate NET formation, thereby providing a trigger framework for the development of severe thrombotic complications.

Keywords: neutrophils, programmed cell death, immunothrombosis, apoptosis, pyroptosis, necroptosis, ferroptosis, neutrophil extracellular traps

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Introduction

Thrombosis remains a serious challenge for medicine, manifesting in many diseases associated with high mortality across different demographic populations [1]. Based on an evolutionarily conserved link between the coagulation system and innate immunity, the process of thrombosis initiation involves cells and specific molecules of the host defense system [2, 3]. Under physiological conditions, this link facilitates the recognition of pathogens and damaged cells followed by their elimination, whereas, under dysregulated conditions, it manifests as thrombotic disorders in infectious and inflammatory pathologies. This process leads to increased blood coagulability and the progression of venous thromboembolism and arterial thrombosis, with high patient mortality rates, as observed, for example, in coronavirus disease COVID-19 [4, 5]. Inflammation involving immune cells strongly contributes to thrombosis development, but the precise mechanisms underlying this link remain incompletely understood.

The term “immunothrombosis” was first proposed in 2013 by Engelmann and Massberg to describe the interplay of innate immune cells, platelets, and blood coagulation factors in the local control of homeostasis aimed at immobilizing foreign pathogens or structures [6]. It is known that inflammation triggers coagulopathies and adverse thrombotic events, highlighting the importance of a balanced interaction between the immune and hemostatic systems [6, 7]. The causal relationship mediated by Toll-like receptors on leukocytes leading to platelet activation is reciprocal, whereby the immune system influences thrombus formation and vice versa [8, 9]. Pathogen-associated and damage-associated molecular patterns (PAMPs and DAMPs) have been shown to induce unregulated activation of blood coagulation factors, platelets, endothelial cells, and the complement system [7]. Together these processes resulting in surface expression of P-selectin on platelets and endothelium, which recruits leukocytes and leads to a thrombo-inflammatory state. According to many authors, neutrophils are the key

drivers of immunothrombosis, exhibiting a high capacity for tissue factor activity through aberrantly mediated signaling of the protease-activated receptor (PAR) coagulation factor [10, 11]. These cells are sensitive to exogenous stimuli, interact with various cell types, and express numerous pattern recognition receptors for damage- and pathogen-associated molecular patterns (DAMPs and PAMPs) on their surface [12]. Upon reaching the site of inflammation and/or injury, they are capable of forming network structures — neutrophil extracellular traps (NETs) — with the release of nuclear DNA and cytosolic granules into the extracellular space [13]. It is well established that during sterile inflammation, neutrophils can also form NETs when exposed to other immune cells, platelets, or activated endothelium. Moreover, excessive NET formation can lead to disseminated intravascular coagulation, serving as a scaffold for thrombus formation, and can also initiate tissue fibrosis with organ failure [3, 14, 15]. In this review, we discuss the various pathways through which programmed neutrophil death can be activated and how these processes may lead to thrombus formation. We also provide an assessment of these pathways with respect to targeted therapy aimed at developing approaches to reduce blood clot formation without increasing the risk of bleeding.

Programmed neutrophil cell death

Neutrophils constitute approximately 50–70 % of all circulating leukocytes, originate from hematopoietic stem cells in the bone marrow, and differentiate under the control of granulocyte colony-stimulating factor (G-CSF) and chemokines (CXCL1, CXCL2, CXCL5, and CXCL8) [16]. Structural features of these cells include a multilobed nucleus, specialized (primary, secondary, and tertiary) granules, and secretory vesicles containing antimicrobial factors. Upon recognition of microbial and/or inflammatory stimuli, they migrate to the site of inflammation through an adhesion/migration cascade regulated by cytokines [17, 18]. This process is initiated by receptor interaction with PAMP and DAMP molecules, followed by rolling, adhesion, and transendothelial migration of the cells. In peripheral tissues, neutrophils are attracted by chemoattractants (CXCL8, IL-1β, leukotriene B4 and others), triggering effector functions including phagocytosis, production of reactive oxygen species (ROS), degranulation, vesicle secretion, and cell death [18]. The speed with which these cells migrate and perform antimicrobial functions, including the production of proteases and microbicidal peptides along with the generation of substantial amounts of ROS — underpins their ability to modulate various immune responses. [16]. Under homeostatic conditions, mature neutrophils constitute a short-lived cell population with a lifespan of up to one day; upon activation, for instance at an inflammatory site, their life cycle can be prolonged [18]. Following tissue inflammation, the release of lipoxins and resolvins affects neutrophil apoptosis, promoting efferocytosis by macrophages, reducing IL-23 levels, and suppressing hematopoietic progenitor activity in the bone marrow [19]. Neutrophils may re-enter the bloodstream and, via reverse migration, return to the bone marrow [18]. In addition to apoptosis, these cells may undergo alternative forms of regulated cell death, including necroptosis, pyroptosis, and NETosis (NET formation) [17]. Each of these alternative mechanisms of neutrophil cell death has important implications for inflammatory responses and the initiation of immunothrombosis.

Neutrophil apoptosis. This evolutionarily conserved type of regulated cell death plays a predominant role in maintaining organismal homeostasis and occurs in response to extrinsic and intrinsic inducers (Figure 1). Activation of the proapoptotic caspase cascade with subsequent cleavage of their substrates induces structural changes in cells, including reduction in cell area, plasma membrane blebbing, chromatin condensation, nuclear DNA fragmentation, and formation of apoptotic bodies [17] (Figure 1). The intrinsic signaling pathway of neutrophil apoptosis is modulated by B-cell lymphoma 2 (Bcl-2) family molecules and is activated upon involvement of various cytosolic factors, including DNA damage, hypoxia, and metabolic stress [19]. Proapoptotic Bcl-2 family proteins, the Bcl-2-associated X protein (Bax) and/or its antagonist Bak, promote outer mitochondrial

membrane permeabilization, leading to the release of cytochrome C and other enzymes into the cytosol [20]. Their release into the cytoplasm triggers the assembly of the apoptosome, which activates caspase-9, which in turn initiates effector caspases 3 and 7 [19] (Figure 1). The extrinsic pathway of apoptosis is induced by ligands binding to death receptors such as CD95/Fas, tumor necrosis factor receptor 1 (TNFR1), and the TNF-related apoptosis-inducing ligand (TRAIL) cytokine (Figure 1).

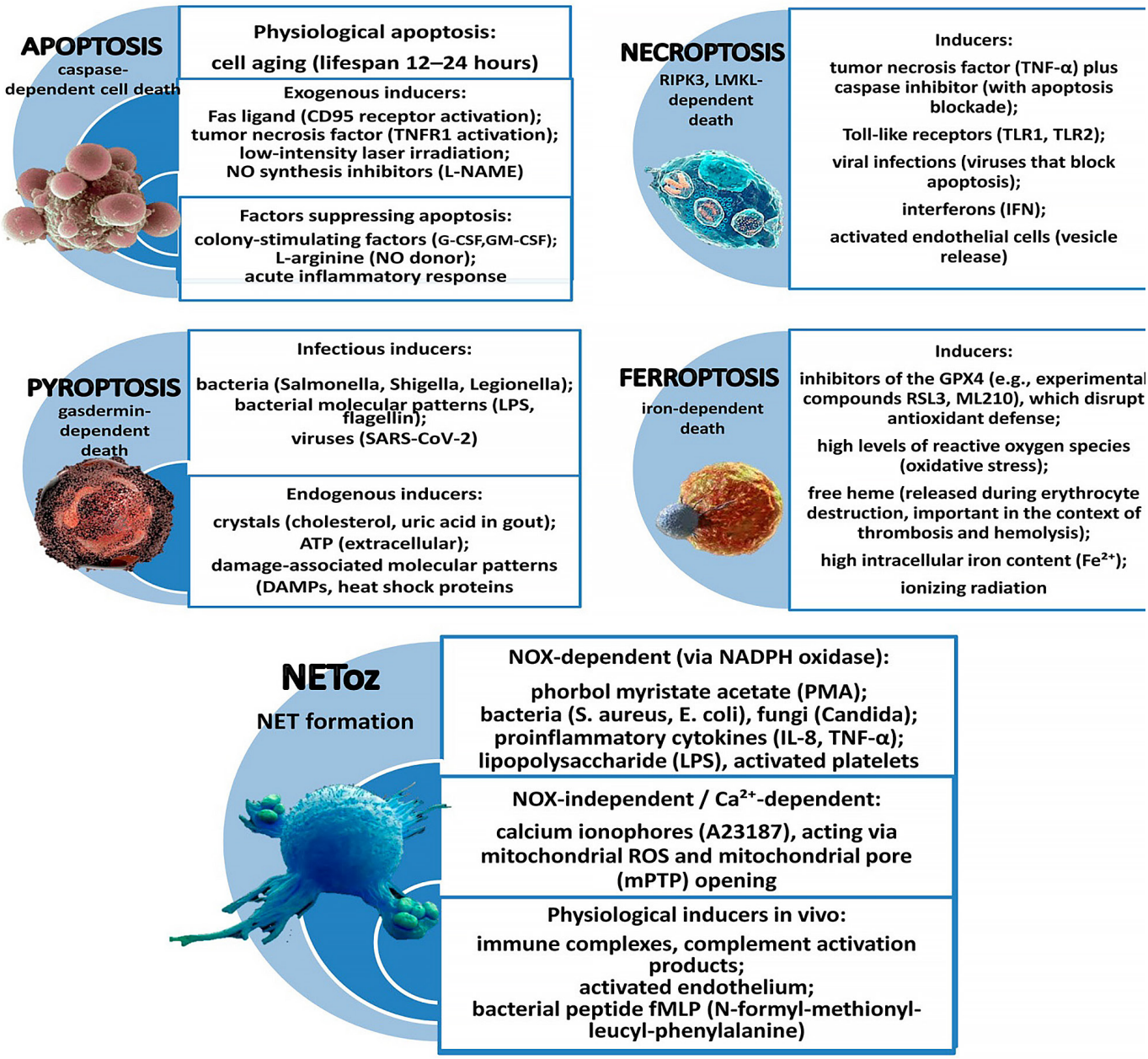

Figure 1. Exogenous and endogenous signals triggering the processes of programmed neutrophil death

Their activation triggers the assembly of the death-inducing signaling complex.

(DISC) with caspases 8 and 10, which promotes the cleavage of procaspases 3 and 7 [19, 20]. The kinetics of CD95/Fas-induced apoptosis can be modulated through the expression levels of pro- and antiapoptotic proteins [20]. Cathepsins are released from azurophilic granules of neutrophils, which cleave and activate caspases 8 and 3, and it has been reported that defective neutrophil apoptosis contributes to the development of chronic inflammatory diseases [21].

Neutrophil pyroptosis. Unlike apoptosis, this type of cell death is proinflammatory, as it is accompanied by plasma membrane rupture and release ofintracellular contents [22]. The key mediator of this mechanism is gasdermin D (GSDMD), which, upon activation, is cleaved by caspases, and its N-terminal fragment inserts into the cell membrane, forming pores. This alters osmotic pressure, increases the cytoplasmic volume of the cell, and leads to its destruction with the release of the proinflammatory cytokines IL-1β and IL-18 [17, 23, 24]. The role of caspase-1-dependent gasdermin D cleavage in neutrophils has long been known, and recent transcriptomic and immunoblotting data indicate that elastase from their cytosolic granules cleaves gasdermin D more efficiently than caspases do [25]. In aging neutrophils, activated protease alone is sufficient to induce pyroptosis, whereas upon bacterial stimulation, the NLRC4 inflammasome is formed, leading to IL-1β-dependent cleavage of gasdermin D by caspase-1 (Figure 1) [26].

Neutrophil necroptosis. Neutrophil necroptosis is independent of apoptotic signaling and is induced by the synergistic activity of receptor-interacting protein kinase-3 (RIPK3, RIP3) and the effector protein mixed lineage kinase domain-like (MLKL) (Figure 1) [27]. The molecular basis of neutrophil necroptosis is currently insufficiently understood; nevertheless, its key role in the development of many cardiovascular diseases and other pathologies has been demonstrated [28]. Necroptosis involves the strictly regulated intracellular assembly of the necrosome, which induces structural alterations in cells resembling those seen in necrosis. Degradation of organelle and granule membranes induced by reactive oxygen species (ROS) triggers endosomal and autophagosomal fusion, leading to the formation of extensive cytoplasmic vacuoles and an increase in cell volume [28]. The nuclear envelope is disrupted, chromatin undergoes condensation, and the plasma membrane becomes permeable, inducing the release of intracellular DAMPs, which exert a proinflammatory effect. This process is induced by ligation of TNFR1 and TRAIL receptors as well as adhesion molecules (CD44, CD11b, CD18, and CD15) on neutrophils (Figure 1) [17, 27, 28]. Unlike apoptosis, necroptosis is triggered upon caspase-8 inactivation, without DNA fragmentation, and is accompanied by a robust immune response driven by DAMPs [18]. Characterization of the necroptosis signaling pathway holds significant promise for the management of inflammation resulting from neutrophil dysfunction [8, 16].

Neutrophil ferroptosis. Neutrophil ferroptosis is a distinct type of programmed cell death characterized by the accumulation and peroxidation of phospholipids containing polyunsaturated fatty acids in the plasma membrane (Figure 1). This process is dependent on intracellular iron levels and is genetically and biochemically distinct from apoptosis, necrosis, and autophagy [29]. Ferroptosis manifests as disruption of plasma membrane integrity, swelling of the cytoplasm and mitochondria, and moderate chromatin condensation [30]. Neutrophils undergoing ferroptosis exhibit mitochondrial dysfunction with increased synthesis of ROS and lipid peroxidation products in the absence of morphological signs [31]. Ferroptosis is regulated by three main systemic pathways: (1) inactivation of the cysteine-glutamate antiporter, leading to inhibition of the antioxidant (REDOX) mechanism; (2) scavenging of peroxyl radicals and lipid oxidation involving the NADPH enzyme system with the suppressor protein FSP1 and coenzyme Q10; and (3) CoA ligase 4- and lipoxygenase-mediated activation of the system that esterifies polyunsaturated fatty acids into phospholipids [31]. Thus, during ferroptosis in neutrophils, redox reactions and iron and lipid transformations occur simultaneously [28, 30].

Neutrophil extracellular traps (NETs, NETosis). This is a lytic form of proinflammatory regulated cell death that is induced by an NADPH oxidase-mediated oxidative burst [32, 33]. NET formation is initiated by various signaling pathways, such as those stimulating

necroptosis, alterations in calcium ion levels, kinase phosphorylation, release of proteases from granules, and caspase-1 activation (Figure 1) [34]. Pyroptosis and NETosis are triggered by different molecules, but both types are mediated by nuclear histone H3-induced chromatin relaxation and DNA decondensation [18]. The formation of the web-like NET structure involves PAMP or DAMP receptors, which trigger a cascade of signaling pathways, culminating in changes in cell morphology with chromatin decondensation and translocation of DNA associated with cytosolic granular proteins [33]. This process depends on the activity of histone-cleaving serine proteases and procaspases. Furthermore, peptidyl arginine deiminase 4 (PAD4) promotes histone citrullination, which facilitates the interaction with negatively charged nuclear DNA, leading to its decondensation [1, 10, 34]. After DNA binds to granule components in the neutrophil cytoplasm, the subcortical actin network breaks down, and the decorated DNA, enclosed by the plasma membrane, is released into the extracellular space. In addition to the well-established role of NETs in trapping pathogens, their significance has been demonstrated in sepsis, autoimmunity, coagulation, and cancer [10, 13, 32, 33]. It has also been reported that NETs regulate the expression of the inflammatory cytokines IL-6 and pro-IL-1β in macrophages and participate in the development of vascular occlusion and thrombosis [1, 14].

Mechanisms of immunothrombosis and neutrophils

The contemporary concept of immunothrombosis pathogenesis, taking into account the complex interplay between hemostasis and inflammation, demonstrates the involvement of hemostatic proteins, platelets, and proinflammatory cells [7]. Coagulation factor III (tissue thromboplastin) is considered a marker of inflammation; it induces the biogenesis of Weibel-Palade bodies containing P-selectin in endothelial cells. This protein acts as a chemoattractant for leukocytes and can bind to platelets either directly or indirectly [7]. It consists of apoprotein III and a phospholipid complex and is expressed on the plasma membrane of fibroblasts, pericytes, vascular smooth muscle cells of subendothelial tissue, and activated monocytes [3, 7, 35]. Tissue thromboplastin interacts with coagulation factor VII, leading to its conversion to VIIa, which forms a complex with phospholipids and Ca^{2+} ions and activates the central component of the coagulation cascade, coagulation factor X [36]. In addition to this pathway, coagulation can also be triggered by contact of prekallikrein and its cofactor kininogen with activated factors XI and XII [37]. Thrombin and other proteases of the coagulation cascade, including factor Xa and VIIa, not only induce fibrin generation but also regulate cell functions, including hemostatic and inflammatory processes [7]. They can bind to G protein-coupled receptors (PARs), which are expressed on platelets (PAR1), thereby initiating platelet activation. Endothelial cells demonstrate the presence of all four members of the PAR receptor family and can be stimulated by activated protein C, as well as by plasmin, factors Xa and VIIa, and thrombin [37, 38].

Signaling through PAR receptors influences long-term mobilization of hematopoietic stem cell populations, the degree of adhesion marker, proinflammatory cytokine expression, and nitric oxide production [39]. These receptors are also expressed on leukocytes and influence proinflammatory and proapoptotic reactions. It has been shown that not only tissue thromboplastin synthesis by monocytes or endothelial cells exerts a procoagulant effect, but also neutrophil extracellular DNA can initiate coagulation through the contact pathway [11]. The fibrinolytic system plays a crucial role in immunomodulation by regulating the balance between pro- and anti-inflammatory processes through fibrin removal. Fibrin acts as a scaffold for immune cells and promotes their recruitment and activation. Endothelial and epithelial cells, as well as monocytes/macrophages, release tissue-type and urokinase-type plasminogen activators (uPA, tPA), thereby influencing the conversion of the main fibrinolytic enzyme plasminogen into plasmin [3, 7]. The acute-phase inflammatory mediator plasminogen activator inhibitor-1 (PAI-1) promotes bacterial elimination, enhances neutrophil migration, and regulates interferon-gamma (IFN-γ) synthesis in these cells, whereas plasminogen activator inhibitor-2 (PAI-2) attenuates the proteolytic activity of neutrophils [38, 39]. Thrombin-activatable carboxypeptidase (TAFI)

removes plasmin binding sites, which does not halt the process of plasmin binding to fibrin. As a result, numerous degradation products, including D-dimer and fibrinopeptide B, are released, which also possess immunomodulatory and chemotactic functions toward neutrophils [37].

It is also necessary to clarify the role of P-selectin (CD62P) interaction between activated platelets and the leukocyte glycoprotein receptor, for which monocytes exhibit the highest affinity, followed by granulocytes and lymphocytes [1, 40]. The initial attachment of platelets to leukocytes is stabilized by the involvement of other receptors and leads to targeted release of soluble mediators from the latter and activation of immune and inflammatory responses [6]. In addition to direct interaction with neutrophils, platelets release extracellular vesicles and soluble mediators, which modulate neutrophil functions [8, 11]. Platelet factor 4 (PF4/CXCL4) affects CD62P expression and IL-8 releasing by the endothelium, thereby influencing neutrophil extravasation [11]. Moreover, platelets stimulate cytokine production and the oxidative burst in neutrophils, which promotes NET formation [41]. The anticoagulant role of neutrophils consists of their ability to phagocytose platelets with membranes selectively modified by annexin A1 determinants of phosphatidylserine, thereby leading to active thrombus resolution [42]. Furthermore, these cells accelerate proplatelet maturation by eliminating defective cells [42].

Role of apoptosis in the context of immunothrombosis

Neutrophil apoptosis is a mechanism that limits and halts immunothrombosis (Figure 2). Its occurrence prevents cells from transitioning into necrosis or NETosis, which can activate platelets and subsequent thrombus formation [43]. This is supported by data demonstrating that suppression of apoptosis leads to an accumulation of "aged" and hyperactive neutrophils in tissues, which promote thrombus formation through the release of ROS and enzymes [44]. Such negative effects of apoptosis arrest, induced by cytokines and growth factors, have been noted in respiratory distress syndrome and multiorgan failure, where uncontrolled immunothrombosis plays a significant role [45]. Conversely, accelerated massive neutrophil apoptosis in sepsis patients with AIDS promotes immunosuppression, leading to neutropenia and impaired cell function, thereby increasing the risk of infections [43]. In turn, impaired clearance of neutrophil apoptotic bodies may lead to secondary necrosis or may serve as a source of autoantigens [19]. Thus, neutrophil apoptosis is a natural limiter of immunothrombosis, ensuring the removal of spent cells and preventing their transformation into triggers of thrombus formation. However, both its timely initiation and termination are critically important.

Pyroptosis, necroptosis, and ferroptosis of neutrophils in immunothrombosis

Unlike apoptosis, neutrophil pyroptosis is accompanied by plasma membrane rupture and the release of vacuolar and lysosomal contents, which recruits other immune cells and amplifies inflammation. The link between these processes is direct and interdependent, with gasdermin D playing a key role [2, 23]. When neutrophils activated, which cleaves gasdermin D, leading to subsequent pore formation in the membrane [23, 24].

Even before neutrophil death, this protein promotes their maturation and activation, increasing integrin expression on the membrane, which allows them to firmly adhere to the vessel wall [25]. This process activates platelets and triggers the coagulation cascade (factor XII, among others), leading to the formation of a fibrin thrombus, to which pathogens and immune cells adhere [2]. For instance, in a mouse model of thrombotic microangiopathy induced by cholesterol crystals, the absence or blockade of gasdermin D reduces immunothrombosis and kidney injury [17]. It has been reported that dysregulation of immunothrombosis involving neutrophil pyroptosis and massive NET formation leads to disseminated intravascular coagulation, lung injury, and multiorgan failure in COVID-19 viral infection [5, 41, 44]. Thus, during pyroptosis, gasdermin D activates neutrophils, which adhere to the vessel wall and begin to produce inflammatory molecules, creating a thrombus formation zone that recruits additional cells.

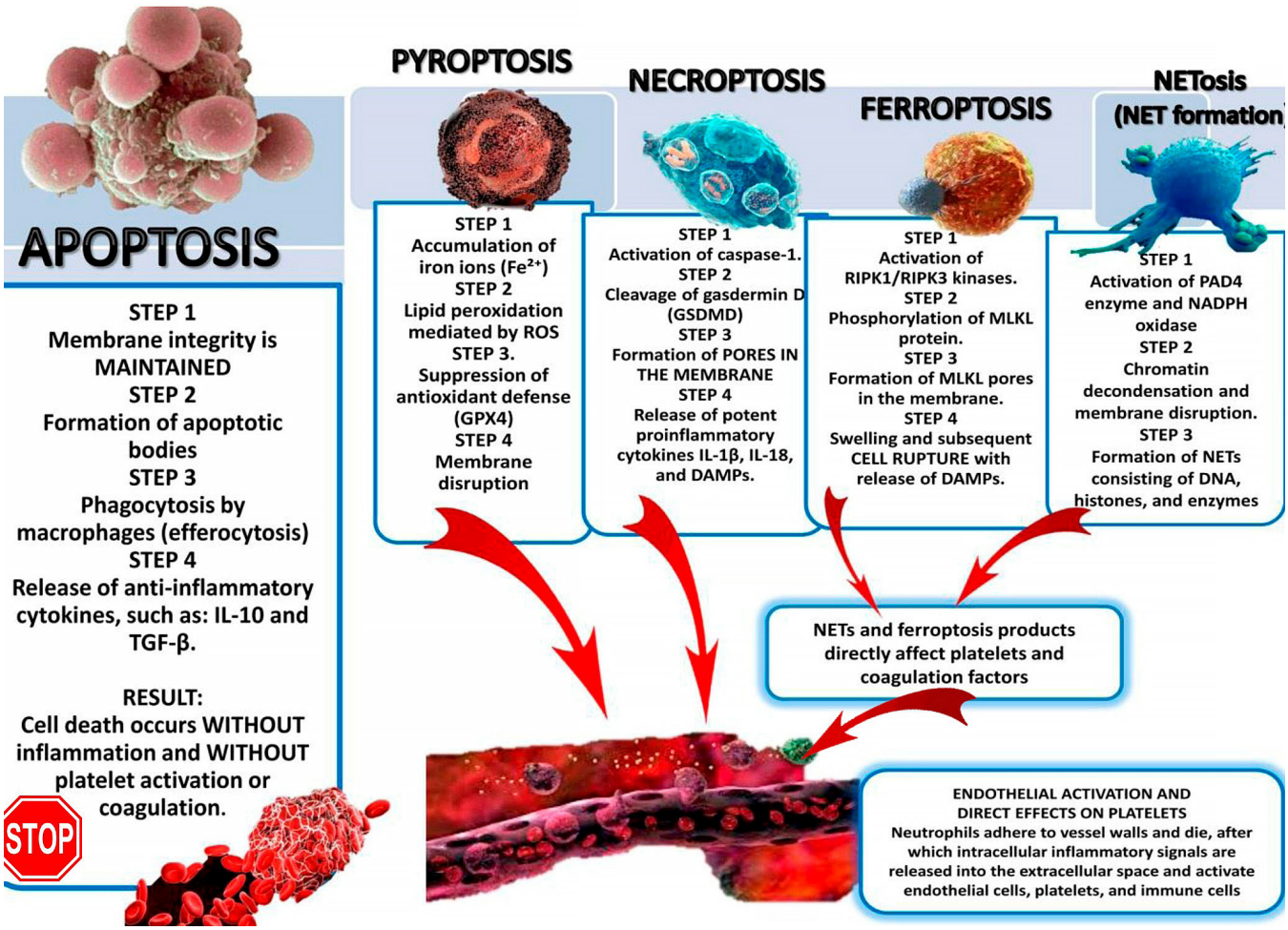

Figure 2. The influence of types of programmed neutrophil death on immunothrombosis

Two alternative neutrophil death programs, necroptosis and ferroptosis, also actively promote the development of immunothrombosis (Figure 2) [8]. Necroptosis is triggered by the activation of RIPK1, RIPK3 kinases and the MLKL protein, which form pores in membranes, leading to cell rupture with the release of DAMPs, whereas the main driving force of ferroptosis are iron ions, which stimulate membrane lipid peroxidation (Figure 1) [27, 29]. For the induction of immunothrombosis, the key link for both processes is the activation of the formation of NETs, which directly activate platelets and bind to coagulation factors [45–47]. During necroptosis, the release of intracellular DAMP molecules enhances inflammation and creates a prothrombotic environment, and inhibition of its key enzyme, RIPK1 kinase, abort this process and the formation of NETs [47]. In sepsis and acute respiratory distress syndrome, necroptosis of endothelial cells and neutrophils has been shown to contribute to hypercoagulability and microthrombosis in pulmonary vessels [45, 47]. Ferroptosis also stimulates the formation of NETs, which directly activate platelets expressing P-selectin on their surface, leading to thromboembolism [46]. This type of cell death is considered a key player in the pathogenesis of immunothrombosis in COVID-19, and it has been suggested that targeted therapy aimed at suppressing it may improve patient outcomes [5]. Understanding

the role of the above-mentioned death mechanisms is critical for the treatment of diseases in which immunothrombosis becomes dysregulated. Inhibition of key molecules, such as RIPK1 in necroptosis, may block the pathological immunothrombosis cascade, whereas for ferroptosis, iron-chelating agents or inhibitors of lipid oxidation are under investigation [45, 46].

Thus, pyroptosis, necroptosis, and ferroptosis represent three distinct yet functionally overlapping programs of neutrophil death that serve as critical drivers and amplifiers of immunothrombosis. Unlike apoptosis, which limits this process, the other types of cell death are united by their proinflammatory and prothrombotic potential, which is realized through several key mechanisms (Figure 2). A central event linking all three types of cell death to immunothrombosis is their ability to trigger or enhance NET formation. Despite this common outcome, each pathway makes a unique contribution to pathogenesis. The main feature of pyroptosis is not merely cell death but the accompanying massive release of potent proinflammatory cytokines (IL-1β, IL-18). This creates a systemic milieu that activates the endothelium and platelets, making them more sensitive to prothrombotic signals [48]. In necroptosis, which is often triggered when apoptosis is blocked by pathogens, DAMPs serve as powerful stimulators of inflammation and provoke thrombotic complications in sepsis and severe lung injury. As a metabolic catastrophe, ferroptosis is unique in its ability not only to affect neutrophils but also to directly activate platelets through lipid peroxidation mechanisms. This death pathway acts as a link between metabolic imbalance, platelet dysfunction, and neutrophil hyperactivity. Hyperactivation of pyroptosis, necroptosis, and ferroptosis transforms the protective response of immunothrombosis — aimed at isolating pathogens in the bloodstream — into a pathological factor. The presented data justify the promise of searching for therapeutic agents capable of selectively inhibiting these neutrophil death pathways. Blockade of key molecules (e.g., gasdermin D in pyroptosis, RIPK3 in necroptosis, and iron ions in ferroptosis) may represent a strategy to restrain pathological immunothrombosis while preserving its physiological protective functions [2, 18, 42, 45]. Of particular interest is a combined targeting, as these pathways may duplicate and amplify one another.

Role of neutrophil extracellular traps in the pathogenesis of immunothrombosis

Neutrophils contribute to the capture and degradation of pathogens through the formation of NETs, accompanied by the release of decondensed chromatin and antibacterial proteins. Initially, these structures were discovered in patients with stroke, where they provided a scaffold within blood vessels for recruiting erythrocytes, platelets, and leukocytes, as well as binding plasma proteins [28, 42]. It has also been demonstrated that in sepsis, inflammation accelerates neutrophil recruitment and activation, leading to NET formation, which initiates connective tissue remodeling and contributes to the development of venous thrombosis in the lungs [8, 10, 32]. In COVID-19 viral infection, conversion of Hageman factor (factor XII) to XIIa promotes immunothrombosis by influencing IL-6 and complement synthesis, with subsequent activation of NET formation [4].

Procoagulant proteins, including von Willebrand factor, factors XI and XII have been found on the insoluble reticular DNA structure containing histones and bactericidal enzymes [36]. Moreover, while histones with immobilized coagulation factors activate platelets, negatively charged DNA triggers activation of the coagulation cascade through XIIa-induced thrombin generation [49]. In contrast, elastase inactivates anticoagulant mechanisms by cleaving thrombomodulin and tissue factor pathway inhibitor [6]. Predisposition to NET formation is primarily exhibited by aging neutrophil subpopulations with high phagocytic capacity [40]. In addition to local effects through the release of tissue thromboplastin-containing vesicles, NETs have a systemic, long-term effect on microthrombus formation and vascular occlusion, inducing immunosuppression [50].

Indeed, during inflammation, the functions of NETs include not only the capture and elimination of pathogens, which enhances the microbicidal effect of neutrophils, but also prothrombotic and procoagulant stimulation [49]. This type of cell death is often recognized as an important therapeutic

target. For example, in sepsis, the effect of the TLR4 receptor blocker and the TNF-a synthesis inhibitor 2-acetamidopyranoside on reducing the level of circulating adhesion receptor ICAM-1, NET formation, and thrombus development has been demonstrated [51]. Statins and angiotensin receptor blockers possess similar effects, as they inhibit TLR4 signaling pathway activity, thereby reducing the release of proinflammatory cytokines [52]. One of the stimulators of NET formation is peptidylarginine deiminase 4 (PAD4); its inhibition reduces vascular damage and endothelial dysfunction [53, 54]. Treatment with low doses of heparin (250 U/kg) reduces NET formation and synthesis of proinflammatory factors, whereas increasing its concentration, conversely, induces NET formation and the production of antibodies against platelet factor 4, leading to thrombosis activation [54, 55]. These findings indicate the need for precise heparin dosing in clinical practice or the use of heparin alternatives.

Conclusion

Unlike apoptosis, which has an anticoagulant effect, the molecular mechanisms of neutrophil death namely pyroptosis, necroptosis, ferroptosis, and NETosis turn these cells into powerful prothrombotic drivers. These types of programmed cell death are united by their capacity to trigger NET formation and differ in their specific mechanisms: a cytokine storm in pyroptosis, DAMP release in necroptosis, and direct platelet activation via oxidative stress in ferroptosis. Collectively, the programs of neutrophil cell death other than apoptosis form a trigger basis for the development of severe thrombotic complications in many critical conditions of the organism.

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Запрограммированная гибель нейтрофилов при иммунотромбозе

Н.Г. Плехова ✉, А.О. Михайлов, Н.В. Цветов, А.Н. Воронова

Тихоокеанский государственный медицинский университет, *г. Владивосток, Российская Федерация*
✉ plekhova.ng@tgmu.ru

Аннотация. Понимание основных механизмов иммунотромбоза необходимо для разработки эффективных методов лечения и профилактики тромботических нарушений. Цель обзора – изложить существующие знания о роли запрограммированной гибели нейтрофилов в молекулярных и клеточных механизмах развития иммунотромбоза, а также представить, каким образом дизрегуляция гемостаза, инициированная смертью этих клеток, связана с различными патологическими состояниями. На основании поиска работ в электронных научных базах данных Google Scholar, PubMed (MEDLINE), Scopus и Web of Science по ключевым словам и их сочетаниям с использованием программы AMSTAR 2 представлена роль гибели нейтрофилов в развитии иммунотромбозов. Изложены данные о типах запрограммированной гибели нейтрофилов, а именно апоптозе, пироптозе, некроптозе, ферроптозе и нейтрофильных внеклеточных ловушках (НВЛ), их молекулярных триггерах и механизмах. Представлена современная концепция патогенеза иммунотромбоза, которая демонстрирует вовлеченность в его патогенез гемостатических белков, тромбоцитов, провоспалительных клеток и учитывает сложную связь между гемостазом и воспалением. По каждому из типов запрограммированной гибели нейтрофилов показано участие в развитии иммунотромбоза. Наряду с этим, изложены сведения о терапевтических стратегиях с использованием иммунометаболических регуляторов и ингибиторов НВЛ, которые потенциально могут ослабить иммунотромботическую активность, не влияя на гемостаз. Такие методы лечения имеют преимущества для лечения пациентов при многих тромбовоспалительных состояниях. *Выводы*. В целом, продемонстрированные данные указывают, что апоптоз нейтрофилов обладает противотромботическим эффектом, тогда как остальные типы запрограммированной гибели способствуют развитию тромбов и сосудистых катастроф. К отличиям последних относятся специфические триггеры, а именно, для пироптоза цитокиновый шторм, для некроптоза выброс молекулярных паттернов смерти и для ферроптоза окислительный стресс. Объединяет указанные типы гибели способность запускать НВЛ, результатом чего является формирование триггерной основы развития тяжелых тромботических осложнений.

Ключевые слова: нейтрофилы, запрограммированная гибель клеток, иммунотромбоз, апоптоз, пироптоз, некроптоз, ферроптоз, нейтрофильные внеклеточные ловушки

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Corresponding author: Natalia G. Plekhova — Dr Biol. Sc., Associate Professor, Head of the Interdisciplinary Research Center, Pacific State Medical University, 2 Ostryakov Ave., Vladivostok, 690087, Russian Federation, E-mail: plekhova.ng@tgmu.ru
Plekhova N.G. SPIN 2685-9578, ORCID 0000-0002-8701-7213
Mikhailov A.O. SPIN 1469-9086, ORCID 0000-0002-2719-3629
Tsvetov N.V. SPIN 6076-0443, ORCID 00009-0009-0318-0661
Voronova A.N. SPIN 3863-4021, ORCID 0000-0001-7571-0750

Ответственный за переписку: Плехова Н.Г. — доктор биологических наук, доцент, заведующий междисциплинарным научно-исследовательским центром, Тихоокеанский государственный медицинский университет Минздрава России, 690087, Владивосток, пр. Острякова 2, Российская Федерация, E-mail: plekhova.ng@tgmu.ru
Плехова Н.Г. ORCID 0000-0002-8701-7213
Михайлов А.О. ORCID 0000-0002-2719-3629
Цветов Н.В. ORCID 00009-0009-0318-0661
Воронова А.Н. ORCID 0000-0001-7571-0750