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NEUTROPHILIC GRANULOCYTES: PHAGOCYTES AND MORE

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Neutrophilic granulocytes are one of the key cellular factors of innate immunity. The review presents data on the morphology, migration and utilization of neutrophilic granulocytes, phagocytosis and degranulation processes, neutrophilic extracellular traps, plasticity of neutrophils, their role in systemic inflammatory reactions and regulation of adaptive immunity.

Keywords: neutrophilic granulocytes; innate immunity; inflammation; neutrophilic extracellular traps.

НЕЙТРОФИЛЬНЫЕ ГРАНУЛОЦИТЫ — ФАГОЦИТЫ, И НЕ ТОЛЬКО

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Нейтрофильные гранулоциты — одни из ключевых клеточных факторов врожденного иммунитета. В обзоре представлены данные по морфологии, особенностям миграции и утилизации нейтрофильных гранулоцитов, процессам фагоцитоза и дегрануляции, нейтрофильным внеклеточным ловушкам, пластичности нейтрофилов, их роли в системных воспалительных реакциях и регуляции адаптивного иммунитета.

Ключевые слова: нейтрофильные гранулоциты; врожденный иммунитет; воспаление; нейтрофильные внеклеточные ловушки.

Neutrophilic granulocytes (neutrophils) are traditionally considered one of the first lines of defense of a macroorganism against microorganisms invading its body [1–4]. In classical morphophysiological studies, I.I. Mechnikov and his students studied the phenomenology of the phagocytic process carried out by neutrophils, including microphages, pseudo-eosinophils, and heterophiles, and proved the irreplaceable role of this process in the functions of the innate immunity of animals against infectious agents of various biological characteristics. I.I. Mechnikov also strongly emphasized the great importance of cytases, which are intracellular microbicidal substances, in ensuring complete phagocytosis. In his research, the functions of phagocytes (e.g., micro- and macrophages) are considered from a comparative evolutionary standpoint, thereby enabling the elucidation of their key role in the formation of innate immunity [1].

In modern studies, patients with congenital impaired neutrophil functions, such as neutropenia, adhesion disorders, and granule deficiency, are usually susceptible to infection by bacteria (e.g., *Staphylococcus aureus*, *Pseudomonas*, and *Burkholderia*) and fungi (e.g., *Aspergillus* and *Candida*) but not viruses and parasites. The sites of entry for infection include the skin, mucous membranes, and lungs, but virtually any part of the body can be affected; and abscesses are common [5].

List of abbreviations

DNA — deoxyribonucleic acid; MMP — matrix metalloproteinases; NADPH oxidase — nicotinamide adenine dinucleotide phosphate oxidase; ICAM — intercellular adhesion molecules; IL — interleukin; MIP — macrophage inhibitory protein; NET — neutrophilic extracellular traps; TLR — Toll-like receptor; TNFα — tumor necrosis factor alpha.

1. Morphology of neutrophilic granulocytes

Neutrophils are among the most numerous types of leukocytes; in humans, these cells are the most numerous leukocyte type. Up to 60% of the hematopoietic activity of the bone marrow can be directed toward the production of neutrophils, and approximately 10^{11} of these cells enter the blood every day. The development of neutrophils in the bone marrow occurs over 14 days, starting with hematopoietic stem cells [3].

The mechanisms regulating neutrophil differentiation are not fully understood, but the role of a specific set of transcription factors and cytokines that seem to direct stem and progenitor cells to differentiate toward neutrophils has been established. The main cytokine regulating granulopoiesis is granulocyte colony-stimulating factor (G-CSF). The effects of G-CSF include induction of myeloid differentiation, proliferation of granulocyte precursors, and release of mature neutrophils from the bone marrow [6].

Stem cells destined to become neutrophils first differentiate into myeloblasts, which retain the ability to develop into eosinophils, basophils, and neutrophils. Subsequent differentiation leads to neutrophilic promyelocytes, a precursor of neutrophils, which then pass through the developmental stages of neutrophilic myelocytes, metamyelocytes, band neutrophils, and mature segmented neutrophils. At the metamyelocyte stage, neutrophilic mitosis ceases, but the development of neutrophils and formation of granules continue.

Intensive granulogenesis begins at the promyelocyte stage, during which lysosome-like initial vacuoles are formed at the level of the Golgi apparatus and then merge in the cytoplasm to form primary, or azurophilic, granules [7].

Azurophilic granules contain antimicrobial cationic peptides defensins, acid hydrolases (e.g., β-glycerophosphatase, *N*-acetyl-β-glycosaminidase, β-glucuronidase, α-mannosidase, cathepsin D, cathepsin B), neutral-alkaline proteases (e.g., elastase, cathepsin G), lysozyme, and myeloperoxidase [8] (Table 1). While the presence of acidic hydrolases renders these granules similar to lysosomes, azurophilic granules differ from real lysosomes at the membrane level by the absence of membrane proteins associated with LAMP-1 and LAMP-2 lysosomes and the mannose-6-phosphate receptor system [9].

Electronic histochemistry has allowed the detection of myeloperoxidase in all elements of the secretory apparatus of promyelocytes, such as in the canals of the endoplasmic reticulum, in the internal cisterns of the Golgi apparatus, and in the initial vacuoles and mature azurophilic granules [10]. Because this enzyme is synthesized only at the promyelocyte stage, it is recognized as a biochemical and cytochemical marker of the promyelocytic stage of human and mammalian neutrophil differentiation [7].

Some azurophilic granules begin to function soon after their formation. One of the functions of these granules is their participation in the physiological destruction of mitochondria by autophagocytosis during the myelocytic stage of maturation [11].

At this stage, the formation of secondary granules begins. The secondary granules of neutrophils constitute a population unique to neutrophils, which is reflected in their other name, that is, “specific”. Specific granules have a wide range of membrane-associated proteins, including cytochromes, signaling molecules, and receptors (see table 1). These granules act as a reservoir of proteins intended for localization on the outer surfaces of phagocytic vacuoles and the plasma membrane [12]. Matrix metalloproteinases (MMPs) are an important family of proteinases found in specific granules; these molecules are stored in the form of inactive enzymes and activated by proteolysis when interacting with the contents of azurophilic granules after the fusion of the granules with phagocytic vacuoles. MMPs generally destroy the membrane components of phagocytosed bacteria, but the function of MMPs of neutrophils is not limited to killing bacteria. For example, MMPs are also important for neutrophil extravasation and diapedesis [13].

The set of antimicrobial proteins and peptides differs between azurophilic and specific granules, and the only common protein between these granule types is lysozyme. An important space in specific granules is occupied by the iron-binding protein lactoferrin, which serves as a marker for specific granules, and antimicrobial peptides called cathelicidins, which, similar to MMPs, are stored in specific granules in the form of inactive propeptides.

The content of the granules can change both during the postnatal development of the organism

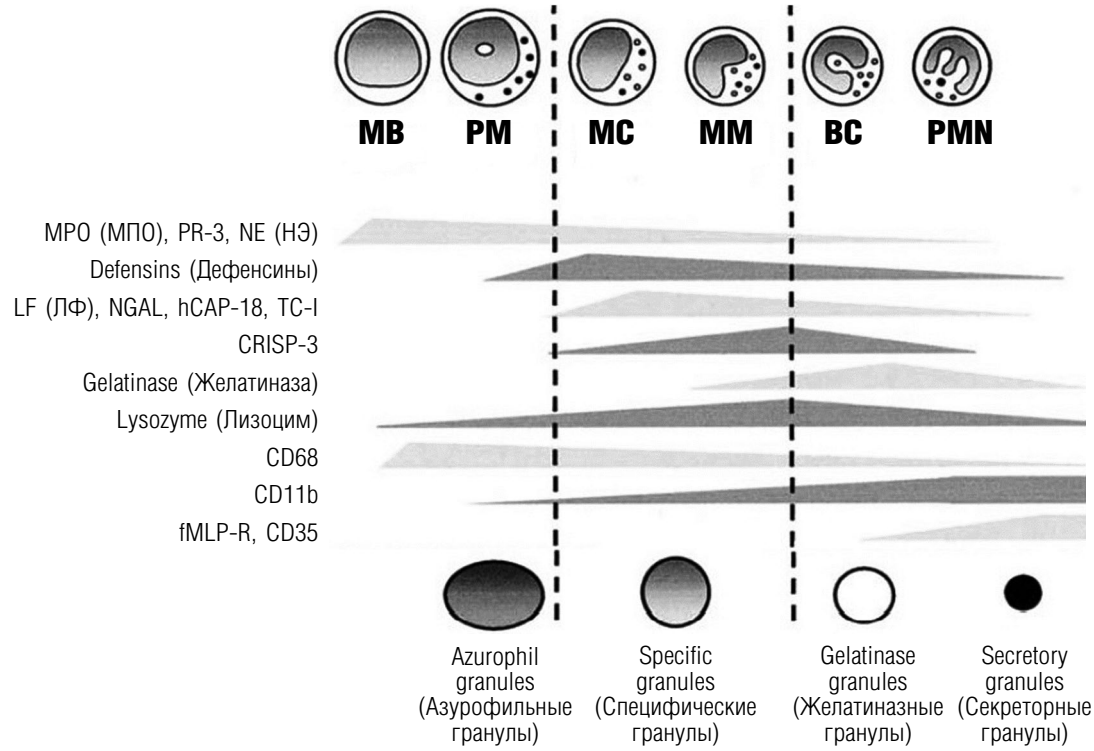
Contents of granules and secretory vesicles of human neutrophils (8)
Содержимое гранул и секреторных везикул нейтрофилов человека (8)

Azurophilic granules	Specific granules	Gelatinase granules	Secretory vesicles
Membrane			
CD63	CD11b/CD18	CD11b/CD18	Alkaline phosphatase
CD68	CD15	Cytochrome b_{558}	CD10
Presenilin 1	CD66	Diacylglycerol deacetylating enzyme	CD11b/CD18
Stomatin	CD67	fMLP-R	CD13
V-H^+-ATPase	Cytochrome b_{558}	Leukolysin	CD14
	fMLP receptor	VAMP-2	CD16
	Fibronectin receptor	V-H^+-ATPase	CD45
	G-protein α-subunit	SNAP-23, -25	CR1
	Laminin receptor	CD87	C1q receptor
	Leukolysin		Cytochrome b_{558}
	Neutrophil specific antigen NB1		CD55
	19-kDa protein		fMLP receptor
	155-kDa protein		Leukolysin
	GTase Rap1 and Rap2		VAMP-2
	Vitronectin receptor		V-H^+-ATPase
	SNAP-23, -25		
	Stomatin		
	Thrombospondin receptor		
	TNF receptor		
	CD87		
	VAMP-2		
Matrix			
Acid β-glycerophosphatase	$β_2$-microglobulin	Acetyltransferase	Plasma proteins
Acid mucopolysaccharides	Collagenase	$β_2$-microglobulin	
$α_1$-Antitrypsin	CRISP-3	CRISP-3	
α-Mannosidase	Gelatinase	Gelatinase	
Azurocidin	hCAP-18	Lysozyme	
Permeability-increasing protein	Histaminase		
β-Glycerol Phosphatase	Heparinase		
β-Glucuronidase	Lactoferrin		
Cathepsins	Lysozyme		
Defensins	Lipocalin 2 (NGAL)		

End of Table / Окончание таблицы

Azurophilic granules	Specific granules	Gelatinase granules	Secretory vesicles
Elastase	Urokinase type plasminogen activator		
Lysozyme	Neuraminidase		
Myeloperoxidase	Transcobalamin I		
N-acetyl-β-glucosaminidase	Stromelysin-1		
Proteinase-3	Leukolysin		
Neuraminidase	Cathelicidin		

Note. CRISP-3 — cysteine rich secretory peptide-3; SNAP — synaptosome-associated protein; VAMP — vesicle-associated membrane protein; GTP — guanosine triphosphate.



The sequence of the granulogenesis process and the synthesis of granular proteins at distinct stages of myeloid cell development [8]. MB — myeloblast; PM — promyelocyte; MC — myelocyte; MM — metamyelocyte; BC — band cell; PMN — polymorphonuclear neutrophil. Granule proteins: MPO — myeloperoxidase; PR-3 — proteinase 3; NE — neutrophil elastase; LF — lactoferrin; TC-I — transcobalamin I; CRISP-3 — cysteine-rich secretory protein-3

Последовательность процесса гранулогенеза и синтеза гранулярных белков на разных стадиях развития миелоидных клеток [8]. MB — миелобласт; PM — промиелоцит; MC — миелоцит; MM — метамиелоцит; BC — палочкоядерный нейтрофил; PMN — сегментоядерный нейтрофил. Белки гранул: МПО — миелопероксидаза; PR-3 — протеиназа 3; НЭ — эластаза нейтрофилов; ЛФ — лактоферрин; TC-I — транскобаламин I; CRISP-3 — богатый цистеином секреторный белок-3

and as a result of the postmitotic development of the cells themselves. For example, approximately 90%–95% of the entire population of neutrophilic promyelocyte granules in the bone marrow of newborn rabbits show a negative reaction toward peroxidase, although they contain other cationic proteins. Peroxidase appears in rabbit neutrophilic promyelocytes in the first weeks of postnatal development and is a specific marker of the granules of these cells only for a certain time after birth [11].

Granules with high gelatinase contents are formed at the metamyelocyte and band cell stages; thereafter, the formation of granules

ceases, and secretory vesicles are formed by endocytosis [14]. Secretory vesicles are noteworthy because of their wide range of membrane-bound proteins, including plasma membrane receptors. These and other data indicate that secretory vesicles function as reservoirs of proteins of the plasma membrane of neutrophils and other membrane proteins [5]. The process of granulogenesis and synthesis of granular proteins at the different stages of development of myeloid cells is shown in Figure 1 [8].

A mature neutrophilic granulocyte contains a segmented nucleus, cytoplasmic granules, a glycogen reserve in the form of a large number of non-membrane rounded bodies, and a well-developed cytoskeleton consisting of microtubules and microfilaments. Other cellular organelles are practically reduced. For example, the Golgi apparatus and rough endoplasmic reticulum are significantly reduced, and free ribosomes and mitochondria are limited in number. These morphological signs indicate that the neutrophil is a specialized cell at the final stage of morpho-biochemical differentiation and is incapable of further cell division [3].

2. Migration of neutrophilic granulocytes

After maturation, neutrophils leave the bone marrow through the tight-fitting pores of the sinusoidal endothelium and enter the bloodstream [15]. The half-life of neutrophils released from the bone marrow is approximately 6 hours in the bloodstream and somewhat longer in tissues. The lifespan of neutrophils can be modulated by soluble signals. When exposed to stimuli such as tumor necrosis factor (TNFα) and Fas ligand (CD95), neutrophils undergo apoptosis or programmed cell death [16, 17]. The large number of neutrophils and their short half-lives imply the existence of special mechanisms for removing neutrophils from the body. The signaling system, including stromal factor 1 (SDF-1) and CXC chemokine receptor 4 (CXCR4), has been shown to be involved in neutrophil clearance. CXCR4, a G-protein coupled receptor, is expressed at low levels in mature neutrophils.

Neutrophils change their phenotype with age and activate CXCR4. This change supports the return of neutrophils to the bone marrow via the chemoattractant SDF-1, which is also known as CXCL12. Upon their return to the bone marrow, neutrophils are phagocytosed by stromal macrophages [18]. Senescent or apoptotic bloodstream neutrophils are generally accepted to be removed by liver and splenic macrophages (i.e., the reticuloendothelial system). However, the data from which these conclusions are formed were obtained from the radioactive labeling of isolated and then reintroduced neutrophils [19]; intravital imaging did not actually reveal that neutrophils are absorbed by macrophages in either of these organs [20]. Approximately 30,000 neutrophils normally migrate into the oral cavity every minute, this only accounts for <1% of neutrophils produced every day [21]. However, if such migration was to occur throughout the gastrointestinal tract, significant elimination of neutrophils is likely to occur. Recent work has shown that neutrophils also penetrate many tissues, including the intestine, under pathogen-free conditions [22], thereby confirming the results of an earlier study on ischemia-reperfusion in the intestine, which revealed neutrophils in the intestinal interstitium [23].

Neutrophils must cross the vascular wall to penetrate into the site of microorganisms invasion. Transection occurs mainly in the post-capillary venules. Here the vessel wall is rather thin, and the vessel diameter is sufficiently large for neutrophils to come into contact with the vessel wall but not too small to be blocked by neutrophils after their contact with the endothelium [24]. The initial attachment of neutrophils to the endothelium is determined by endothelial cells responding to stimuli such as TNFα, IL-1β, and IL-17, which are generated during infection or inflammation. This stimulation results in the expression of P-selectin, E-selectin, and some members of the integrin superfamily (e.g., ICAM and vascular cell adhesion molecules [VCAM]) on the inner endothelial surface of the vessels. Selectins bind P-selectin ligand 1 (PSGL-1) and L-selectin, which are expressed constitutively at the tips of neutrophilic microvilli [25–27]. These bonds are formed and disconnected sequentially, thereby providing a rolling effect of neutrophils on the surface of the vessel.

After establishing strong adhesion, transendothelial migration may be conducted in two ways: transcellularly, during which neutrophils enter individual endothelial cells, or paracellularly, during which neutrophils pass between endothelial cells. The key players involved in

the direction of paracellular or transcellular migration are the main neutrophil β_2 integrins LFA-1 and Mac-1 and their ligands ICAM-1 and ICAM-2 [28].

3. Phagocytosis and degranulation

Neutrophils are professional phagocytes. The uptake stage of these cells is initiated after opsonization of the microorganism and interaction with appropriate receptors such as Fcγ receptors, C-type lectins, or complement receptors. Pseudopodia encompass the phagocytic object, invagination of the membrane occurs, and the microorganism is submerged into the phagocytic vacuole formed inside the phagocyte [29]. This process is mediated by a complex pathway of activation of intracellular signaling cascades and accompanied by rearrangements of the cytoskeleton. During phagocytosis, azurophilic and specific granules fuse with the phagosome and release their antimicrobial contents into it. Meanwhile, nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) is assembled from a group of membrane-bound flavocytochromes (e.g., cytochrome b_{558}, which consists of $gp91^{phox}$ and $p22^{phox}$ subunits) and cytoplasmic components (e.g., $p47^{phox}$, $p67^{phox}$, $p40^{phox}$, and Rac). The activity of NADPH oxidase leads to the formation of oxygen radicals and their reaction products. These products are collectively known as reactive oxygen species and include the superoxide radical – $O_2^{\bullet -}$, the hydroxyl radical – $HO^{\bullet}$, and hydrogen peroxide H_2O_2, which enter the phagocytic vacuole, where they contribute to the destruction of microorganisms [31]. NADPH oxidase is critical for the destruction of microorganisms because the absence or dysfunction of this enzyme leads to chronic granulomatous disease, which is characterized by an increased predisposition to bacterial and fungal infections [32].

Degranulation is initiated immediately upon contact of the neutrophil with the phagocytosed object; here, some of the granules located near the outer cell membrane rupture, their membranes merge with the cell membrane, and the contents are released into the extracellular space [11]. Interestingly, the mechanisms of degranulation into the extracellular space and into the phagolysosome are regulated differentially. The first variant of degranulation determines the sequence of mobilization, during which lighter granules (secretory vesicles > gelatinase granules > specific granules > azurophilic granules) are degranulated first in response to stimuli. In the second variant of degranulation (i.e., formation of phagolysosomes), azurophilic and specific granules predominantly merge with the phagocytic vacuole [5], thereby allowing the immediate delivery of a complete set of antibiotic compounds to the phagosome and ensuring the functioning of NADPH oxidase.

Over 6 hours of phagocytosis, the expression of 305 genes increases while that of 297 genes decreases [33]. In line with the concept of neutrophils as the first line of defense, previous studies showed an increase in the expression of various pro-inflammatory mediators in neutrophils shortly after the onset of phagocytosis. Among these genes are genes that encode the chemokines and cytokines necessary to attract macrophages, T cells, and neutrophils and modulate their inflammatory response (e.g., monocytic chemotactic protein MCP-1, also known as CCL2, macrophage inhibitory proteins MIP-1α [CCL3], MIP-2α [CXCL2], MIP-2β [CXCL2], MIP-3α [CCL20], oncostatin M, and IL-1β) [33, 34]. Following an early pro-inflammatory response, neutrophils initiate a subsequent transcriptional response that promotes apoptosis and further uptake and digestion by macrophages. At this stage, the expression of genes encoding pro-apoptotic proteins, including mediators and receptors of the external apoptotic pathway (e.g., TNFα, TRAIL, TNFR-1, and TRAILR), caspase 1, and BAX (Bcl-2 family protein), as well as members of the TLR2 signal transduction pathway (e.g., TLR2, kinase-1 associated with the IL-1β receptor, caspase-8, IL-1β, an antagonist of the IL-1β receptor, and the light chain of the NFκB transcription factor [NFκB1]) is enhanced [33]. Phagocytosis-induced apoptosis is abolished by the inhibition of protein synthesis, which definitely indicates the regulation of neutrophil apoptosis at the translational level [35].

Even the death of neutrophils in the foci of inflammation can be considered a protective reaction of the macroorganism. Earlier studies, for example, have established that pseudotuberculosis bacteria are not mainly inactivated by phagocytic reactions but by the death of neutrophils with the accumulation of nuclear decay products in the foci of inflammation [36].

4. Neutrophilic extracellular traps

Over the last few years, interest in the extracellular functions of neutrophils has sharply increased because of the discovery of the so-called neutrophil extracellular traps (NETs), which are extracellular DNA strands associated with peptides and proteins [37].

Since the first description of these traps was published [38], the NET phenomenon has been considered an alternative to neutrophil death resulting from either apoptosis or pyroptosis. The mechanisms underlying NETosis, as this cell death pathway has been called, have been partially determined *in vitro*, usually by assaying neutrophils stimulated for 1–3 hours with phorbol-12-myristate-13-acetate under serum-free conditions or very low concentrations of whey proteins [39]. NETosis under these experimental conditions depends on the presence of the main neutrophil serine protease elastase [40], myeloperoxidase [41], and active NADPH oxidase [42]. Therefore, NETosis should not be expected in patients with myeloperoxidase deficiency, a relatively common hereditary disorder, or chronic granulomatous disease, which is a more severe immunodeficiency characterized by the inability of neutrophils to produce reactive oxygen species [43]. Because myeloperoxidase deficiency does not always lead to severe clinical manifestations, NETosis, as defined above, may be assumed to play a minor (if any) role in immune defense. Similarly, patients with Papillon–Lefebvre syndrome, in which neutrophils lack either elastase or other serine proteases and, therefore, cannot maintain NETosis [44], do not show increased susceptibility to systemic infections and usually only suffer from severe periodontal disease [45]. NETs are known to be capture bacteria [46], fungi [47], and even viruses [48] and can partially protect T cells from infection with the human immunodeficiency virus [49]. Some studies have questioned the initial observation that neutrophil NETs destroy entrained bacteria [50]. However, capturing viable bacteria is likely to restrain microorganisms and, thus, prevent the spread of infection.

According to some reports, NETs contribute to the pathogenesis of a number of autoimmune diseases in which the target antigens are often constituents of NETs, including DNA, as well as myeloperoxidase and proteinase 3, as has been observed in systemic lupus erythematosus and Wegener's granulomatosis [51].

A conditional extracellular variant of neutrophils capable of killing microorganisms by using a network of cytonemes, which are filamentous tubulovesicular processes of living neutrophils, has also been reported [52].

5. Neutrophilic granulocytes and systemic inflammatory diseases

During systemic infections leading to sepsis, the finely tuned mechanisms regulating the sequential recruitment of neutrophils and monocytes become unregulated [53]. Sepsis is clinically defined as infection with several of the following symptoms: fever, increased or decreased white blood cell count, tachypnea, edema, hemodynamic changes, and high serum chemokine and C-reactive protein concentrations [54, 55].

As sepsis worsens, septic shock develops, leading to multiple organ failure [55–57]. Any delay in the immune response increases mortality, and septic shock has the highest mortality rates among all disease states of an infectious nature [58]. Although recruiting neutrophils is key to protecting the host from infection, their excessive mobilization can also damage body tissues.

In models of endotoxemia in humans and sepsis in mice, high concentrations of cytokines and chemokines circulating in the blood plasma disrupt neutrophil chemotaxis, activating both neutrophils and endothelium simultaneously. This event can also lead to a prolonged immunosuppressive phase. For example, a high concentration of plasma chemokines leads to a decrease in the activity of chemokine receptors on neutrophils in patients with severe septic pathology [59].

Although humans and mice show similar symptoms of sepsis and the mechanisms observed in mice are useful for understanding sepsis in humans, experimental and clinical sepsis show remarkable differences. First, the concentrations of bacteria and bacterial components in the circulation, as well as their role in disease progression, differ between mice and humans because rodents are much more resistant to infections than humans [60]. In addition, the critical component of severe sepsis in humans, that is, multiple organ failure, has not been completely

observed in rodents, likely because mice that receive high doses of lipopolysaccharides die before they can develop these complications [61].

6. Plasticity of neutrophilic granulocytes

An increasing body of evidence indicates the existence of different functional subgroups of neutrophils that play different roles in the body's defense-adaptive responses during infection, inflammation, and cancer [62–66]. For instance, three separate populations of neutrophils have been observed in mice infected with methicillin-resistant *Staphylococcus aureus* [66], and each of these populations possesses a unique spectra of cytokines and chemokines, as well as the ability to express surface TLRs and CD49d/CD11b. In general, neutrophils from mice with a moderate manifestation of a systemic inflammatory response have a pro-inflammatory phenotype (IL-12$^+$ CCL3$^+$), while neutrophils from mice with a severe form of systemic inflammatory response syndrome have an anti-inflammatory phenotype (IL-10$^+$ CCL2$^+$) [66]. These "pro-inflammatory" and "anti-inflammatory" neutrophils can regulate the direction of the immune response during infection by polarizing M1 and M2 macrophages, respectively [67]. Similar phenotypes of neutrophils have been observed in mice with tumors [68]. Different populations of neutrophils have also been identified in volunteers who received lipopolysaccharides in comparison with those who did not receive lipopolysaccharides [64, 69].

In the cases described above, that neutrophils can correct their phenotype in accordance with infection or stress and are not separate lines cannot be excluded. Indeed, neutrophils are quite plastic and capable of phenotypic changes. Neutrophils exhibit a different set of adhesion molecules and chemokine receptors during chronic inflammation [70]. Pathogens are also capable of causing phenotypic changes in neutrophils. For example, when mice are infected with *Trypanosoma cruzi*, neutrophils assume an anti-inflammatory phenotype with IL-10 production and simultaneously inhibit the production of interferon-γ and T-cell proliferation [71]. During the interaction of neutrophils with invariant natural killer (iNKT) cells in a CD1d-dependent manner, the anti-inflammatory phenotype of neutrophils transforms into a pro-inflammatory phenotype [72], which is especially interesting because iNKT cells can recognize autoantigens and bacterial antigens and produce various cytokines [73, 74].

7. Neutrophilic granulocytes and adaptive immunity

Neutrophils modulate important components of the adaptive immune response and can regulate the activity of B and T cells [75]. Neutrophils produce a factor that activates B cells (i.e., BAFF, also known as a stimulator of B lymphocytes) and a proliferation-inducing ligand (i.e., APRIL), both which are necessary for the survival and activation of B cells [76]. Activation of neutrophils by lipopolysaccharides in the spleen leads to the formation of BAFF, APRIL, and IL-21, which act on B cells in the marginal zone responsible for the production of antibodies to T-independent antigens [77].

On the one hand, neutrophils can serve as immunosuppressants by inhibiting the proliferation and activation of T cells, likely because of the large amount of arginase 1 present in neutrophilic azurophilic granules and the production of reactive oxygen species [69, 61]. On the other hand, neutrophils can also function as antigen-presenting cells. During stimulation with interferon-γ in neutrophils, the level of main histocompatibility complex class II proteins, together with costimulatory molecules, increases [78]. As a result, neutrophils can promote Th1 and Th17 differentiation.

Given their demonstrated functions, neutrophils can be considered not only professional phagocytes but also cells capable of performing a unique set of specialized functions [79]. They are participants and regulators of many processes, such as acute damage and repair, cancer [80], autoimmunity, and chronic inflammation [81]. Neutrophils promote adaptive immunity by facilitating the development of specific adaptive immune responses or directing the subsequent adaptive immune response.

Activated neutrophils are capable of producing cytokines, chemokines, and other biologically active compounds. Given significant reductions in the translational apparatus, the level of such production is actually very low; however, if the amount of neutrophils accumulating in the foci of inflammation is considered, such synthesis

may still have biological significance. The main "weapons" of neutrophils are compounds synthesized during granulocytogenesis in the bone marrow. Neutrophil granules contain a wide range of biologically active substances, such as defensins, cathelicidins, proteases, lactoferrins, and myeloperoxidase, which are not only antimicrobial compounds but also exhibit various immunoregulatory properties [82–86].

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