REVIEWS

REDOX REGULATION OF THE NLRP3-MEDIATED INFLAMMATION AND PYROPTOSIS

N.Yu. Rusetskaya*, N.Yu. Loginova, E.P. Pokrovskaya, Yu.S. Chesovskikh, L.E. Titova

V.I. Razumovsky Saratov State Medical University,
112 B. Kazachya str., Saratov, 410012 Russia; *e-mail: meduniv@sgmu.ru

The review considers modern data on the mechanisms of activation and redox regulation of the NLRP3 inflammasome and gasdermins, as well as the role of selenium in these processes. Activation of the inflammasome and pyroptosis represent an evolutionarily conserved mechanism of the defense against pathogens, described for various types of cells and tissues (macrophages and monocytes, microglial cells and astrocytes, podocytes and parenchymal cells of the kidneys, periodontal tissues, osteoclasts and osteoblasts, as well as cells of the digestive and urogenital systems, etc.). Depending on the characteristics of redox regulation, the participants of NLRP3 inflammation and pyroptosis can be subdivided into 2 groups. Members of the first group block the mitochondrial electron transport chain, promote the formation of reactive oxygen species and the development of oxidative stress. This group includes granzymes, the mitochondrial antiviral signaling protein MAVS, and others. The second group includes thioredoxin interacting protein (TXNIP), erythroid-derived nuclear factor-2 (NRF2), Kelch-like ECH-associated protein 1 (Keap1), ninjurin (Ninj1), scramblase (TMEM16), inflammasome regulatory protein kinase NLRP3 (NEK7), caspase-1, gasdermins GSDM B, D and others. They have redox-sensitive domains and/or cysteine residues subjected to redox regulation, glutathionylation/deglutathionylation or other types of regulation. Suppression of oxidative stress and redox regulation of participants in NLRP3 inflammation and pyroptosis depends on the activity of the antioxidant enzymes glutathione peroxidase (GPX) and thioredoxin reductase (TRXR), containing a selenocysteine residue Sec in the active site. The expression of GPX and TRXR is regulated by NRF2 and depends on the concentration of selenium in the blood. Selenium deficiency causes ineffective translation of the Sec UGA codon, translation termination, and, consequently, synthesis of inactive selenoproteins, which can cause various types of programmed cell death: apoptosis of nerve cells and sperm, necroptosis of erythrocyte precursors, pyroptosis of infected myeloid cells, ferroptosis of T- and B-lymphocytes, kidney and pancreatic cells. In addition, suboptimal selenium concentrations in the blood (0.86 μM or 68 μg/l or less) have a significant impact on expression of more than two hundred and fifty genes as compared to the optimal selenium concentration (1.43 μM or 113 μg/l). Based on the above, we propose to consider blood selenium concentrations as an important parameter of redox homeostasis in the cell. Suboptimal blood selenium concentrations (or selenium deficiency states) should be used for assessment of the risk of developing inflammatory processes.

Key words: NLRP3 inflammasome; pyroptosis; redox regulation; thioredoxin; glutathione peroxidase; selenium

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Abbreviations used: AIM2 – absent in melanoma 2 (protein), AP-1 – activator protein-1; ARE – antioxidant responsive element; ASC – apoptosis-associated speck-like protein containing a caspase recruitment domain; ASK1 – apoptosis-regulating signal kinase 1; CARD – caspase activation and recruitment domain; c-FLIP – cellular FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein; CIITA – Class II, major histocompatibility complex, transactivator; CTL – CD8T, cytotoxic lymphocytes; Cul3 – Cullin-3-contaning ubiquitin ligase complex E3; DAMP – damage-associated molecular pattern; DC – dendritic cells; DD – death domain; dsDNA – double stranded DNA; dsRNA – double stranded RNA; EPR – endoplasmic reticulum; ESCRT – endosomal sorting complex required for transport; FADD – fas-associated death domain protein; GCL – glutamate-cysteine ligase; GPX – glutathione peroxidase; GSDM – gasdermin; GSDMD – gasdermin D; HMGB-1 – high-mobility group protein B1; HMOX1 – heme oxygenase 1; HSP – heat shock protein; IFN-I – the type-I interferons; IKK – inibitor of κB kinase; IL – interleukin; IP3 – inositol 1,4,5-trisphosphate; IP3R – IP3 receptor; IRF1 – interferon regulatory factor 1; JNK1 – c-Jun N-terminal kinases; Keap1 – Kelch-like ECH-associated protein 1; LAMP – lifestyle-associated molecular patterns; LDH – lactate dehydrogenase; LDL – low density lipoproteins; LPS – lipopolysaccharides; MAM – mitochondria-associated membrane; MAPK – mitogen activated protein kinase; MAVS – mitochondrial antiviral signaling protein; MCU – mitochondrial calcium uniporter; mtDNA – mitochondrial DNA; mtETC – mitochondrial electron transport chain; mtRNA – mitochondrial RNA; mtROS – mitochondrial reactive oxygen species; MYD88 – myeloid differentiation factor; NAIP – NLR family apoptosis inhibitory protein; NEK7 – never in mitosis A-related kinase; NF-κB – nuclear factor-κB; NINJ1 – ninjurin 1; NK – natural killer (cell); NLRP – nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain containing; NOD2 – nucleotide-binding oligomerization domain containing 2; NOX – NADPH-oxidase; NQO1 – NAD(P)H quinone oxidoreductase 1; NRF2 – nuclear factor (erythroid-derived 2)-like 2; PAMP – pathogen-associated molecular pattern; PGAM5 – phosphoglycerate mutase 5; PIP2 – phosphatidylinositol-4,5-bisphosphate; PKC – protein kinase C; PLCγ1 – phosphoinositide-specific phospholipase C; PM – plasma membrane; RIG-I – retinoic acid-inducible gene 1; ROS – reactive oxygen species; sMAF protein – small musculoaponeurotic fibrosarcoma protein; SOD – superoxide dismutase; STAT3 – signal transducer and activator of transcription 3; TLR – toll like receptor; TNFR – tumor necrosis factor receptor; TNF-α – tumor necrosis factor-α; TRIF – TIR-domain-containing adapter-inducing interferon-β; TRX – thioredoxin; TRXR – thioredoxin reductase; TXNIP – thioredoxin interacting protein; vRNA – viral RNA.

INTRODUCTION

Inflammation is the initiator of many pathologies, for example, diseases of the central nervous system (multiple sclerosis, Alzheimer's disease and Parkinson's disease), metabolic diseases (non-alcoholic fatty liver disease, gout, type 2 diabetes mellitus and insulin resistance), cardiovascular diseases, rheumatoid arthritis [1–7]. In addition, an excessive inflammatory response, defined as a cytokine storm, accompanies infection caused by the SARS-CoV-2 coronavirus [8].

The assembly of the inflammasome is key event in the development of inflammation. According to modern data, inflammasomes are expressed not only in monocytes, macrophages, and lymphocytes, but also in many other cells [9–11]. Inflammasomes in monocytes and macrophages function as a part of the innate immune system and they are responsible for the inflammatory responses, while lymphocyte inflammasomes (T and B cells) are involved in regulation of the adaptive immune response. In this regard, inflammasomes can be considered as a "switch" between the innate and adaptive immune response, needed for precise control of the body immune defense [11]. The innate immune system is the first line of the immune defense necessary to recognize and eliminate pathogens. However, almost all tissues, organs and hematopoietic cells are involved in the adaptive immune system. These include macrophages, mast cells, neutrophils, eosinophils, dendritic cells (DCs) and natural killer (NK) cells, as well as non-hematopoietic cells, including skin cells and epithelial cells mucous membranes of the gastrointestinal tract, genitourinary system and respiratory tract [10, 11].

Through a long process of evolution, the innate immune system has created numerous receptors capable of recognizing and binding certain molecular patterns known as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). PAMPs include components of bacterial cells, such as lipoteichoic acid, lipoproteins, peptidoglycans, lipopolysaccharide (LPS), flagellin, and nucleic acids [11, 12]. In addition, PAMPs include components of viruses, in particular, the S (spike) protein of coronavirus [13].

The DAMP group includes adenosine triphosphate (ATP), mitochondrial DNA (mtDNA), heat shock proteins, interleukins IL-1β and IL-18, heme, vimentin and the cytokine mediator HMGB-1 (high mobility group protein B1), or amphoterin. The authors [14] identified new groups of molecular triggers of inflammation: lifestyle-associated molecular patterns (LAMPs), as well as inducible and constitutive DAMPs (Table 1) [14–16].

Recognition of PAMPs and DAMPs by inflammatory sensors, including NLRP1, NLRP3, NLRC4, NAIP, AIM2, and pyrin, initiates a chain of events culminating in the inflammatory cascade and pyroptosis [17]. For example, AIM2 binds exclusively to double-stranded DNA (dsDNA) [18]; NAIP directly

Table 1. Characteristics of PAMP, DAMP, and LAMP [14–16]*

Molecule	Characteristics	Examples
PAMP	Conservative microbial molecules responded by pattern recognition receptors	LPS
		β-glucan
DAMP	Any molecule that is released during, after, or as a consequence of a disruption of cellular homeostasis, such as damage or injury	HMGB-1 or amphoterin
		ATP
		Heme
Early DAMP or alarmins	Endogenous molecules released by damaged cells during cell death	Vimentin (cytoskeletal protein responsible for maintaining cell integrity)
	Cause chemotactic and immunoactivating reactions by interacting with PRR	Defensins, cathelicidin, eosinophil-derived neurotoxin
LAMP	Non-PAMP, non-DAMP molecules causing an inflammatory response with the prospect of developing chronic inflammation	Cholesterol, oxidized LDL, sodium urates
Inducible DAMP (iDAMP)	Inflammatory molecules that are actively produced or modified during cell death and reflect the cellular response to stress and cell death signaling pathways	IL-1β, IL-18, heat shock proteins
Constitutive DAMP (cDAMP)	Inflammation-induced molecules that are already present intracellularly before cell death/stress and are released by dying cells	HMGB-1 or amphoterin
		mtDNA
		ATP
		Heme

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binds flagellin and components of type III secretion systems (T3SS) of Gram-negative bacteria such as *Salmonella enterica* serovar Typhimurium and this results in activation of the NLRC4 inflammasome [19]; human caspase-4 and caspase-5 are activated directly by LPS entering the cell without the participation of toll-like receptors (TLRs) [20, 21]. It has recently been shown that human NLRP1 is activated by double-stranded RNA (dsRNA) [22].

At the same time, activation of NLRP3 does not occur due to binding to the activating ligand. NLRP3 is activated by intracellular signals. These include cardiolipin translocation from the inner to the outer mitochondrial membrane, production of reactive oxygen species (ROS), mtDNA oxidation, calcium influx, a decrease in cellular cAMP, destruction of lysosomes and subsequent leakage of cathepsin B, outflow of potassium from the cell, increase in the cell volume, formation of pores in the plasma membrane (PM) and its rupture [23]. These events accompany cell death, called pyroptosis. In addition, NLRP3 activators are also coronavirus RNA and S protein, which, after penetration into the host cell, contribute to the development of inflammation and cell death [8].

Activation of the NLRP3 inflammasome occurs in two stages: 1) priming, 2) activation signaling pathways (canonical, non-canonical, and alternative). Canonical and non-canonical activation of the inflammasome leads to pyroptosis.

1. MECHANISMS OF NLRP3 ACTIVATION

To date, priming and three pathways for activation of the NLRP3 inflammasome have been described: the canonical, non-canonical and alternative pathway. The priming step promotes the expression of inflammasome components, and the activation step is triggered by several types of molecules that specifically activate NLRP3. After inflammasome assembly, mature forms of interleukins IL-1β and IL-18 and gasdermins are formed. Gasdermins undergo oligomerization and form pores spanning the plasma membrane and membranes of intracellular organelles. Mature forms of IL-1β and IL-18 (which are DAMPs) act as triggers of inflammation leave the cell through the gasdermin pores. By the time the plasma membrane ruptures during the process of pyroptotic death, all intracellular organelles (nucleus, mitochondria, lysosomes, endoplasmic reticulum, Golgi complex) are significantly damaged or destroyed [9, 24].

Similar activation of the inflammasome has been found not only in macrophages and monocytes [25], but also in other types of cells, in particular, in microglia [26] and astrocytes [27], podocytes [28] and parenchymal cells of the kidneys [29], periodontal tissues [30] and bone tissue cells: osteoclasts and osteoblasts [31], as well as in the cells of the digestive system [32] and many others [9].

1.1. NLRP3 Inflammasome Priming (Signal 1)

Priming involves PAMPs, DAMPs or alarmins (dsDNA), mtDNA, ATP, ROS, heme or urates released by neighboring necrotic cells or damaged tissues. This leads to transcriptional and translational induction of various innate immune effectors, including NLRP3 and the proforms of interleukins IL-1β, pro-IL-1β (Fig. 1). It should be noted that NLRP3 priming by DAMPs represents a basis for sterile chronic inflammatory processes [33–37].

1.2. Characteristics of the NLRP3 Inflammasome Components

The NLRP3 inflammasome consists of the sensor NLRP3, the adaptor ASC, and the effector enzyme pro-caspase-1 [38]. The NLRP3 sensor is an NLR (nucleotide-binding oligomerization domain containing leucine-rich repeats). It contains an N-terminal pyrin domain (PYD), a central NAIP (NLR family apoptosis inhibitory protein), CIITA (major histocompatibility complex transactivator class II), NACHT or nucleotide-binding oligomerization domain (NOD), which hydrolyzes ATP, and a C-terminal leucine-rich repeat (LRR) domain (Fig. 2). During inflammasome assembly, NLRP3 interacts with the N terminus of the adapter protein ASC via PYD-PYD interactions. The C terminus of ASC has a caspase activation and

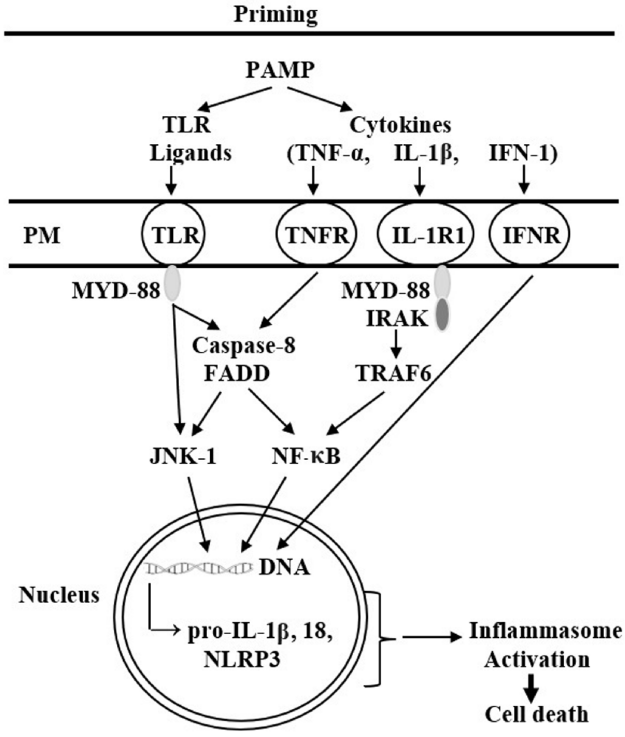

Figure 1. PAMPs trigger priming by interacting with the corresponding receptors (TLR, TNFR, IFNR) followed by subsequent activation of the NF-κB/JNK-1 signaling pathways AND expression of NLRP3 inflammasome components and pro-interleukins (pro-IL-1β, pro-IL-18).

recruitment domain (CARD), which can bind to procaspase-1 through CARD-CARD interactions and promote dimerization and activation of caspases (Fig. 3). Due to its properties, ASC forms large fibrillar aggregates known as "specks" [39, 40]. The three-dimensional structure of the inflammasome is presented in the Protein Data Base (ID 8EJ4).

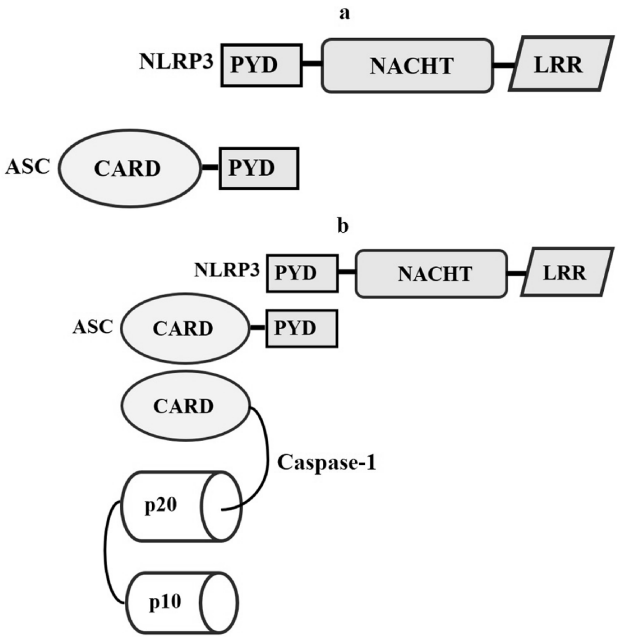

Figure 2. The structure of the NLRP3 inflammasome: **a**) NLRP3 domains; **b**) Sensory-adapter-effector mechanism of NLRP3 inflammasome assembly. Adapted from [40].

1.3. The Canonical Activation of the NLRP3 Inflammasome (Signal 2)

Following the priming step, the NLRP3 inflammasome can be activated by a wide range of stimuli, including ATP, K^+ ionophores, heme, solid particles, pathogen-associated RNA, as well as bacterial and fungal toxins and components [21]. It should be noted that NLRP3 does not directly interact with any of these agonists. It is suggested that they trigger a series of events in the cell that mediate active inflammasome assembly (Fig. 4). Such processes include:

- changes in the concentration of potassium, sodium and calcium ions in the cell cytosol (outflow of potassium ions and chloride anions, mobilization and/or influx of calcium ions) [35, 41–48];
- destruction of lysosomes in response to large particle activators, leading to the release of cathepsins, which activate NLRP3 [49];
- translocation of NLRP3 into mitochondria through remodeling of the microtubule network, providing NLRP3 interaction with mitochondrial ASCs and inflammasome assembly [49–51];
- damage and dysfunction of mitochondria, including the effect of SARS-CoV-2 viral RNA (vRNA) [52, 53]. The interaction of vRNA with MAVS impairs the functioning of the mitochondril electron transport chain (mtETC), leading to the release of mtDNA and mtROS, and cardiolipin movement to the outer mitochondrial membrane followed by subsequent assembly of the NLRP3 inflammasome [52–55].

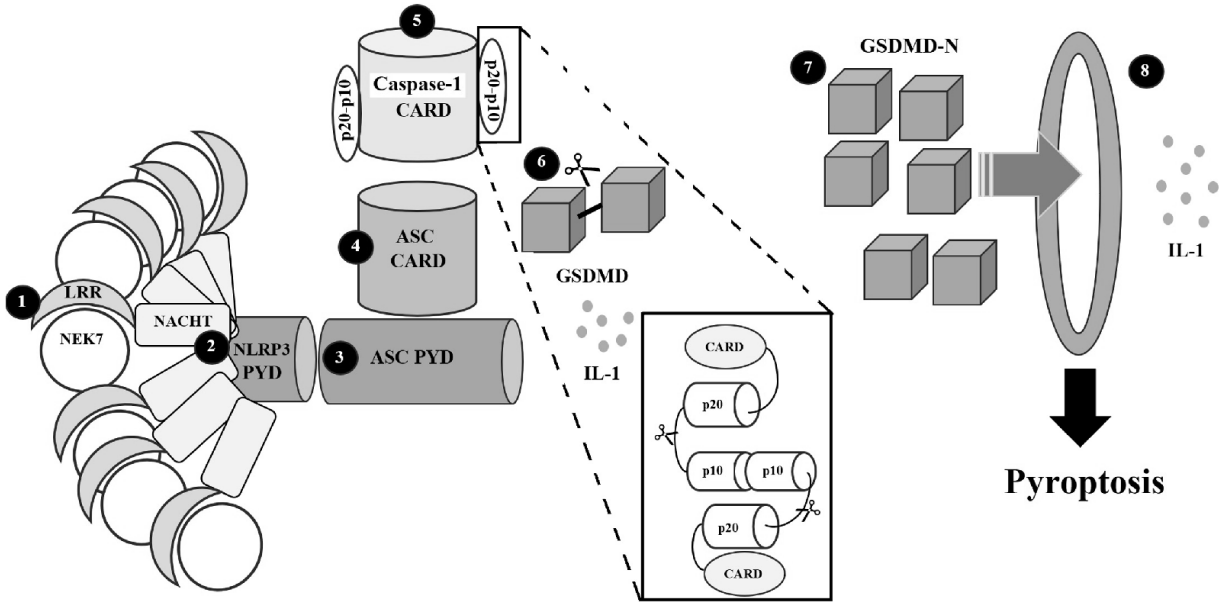

Figure 3. A molecular model of NLRP3 inflammasome assembly: a change in NLRP3 conformation leads to the binding of NLRP3 to NEK7 (*1*); this induces formation of the NLRP3 inflammasome (*2*) and promotes the formation of NLRP3 PYD as a filament. The NLRP3 PYD filament recruits ASC (*3*) to form the ASC PYD filament. CARD ASC also clusters and forms a filament (*4*). The ASC CARD filament recruits caspase-1 to form the caspase-1 CARD filament (*5*). Dimerization and autoprocessing of the caspase-1 domain (p20/p10) results in its activation. Active caspase-1 then cleaves IL-1 family procytokines to produce mature cytokines (*6*). Caspase-1 also cleaves GSDMD to produce the active N-terminal fragment of GSDMD to form membrane pores (*7*), which promotes cytokine release and pyroptosis (*8*). Adapted from [40].

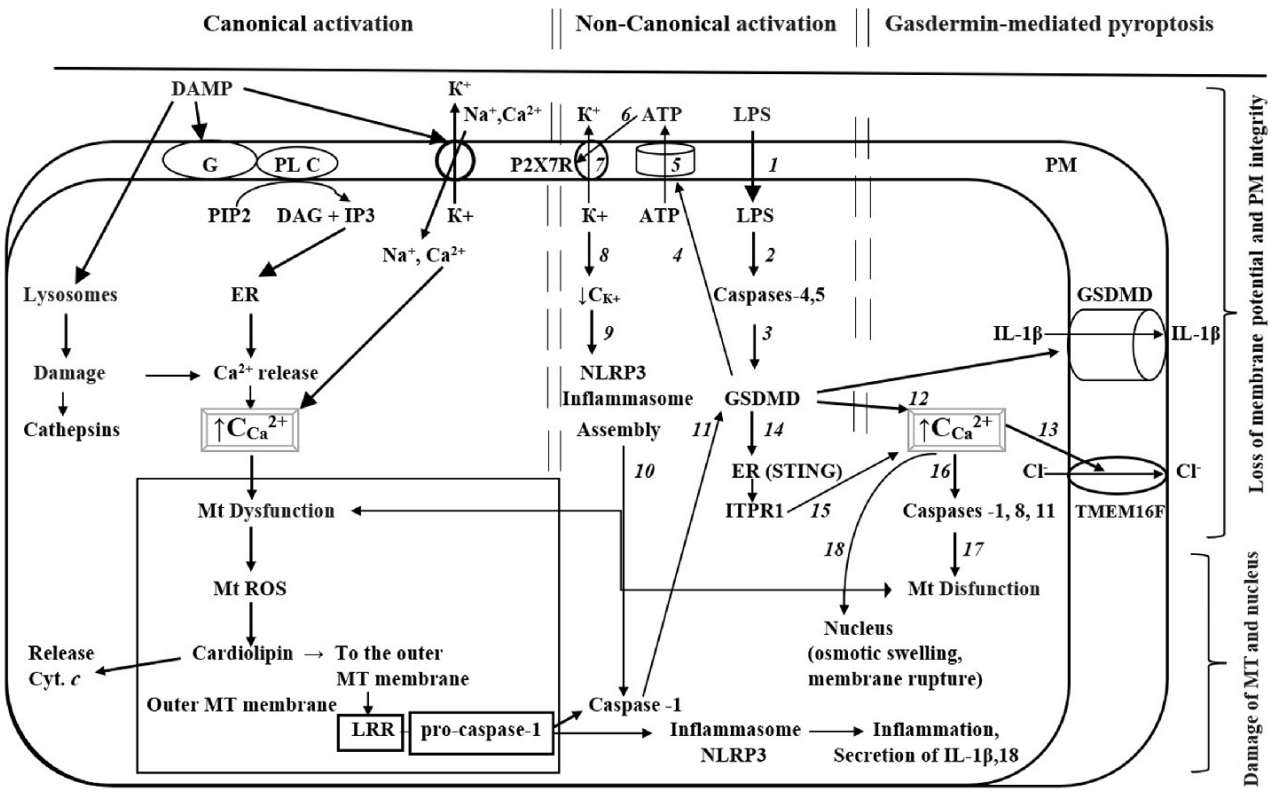

Figure 4. Inflammasome activation and GSDM-mediated pyroptosis. *Canonical activation of the NLRP3 inflammasome* is carried out by means of DAMPs, which act according to one of three scenarios, leading to an increase in calcium ion concentrations in the cell cytosol: 1) G-protein-coupled phospholipase C (PL C) promotes the formation of inositol triphosphate (IP3), which stimulates calcium ion release from the endoplasmic reticulum (ER); 2) phagocytosed DAMPs promote the destruction of lysosomes and the release of calcium ions and cathepsins from them; 3) change in transmembrane ion transport: outflow of potassium ions from the cell, influx of sodium and calcium ions into the cell. Regardless of the pathways of calcium ions to the cytosol, they penetrate into mitochondria, impair the electron transport chain functioning, stimulate mtROS production, movement of cardiolipin from the inner to the outer mitochondrial (MCh) membrane, which leads to the release of cytochrome *c* (Cyt. *c*) into the cytosol. Cardiolipin on the outer surface of mitochondria serves as a platform for the assembly of the NLRP3 inflammasome. mtROS and oxidized mtDNA promote the assembly of the NLRP3 inflammasome and the formation of free active caspase-1, which enhances mitochondrial damage. *Non-canonical activation of the NLRP3 inflammasome* occurs when LPS bypasses toll-like receptors (*1*). In the cytosol of cells, LPS (*2*) activates caspases-4 and -5 (in humans) and -11 (in mice), promoting GSDM activation (*3*) and formation of a channel (*4*) in the plasma membrane, through which ATP exits the cell (*5*) and activates the P2X7R receptor (*6*); this results in the outflow of potassium from the cell and the influx of calcium ions into the cell (*7*). A change in the concentration of these ions in the cytosol (*8*) serves as a signal for the assembly and activation of the NLRP3 inflammasome (*9*), the formation of active caspase-1 (10), mature forms of interleukins and their exit from the cell, which ultimately leads to inflammation and death cells by pyroptosis. *GSDM-mediated pyroptosis.* Caspase-1-dependent cleavage of GSDMD (*11*), the formation of GSDMD pores is accompanied by an increase in the concentration of calcium ions in the cell cytosol (*12*) and subsequent activation of Ca^{2+}-dependent transmembrane protein 16F (TMEM16F) (*13*), promoting the outflow of Cl^- ions (*13*). The influx of Ca^{2+} ions during the inflammatory process also activates STING (TMEM173) on the ER membrane. Activated STING then binds to and activates the ITPR1 calcium channel, causing further Ca^{2+} release from ER (*14, 15*). Elevated Ca^{2+} levels promote the activation of inflammatory caspases-1/11 or -8 (depending on the pathogen) (*16*); this leads to further damage to the mitochondria (*17*). Finally, elevated Ca^{2+} levels promote nuclear swelling and rupture (*18*) and trigger the cleavage of PM lipids by the phosphoinositide-specific phospholipase C PLCγ1, promoting the progression of pyroptosis and inflammation.

Canonical activation of the inflammasome is accompanied by activation of caspase-1, which promotes the formation of the active N-terminal fragment of gasdermin (GSDM) D, needed for the formation of gasdermin pores in PM and the release of mature IL-1β through the gasdermin pores [40].

1.4. The Non-Canonical Activation of the Inflammasome

Non-canonical activation of the inflammasome is caused by LPS from the cell wall of Gram-negative bacteria, independent of the TLR4-mediated signaling [57]. This non-canonical inflammasome provides an additional level of defense against

pathogens that have evolved to bypass TLR4 on the cell surface [58]. The non-canonical inflammasome includes caspase-4,5 in humans and caspase-11 in mice, but not caspase-1. Caspases-4,5,11 directly bind to intracellular LPS. Non-canonical activation of inflammasomes in human cells that express high levels of caspase-4 does not require priming [59]. Caspases-4,5,11 cause pyroptosis through the processing of gasdermins, followed by their oligomerization and formation of the gasdermin pores in the PM, as well as the processing of pannexin-1, a protein that forms channels in the PM through which ATP is released from the cell. This extracellular ATP activates the P2X7 receptor (P2X7R), an ATP-gated cation-selective channel that opens a pore that triggers K^+ efflux out of the cell; this results in the NLRP3 inflammasome assembly and IL-1β release [60] (Fig. 4).

Consequently, non-canonical activation of the inflammasome, as well as canonical activation, is accompanied by the oligomerization of gasdermins that form pores in the PM. This is one of the key events leading to pyroptosis.

1.5. The Alternative Pathway for Inflammasome Activation

The alternative activation pathway functions independently of the canonical or non-canonical pathways of NLRP3 inflammasome activation [61]. Signaling in the alternative pathway occurs through the TLR4-TRIF-RIPK1-FADD-CASP8 signaling pathway. The alternative pathway of inflammasome activation is not accompanied by K^+ efflux and PM rupture and, therefore, unlike canonical and non-canonical inflammasome activation, does not lead to pyroptosis [34].

2. GASDERMINS (GSDMs)

In humans, there are six major families of GSDMs: GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and GSDMF/DFNB59. GSDMA, GSDMB, GSDMC, GSDMD are expressed mainly in the skin and epithelium of the gastrointestinal tract, while gasdermins GSDME and GSDMF/DFNB59 are expressed mainly in the heart, brain, kidneys and inner ear. Detailed characteristics of GSDMs are given in Table 2 [62].

2.1. Characteristics of GSDMs

Among members of six GSDMs families, the best studied is GSDMD. GSDMD is a cytoplasmic protein with a molecular weight of 53 kDa, which consists of 242 amino acid residues. GSDMD has two conserved domains: an N-terminal effector domain and a C-terminal inhibitory domain. In the inactive state, the N-terminal and C-terminal domains are connected by a long loop. Cleavage of the C-terminal inhibitory domain is carried out by caspases-1,4,5,8 and a number of other enzymes (Table 2) [62].

Active caspase-1 cleaves the C-terminal domain of GSDMD, by hydrolyzing the peptide bond formed by the aspartate residue D276 [63]. After cleavage of the C-terminal domain, the N-terminal domain of GSDMD interacts with phosphatidylinositol phosphates and phosphatidylserine [64]. This causes conformational changes, oligomerization, and the formation of GSDMD pores in the PM with a diameter from 215 Å to 20 nm [63–67].

The GSDMD pore channel is predominantly negatively charged [68]. It has been experimentally demonstrated that positively charged and neutral ions and molecules are transported faster through the GSDM pores than negatively charged ones. The GSDMD pore mediates the efflux of potassium ions from cells; this is a common factor in triggering the NLRP3 inflammasome in response to various stimuli and cellular stressors [69]. The GSDMD pore also mediates the release of mature IL-1 by means of electrostatic filtration [70]. Immature pro-IL-1 and pro-IL-18 have an “acidic” negatively charged domain that prevents the release of pro-IL-1 and pro-IL-18 through the GSDMD pore. Caspase-1 promotes the proteolytic cleavage of the “acidic” domain of the pro-cytokines IL-1β and IL-18 and this promotes release of mature proinflammatory IL-1β and IL-18 from the cell through the GSDMD pore [68].

GSDMB is activated by caspase-1 and granzyme A. In addition, granzymes can proteolytically activate caspase-1. Granzymes enter the cell through perforins (pore-forming proteins of cytotoxic T-killer and natural killer, NK) during the formation of an immunological synapse [71]. Oltra et al. [72] identified a set of charged amino acids encoded by exon 6 of the *GSDMB* gene (Arg225, Lys227, Lys229, and Glu233), which are located next to a group of amino acids with complementary charges (Glu42, Arg152, Glu153). Some of these residues are conserved and are present in other gasdermines. Granzyme A cleaves GSDMB at residues Lys244 and Lys229 to form the pore-forming fragment GSDMB [71]. The authors of [72] suggest that charged amino acid residues are necessary for oligomerization and binding to lipids both in the PM and in the membranes of intracellular organelles, including mitochondria, lysosomes, and ER. This suggestion is supported by the increased production of free radicals in the mtETC, phospholipid peroxidation, formation of the gasdermin pores, and influx and/or mobilization of calcium ions from damaged lysosomes and ER [73–75] (Fig. 4). Besides activation of GSDMB and caspase-1, granzymes A and B, hydrolyze domains of mtETC complex I, resulting in electron leakage to oxygen with the formation of superoxide anion radical and other ROS [76, 77]. This is discussed in more details in section 3.8.

Table 2. Members of the GSDM family: structure and functions (adapted from [62])

Gasdermin	Domain	Activating enzyme	Lipid binding site	Type of lipid	Tissue/cell specific expression in man	Biological function
GSDMA	GSDM-NT and GSDM-CT	No data	GSDM-NT	Phosphoinositides, cardiolipin, phosphatidic acid, phosphatidylserine	Skin, tongue, esophagus, stomach, mammary glands, bladder, umbilical cord, and T lymphocytes	Mitochondrial homeostasis
GSDMB	GSDM-NT and GSDM-CT	Granzyme A and caspase-1	GSDM-NT	Phosphoinositides, phosphatidic acid, phosphatidyl-glycerol sulfatide	Airway epithelium, gastrointestinal tract, brain, endocrine tissue, bone marrow, lungs, liver, kidneys, testes, and lymphocytes	Pyroptosis, antitumor immunity
GSDMC	GSDM-NT and GSDM-CT	Caspase-8	GSDM-NT	No data	Cerebral cortex, endocrine tissues, skin, trachea, spleen, esophagus, stomach, intestines, vagina, and bladder	No data
GSDMD	GSDM-NT and GSDM-CT	Caspases 1/4/5/8, cathepsin G, neutrophil elastase, Enterovirus 71 3C protease (EV71)	GSDM-NT	Phosphoinositides, cardiolipin, phosphatidic acid	Almost all human organs and tissues, including various subpopulations of leukocytes	Inflammation, pyroptosis, cytokine release, NETosis*, bacterial killing
GSDME	GSDM-NT and GSDM-CT	Caspases 3/7/8, granzyme B	GSDM-NT	Phosphoinositides, cardiolipin, phosphatidylserine	Brain, endocrine tissue, muscle tissue, gastrointestinal tract, endometrium, and placenta	Pyroptosis, antitumor immunity
GSDMF/ PVJK	GSDM-NT and zinc finger	No data	GSDM-NT	No data	Inner ear, auditory system neurons, testicles	No data

NETosis* – programmed death of neutrophils.

In addition, the formation of GSDM pores causes a chain of events: the outflow of potassium ions from the cell, the influx of calcium ions and water into the cytosol, cell swelling and rupture of the PM. All these events lead to pyroptosis [78–82].

2.2. GSDMs and Ion Currents

The assembled GSDMD pores can have a diameter of up to 20 nm [63–67, 82, 83]. These pores allow the secretion of smaller intracellular proteins such as IL-1 (17 kDa) but do not allow the release of larger proteins such as lactate dehydrogenase (LDH) (140 kDa) or the inflammatory mediator HMGB1 (150 kDa) [83–85]. These larger proteins are released after cell lysis [86]. GSDMD pores also act as nonselective ion channels. Soon after the pores are assembled, extracellular Ca^{2+} ions enter the cell through these pores. This influx of ions triggers several processes in the cell. First, it activates ESCRT (endosomal sorting complexes required for transport) proteins I and III, which are assembled on the PM to remove GSDM pores by their encapsulation in vesicles. If successful, membrane integrity is restored and cell lysis and IL-1β secretion are prevented [87]. In addition, the influx of Ca^{2+} ions through the GSDMD pores activates Ca^{2+}-dependent transmembrane protein 16F (TMEM16F), a membrane phospholipid scramblase that promotes transition of phosphatidylserine (PS) from the inner to the outer PM monolayer [88]. Activation of TMEM16F also causes changes in cellular ion currents, at least in part due to the efflux of Cl^- ions; this further contributes to the loss of ion homeostasis and cell death. The influx of Ca^{2+} ions during the inflammatory process also activates STING (TMEM173) on the ER membrane [89]. Activated STING then binds to the calcium channel ITPR1 and

activates it, causing further release of Ca^{2+} from ER stores. Elevated Ca^{2+} levels promote activation of inflammatory caspases-1/11 or -8 (depending on the pathogen). Finally, elevated Ca^{2+} levels trigger the cleavage of PM lipids by phosphoinositide-specific phospholipase C PLCγ1, promoting the progression of pyroptosis and inflammation [89].

2.3. Pyroptosis

Loss of cell viability is caused by ion influx, loss of membrane potential, and PM rupture. An increase in the concentration of calcium ions in the cytosol contributes to mitochondrial damage, cell swelling, loss of lysosome stability, loss of nuclear integrity and, finally, PM rupture [90–93].

2.4. Plasma Membrane Rupture

PM rupture during GSDM pore formation was considered a passive process. However, recent work [94] has shown that the conserved extracellular α-helix of ninjurin (NINJ1, cell adhesion protein) is a mediator of cell lysis during pyroptosis [95, 96]. NINJ1 expression is stimulated by oxidative stress, which develops during mitochondrial damage and mtROS production [97].

Consequently, after canonical and/or non-canonical activation, the NLRP3 inflammasome triggers an extreme form of programmed cell death, pyroptosis, aimed at limiting the replication of intracellular pathogens and immunosuppression in sepsis [38, 55]. The leading role in pyroptosis is played by GSDMs, ninjdurin, granzymes, caspases, and the regulatory protein kinase NEK7, the functioning of which is associated with mitochondrial dysfunction and the development of oxidative stress. The different types of regulation of the NLRP3 inflammasome and gasdermins are considered in the next section.

3. REGULATION OF NLRP3 INFLAMMASOME AND GSDMs

Activation of the NLRP3 inflammasome helps to protect the host cell from microbial and viral infections. However, the exposure to pathogens and/or cytokines is accompanied by the development of oxidative stress, mediated by mitochondrial dysfunction, leading to activation of the NLRP3 inflammasome and the development of a number of inflammatory diseases. Therefore, it is critical that the NLRP3 inflammasome activation is precisely regulated to provide adequate immune protection without damaging human tissues. To date, several ways of NLRP3 regulation are known. These include phosphorylation/dephosphorylation, ubiquitination/deubiquitination, sumoylation, alkylation, S-nitrosylation, S-glutathionylation, as well as interaction with NLRP3 redox patterns [34]. The last two types of regulation are of particular interest, since these processes are redox-sensitive and are regulated by ROS on the one hand and the antioxidant system on the other (Fig. 5).

3.1. Activation of NLRP3 by S-Glutathionylation

S-Glutathionylation is a post-translational redox modification that represents the reversible formation of mixed disulfides between the tripeptide glutathione and a low pKa cysteine residue [98]. This reaction is catalyzed by glutathione transferase Omega 1 (GSTO1-1), which belongs to the cytosolic glutathione transferase (GST) superfamily [99] and is able to deglutathionylate the regulatory protein kinase NEK7 at Cys253, promoting its interaction with NLRP3 and activation of the inflammasome. The addition of glutathione at the Cys79 and Cys253 residues of NEK7, on the contrary, limits activation of the NLRP3 inflammasome [100]. The activity of caspase-1 is regulated in a similar way. Glutathionylation of caspase-1 at Cys397 and Cys362 reduces the activity of caspase-1, while an increase in the formation of ROS, a decrease in the redox potential of cells, glutathione oxidation, and deglutathionylation of caspase-1 lead to the activation of caspase-1. It should be noted that the use of antioxidants, such as curcumin, leads to an increase in S-glutathionylation of caspase-1, suppression of its activity, and a decrease in the production and secretion of mature IL-1β [101], which ultimately promotes survival during lethal endotoxic shock [102, 103]. The expression of glutathione-S-transferases is regulated by the transcription factor NRF2 (regulation of NRF2 is discussed in sections 3.4–3.7.) [104].

3.2. Regulation of NLRP3 Interacting Patterns

NLRP3 interacting proteins are involved in the inflammasome regulation. These include molecular chaperone Hsp90 and its co-chaperone SGT1, thioredoxin-interacting protein (TXNIP), guanylate binding protein 5 (GBP5), RNA-dependent protein kinase (PKR), migration inhibitory factor (MIF), microtubule affinity regulatory kinase 4 (MARK4), and serine/threonine protein kinase NEK7 [34]. Hsp90 is required to protect NLRP3 from proteasome degradation and autophagy. Hsp90 recruits SGT1 to NLRP3 to form a complex that maintains NLRP3 in an inactive but signal-competent state [105]. Hsp90 expression is regulated by the transcription factor NRF2 (NRF2 regulation is discussed in sections 3.4–3.7) [104].

TXNIP, as an oxidative sensor, interacts with thioredoxin (Trx1) under reducing conditions (regeneration of reduced thioredoxin is carried out by selenium-dependent TRXR; its expression is also regulated by NRF2). ROS induced by NLRP3 stimuli oxidize Trx1 and cause dissociation of TXNIP from Trx1, leading to TXNIP interaction with NLRP3 and subsequent activation of the NLRP3 inflammasome.

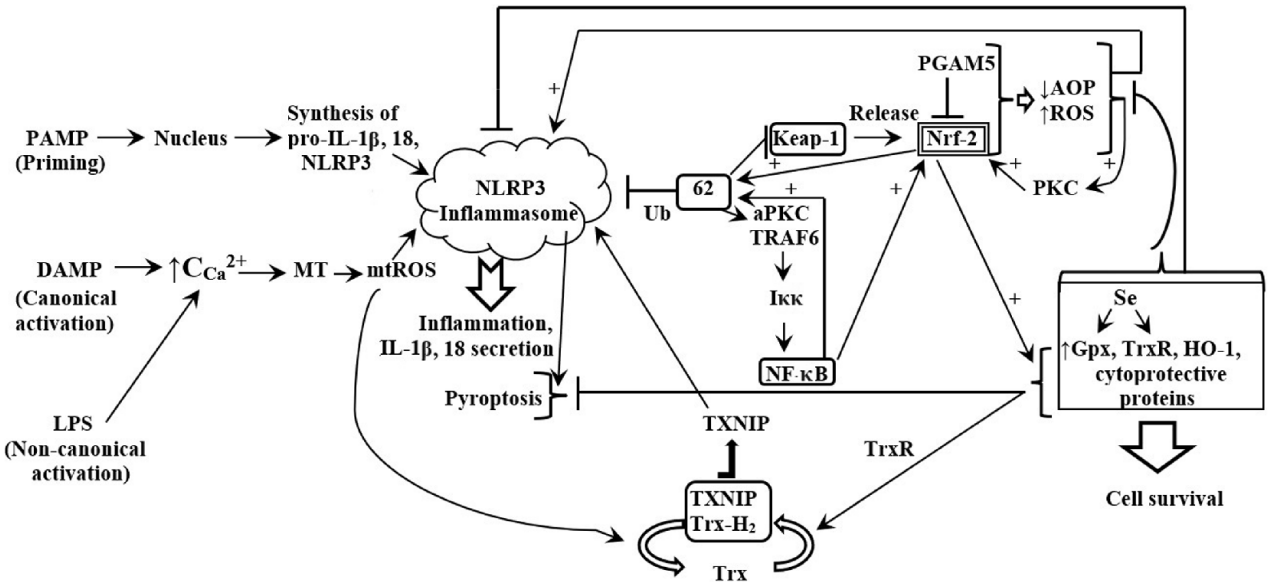

Figure 5. Regulation of the NLRP3 inflammasome. The inflammasome activation is accompanied by mtROS generation; this causes oxidative stress in the cell, oxidation of Trx1-H2 (reduced) and dissociation of oxidized Trx1 from the complex with TXNIP. Free TXNIP interacts with NLRP3, activating the NLRP3 inflammasome and stimulating the development of inflammation, secretion of IL-1β and IL-18, and cell death through pyroptosis. To restore redox homeostasis and prevent cell death by pyroptosis, in parallel with the activation of the NLRP3 inflammasome, the synthesis of the nuclear factor transcription factor NRF2 occurs; its activation leads to the expression of cytoprotective proteins and enzymes (GPX(Se), TRXR(Se), HO-1, etc.), responsible for antioxidant defense (AOD) and cell survival. Cytoprotective proteins and enzymes neutralize ROS and suppress the NLRP3 inflammasome and pyroptosis. The most important regulators of NRF2 activity are Keap1, p62, and NF-κB. ROS generated during oxidative stress oxidize specific cysteine residues of Keap1, promoting the release of NRF2 from the complex with Keap1. p62 binds to the same region of Keap1 as NRF2 and releases Nrf-2 from its inhibitor, resulting in the expression of the NRF2 target genes. NRF2 also stimulates p62 expression. NF-κB stimulates the expression of Nrf-2 and p62. The latter binds to atypical protein kinase C (aPKC) and TRAF6, resulting in activation of IKK and NF-κB, thereby increasing the regulation of NRF2 and p62. In addition, p62 also degrades ubiquitinated (Ub) components of the inflammasome. PGAM5 interacts with both Keap1 and NRF2, causing negative regulation of NRF2. ROS activate protein kinase C (PKC), which phosphorylates and thereby activates NRF2 to maintain redox homeostasis and cell survival. Selenium-dependent TRXR restores Trx to Trx1-H2, which binds to TXNIP and terminates its activating effect on the NLRP3 inflammasome. →+ – activation; ┤ – negative regulation (suppression, inhibition).

In addition, TXNIP is essential for NLRP3 inflammasome activation, induced by ATP, sodium urate, and islet amyloid polypeptide [106].

GBP5 is critical important for activation of the NLRP3 inflammasome in response to ATP, nigericin, and pathogenic bacteria. GBP5 binds to the pyrin domain of NLRP3, and tetrameric GBP5 promotes NLRP3-mediated ASC oligomerization [107]. In addition, MIF and MARK4 also interact with NLRP3 and promote its activation [34, 106] (Fig. 5).

Nevertheless, the redox regulation of the inflammasome by the oxidative sensor TXNIP is of the greatest interest.

3.3. Redox Regulation of the Inflammasome by the Oxidative Sensor TXNIP

The NLRP3 inflammasome is controlled by ROS and also by the selenium-containing enzyme TRXR. In the reduced state, Trx1 interacts with and inhibits TXNIP. In this complex, TXNIP cannot interact with and activate NLRP3. Under the influence of ROS, Trx1 undergoes oxidation followed by dissociated from TXNIP. The latter binds to NLRP3 thus stimulating inflammasome assembly [108].

In order to restore redox homeostasis and prevent cell death by pyroptosis, transcription factor NRF2 is synthesized in parallel with the activation of the NLRP3 inflammasome. NRF2 activation leads to the expression of cytoprotective proteins and enzymes (GPX, TRXR, HO-1, etc.) responsible for cell survival [104, 109].

It should be noted that damaged mitochondria produce a by-product metabolite of the tricarboxylic acid cycle, itaconate (methylene succinate), which can activate the anti-inflammatory cellular programming of NRF2 through alkylation of cysteine residues in the KEAP1 protein. Activation of inflammasomes can be inhibited through activation of NRF2 and the downstream protein HO-1, which is responsible for intracellular antioxidant protection [38].

3.4. Transcription Factor NRF2

NRF2 is a key regulator of cytoprotective gene expression [110]. Transcription of the *Nfe2l2* gene encoding NRF2 is induced by an NRF2-mediated positive feedback loop created using NF-κB. NRF2 is composed of seven Neh domains, which regulate its activity by binding to other proteins or DNA. Neh1 is required for NRF2 transcriptional activity because it contains a bZIP DNA binding region and mediates interaction with small MAF proteins. NRF2s binding to MAF targets antioxidant response elements (AREs) in the promoter region of several hundred genes, including many genes encoding cytoprotective proteins [111]. Among the protein products of these genes are proteins of the glutathione system (for example, glutamate cysteine ligase, glutathione S-transferase, glutathione peroxidase-2 and -3, glutathione disulfide reductase) and thioredoxin (for example, TRXR 1 and 3). They form the basis of the cell antioxidant system. In addition, NRF2 regulates genes encoding enzymes necessary for the detoxification of ROS and xenobiotics (for example, NQO1 (NAD(P)H-dehydrogenase [quinone] 1)), NADPH regeneration (for example, glucose-6-phosphate dehydrogenase and phosphogluconate dehydrogenase of the pentose phosphate cycle, and also malic enzyme), heme and iron metabolism (for example, HO-1 light and heavy chains of ferritin and others) [54]. It was previously found that NRF2 directly prevented transcription of genes encoding the proinflammatory cytokines IL-6, proIL-1β and proIL-1α [104, 109].

NRF2 is also indirectly involved in the regulation of activation of the NLRP3 inflammasome: one of the cytoprotective enzymes synthesized under control of NRF2, TRXR, is necessary for the reduction of thioredoxin in TXNIP (see above).

In addition, TRXR is involved in the regulation of the following proteins and enzymes: sirtuin-1, caspase-3, ASK1 (apoptosis signaling kinase 1), MAPK (mitogen-activated protein kinase), NF-κB transcription factors, STAT3 (signal transducer and activator of transcription 3), as well as Myd88 (myeloid differentiation factor 88), disintegrin and metalloproteinase 17 (ADAM17). It should be noted that one of the stimuli for ADAM17 activation is the coronavirus spike protein [108].

3.5. Canonical Activation of NRF2

Kelch-like ECH-associated protein 1 (Keap1) is the most important regulator of NRF2 activity [112]. In the cytoplasm, two molecules of this adapter bind to the N-terminal Neh2 domain of NRF2 and mediate its polyubiquitination by interacting with the E3 ubiquitin ligase complex Cul3/Rbx1 (Cullin 3/RING-box 1). This leads to constant degradation of NRF2 in the proteasome. Small amounts of NRF2 escape Keap1-dependent degradation and cause constitutive and weak expression of NRF2 target genes upon their entry into the nucleus. Keap1-dependent ubiquitin ligase is redox-sensitive. Oxidative stress or electrophiles oxidize specific cysteine residues of Keap1, causing conformational changes in the adapter protein and inhibition of E3 ubiquitin ligase activity. At the same time, Cul3 remains associated with Keap1 [112]. Activation of NRF2 by oxidation of Keap1 cysteine residues is known as canonical NRF2 activation. Interestingly, oxidation of Keap1 by many different NRF2 activators appears to be a highly specific process. These activators can be grouped into different classes, depending on their specificity for Keap1 cysteine residues. For example, the NRF2 activator sulforaphane, which is a component of broccoli sprouts, or dimethyl fumarate, an anti-inflammatory drug approved in the European Union and the United States for the treatment of patients suffering from psoriasis or multiple sclerosis, oxidize mainly the Cys151 residue in Keap1 [109] (Fig. 3).

3.6. Non-canonical Activation of NRF2

Non-canonical activation of NRF2 is caused by binding of Keap1 to p62 (also known as sequestosome 1 (SQSTM1)) [113]. p62 is a multidomain and multifunctional protein that protects cells from stress through autophagic clearance and activation of NRF2 [113]. The Kir domain of p62 binds to the same region of Keap1 as NRF2 and thus releases NRF2 from its inhibitor, leading to expression of NRF2 target genes. In autophagy-deficient cells, phosphorylated p62 aggregates with Keap1 in the cytoplasm, causing persistent activation of NRF2 [114]. This results in a positive feedback loop as NRF2 induces the expression of p62, regulating NF-κB, which in turn increases NRF2 expression.

In various types of cancer, NRF2 is activated due to epigenetic silencing of the *Keap1* gene through promoter methylation [115, 116]. Increased expression of the target gene NRF2 maintains stress resistance of cancer cells and causes changes in their metabolic pathways [117].

NRF2 regulation also involves phosphoglycerate mutase family member 5 (PGAM5), which is a mitochondrial serine/threonine phosphatase. PGAM5 interacts with Keap1, promoting its Keap1-dependent ubiquitination and subsequent proteasomal degradation [118]. In addition, PGAM5 also interacts with NRF2 and negatively regulates its transcriptional activity [119]. It is known that PGAM5 is a central player in necroptotic cell death [109, 119].

Activation of NRF2 after dissociation of the NRF2-Keap1 complex can also be mediated by protein kinase C (PKC), which phosphorylates NRF2 at the Ser40, causing its dissociation from Keap1, translocation into the nucleus, and induction of target gene expression. This occurs in response to oxidative

stress, which activates PKC and maintains canonical NRF2 activation [120]. Another example is p21, a major target of p53 and a cell cycle inhibitor, which interacts with NRF2 and thereby releases it from Keap1 [109].

3.7. Non-canonical NRF2 Activation and Inflammation Inhibition

The multifunctional and multidomain protein p62 is proposed to be a critical regulator of the NRF2, NF-κB, and NLRP3 inflammatory pathways [121]. p62 maintains NRF2 and NF-κB activity but inhibits the NLRP3 inflammasome. p62 was initially identified as an important mediator of NF-κB. p62 interacts with atypical PKC via its N-terminal PB1 domain, which is required for self-oligomerization. In addition, p62 binds TRAF6 (tumor necrosis factor receptor-associated factor 6) via its TRAF6 binding domain and it can also activate RIP1 (receptor-interacting serine/threonine protein kinase 1) [121] and IκB kinase (IKK), which induces translocation of NF-κB upon phosphorylation and inhibition of its inhibitor IκBα. Activation of inflammation in macrophages triggers the formation of autophagosomes. Inflammasome activation and IL-1β production are inhibited by Lys63-dependent polyubiquitination of inflammasomes. In addition, p62 is required for elimination of damaged mitochondria through autophagy. Inflammatory agonists are thought to induce NLRP3 inflammasome assembly upon mitochondrial damage, development of oxidative stress, and release of inflammasome activation signals. p62-dependent mitochondrial destruction is accompanied by a decrease in NLRP3 activation. It is suggested that oxidation of p62 cysteine residues enhances autophagy [122]. Interestingly, NF-κB plays a central role in controlling this crosstalk. Its activation is required not only for priming of the NLRP3 inflammasome (induction of NLRP3 and proIL-1β expression), but also for the induction of p62 expression, which limits inflammasome activation. Since p62 supports the activation not only of NF-κB but also NRF and a positive feedback loop occurs due to induction of p62 expression by NRF2 [109]. Analysis of the literature data allowed us to draw up a scheme for the regulation of the NLRP3 inflammasome, presented in Figure 5.

Therefore, oxidative stress is a key factor in the activation of the NLRP3 inflammasome, which promotes caspase-1 activation, GSDM pore formation, and the resulting pyroptosis.

3.8. Post-Translational Regulation of GSDMs

The GSDM functioning is associated with the N-terminal GSDMD-NT domain and is regulated both by addition of certain metabolites (fumarate, itaconate and palmitic acid) and by oxidation of certain cysteine residues [123]. Specifically, fumarate addition, known as succination (i.e., acylation with succinate), occurs at the residues Cys191 (human)/Cys192 (mouse) in GSDMD and Cys45 (mouse) in GSDME as a result of a switch in the metabolic profile of macrophages and dendritic cells from oxidative phosphorylation to aerobic glycolysis. In GSDMD, Cys191 is located adjacent to Leu192, which is the contact point of the C-terminal domain of GSDMD responsible for autoinhibition. Because Leu192 mutation blocks GSDMD-NT binding to membrane lipids, succination of Cys191 could have a similar effect on GSDMD. This suggestion was confirmed by cysteine-modifying drugs that blocked pyroptosis and death in a model of lethal endotoxemia [124]. Another metabolic regulator of GSDMs is itaconate, which directly binds to GSDMD at the Cys77, blocking caspase-1-dependent cleavage of GSDMD and protecting the cell from pyroptosis during prolonged exposure to LPS. At the same time, palmitoylation at Cys407 and Cys408 residues, on the contrary, promoted GSDME-NT dissociation from GSDME-CT followed by subsequent formation of GSDM pores [124].

3.9. Redox Regulation of GSDMs

Inflammatory stimuli are known inducers of mtROS. mtROS production is known to trigger pyroptosis of infected macrophages, thus acting as a defense against intracellular infections. It was previously reported that mtROS regulated GSDMD through direct oxidation of human GSDMD at Cys38, Cys56, Cys268, and Cys467 [123]. These data are presented schematically in Figure 6.

At the same time, mtROS formation is a consequence of mitochondrial damage, destruction of mtETC complex I by caspase-3 and granzyme B. mtROS oxidize cardiolipin and promote its movement to the outer surface of mitochondria, resulting in the release of cytochrome *c* from mitochondria into the cytosol and increased oxidative stress [125–127]. All these events lead to the assembly of the inflammasome, activation of caspase-1, GSDMs, formation of mature proinflammatory cytokines and pyroptosis [125, 128].

Consequently, inflammation develops in jointly with oxidative stress. Prevention of oxidative stress, inflammation and cell death involves an antioxidant system, including superoxide dismutase (SOD), catalase, glutathione peroxidase and thioredoxin systems [129].

4. THE ROLE OF ANTIOXIDANTS IN REDOX REGULATION OF INFLAMMATION AND CELL DEATH

The main antioxidant enzymes are glutathione peroxidases (GPXs), which, with the participation of glutathione (GHS), reduce H_2O_2 and lipid hydroperoxides [129]. Eight GPXs are known [130]. GPXs1-4 and GPX6 are selenium-dependent and contain a selenocysteine residue in their active

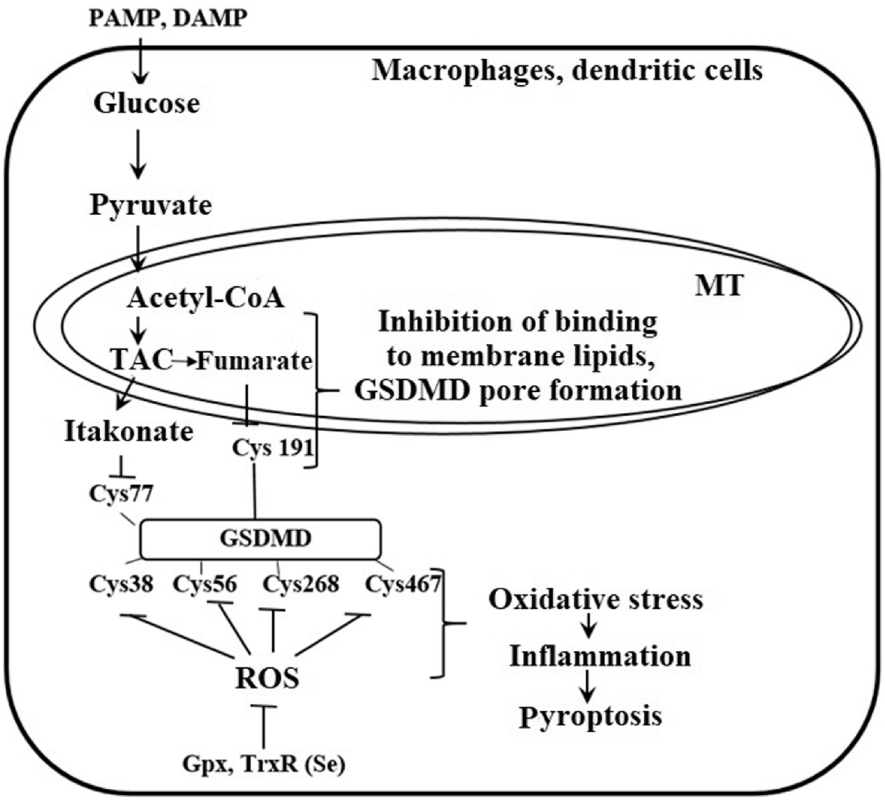

Figure 6. Regulation of GSDMD. Explanations are given in the text.

sites [131]. Other important antioxidant enzymes are TRX, TRXR, thioredoxin peroxidase (PRX) and glutaredoxins [129]. Most of these antioxidant enzymes use NADPH as the reducing equivalent. NADPH not only maintains catalase in an active form, but also acts as a cofactor for thioredoxin and glutathione reductases, reducing oxidized glutathione and thioredoxin to their reduced forms for subsequent use as a cosubstrate of TRXR and GPX, respectively [129]. The most abundant non-enzymatic antioxidant in cells is GSH. It should be noted that the expression of both antioxidant enzymes and NADPH-producing enzymes (glucose-6-phosphate dehydrogenase, phosphogluconate dehydrogenase and malic enzyme) is regulated by NRF2 [104] (see sections 3.4-3.7).

However, it was found that loss of the selenium-dependent enzyme glutathione peroxidase 4 (GPX4) increased lipid peroxidation (LPO)-dependent caspase-11 activation and GSDMD cleavage in non-canonical pyroptosis [123]. The main function of GPX4 is to suppress membrane LPO. Structural and biochemical studies have shown that GPX4 interacts with the polar head of phospholipids to inhibit lipid peroxidation, thereby protecting membrane integrity. It should be noted that an important inhibitor of GPX4 is the phospholipid scramblase TMEM16A, which promotes transition of phosphatidylserine from the inner to the outer monolayer of the biomembrane during programmed cell death. It has been found that TMEM16A, interacting with GPX4, causes its ubiquitination and degradation. However, disruption of the TMEM16A-GPX4 interaction eliminates GPX4 inhibition [132].

According to recent data, GPX4 dysfunction can cause various types of programmed cell death: apoptosis of nerve cells and spermatozoa, necroptosis of erythrocyte precursors, pyroptosis of infected myeloid cells, ferroptosis of T and B cells and kidney and pancreatic cells [133], as well as parthanatosis (a type of cell death accompanied by oxidative DNA damage) during hypoxia, oxidative stress, hypoglycemia and inflammation accompanying stroke and neurodegenerative diseases [133–135].

However, the most significant factor in the reduction of GPX4 activity is selenium deficiency, since a decrease in selenium levels causes inefficient translation of the GPX4 Sec UGA codon and premature termination of translation [136-138].

5. THE ROLE OF SELENIUM IN CELL REDOX HOMEOSTASIS

Redox homeostasis in the cell depends on the production of ROS and the work of the antioxidant defense system. ROS are produced in cells under aerobic conditions; they are involved in cell proliferation, differentiation, apoptosis and other physiological processes. The most important antioxidant enzymes are selenium-dependent GPX and TRXR. The main function of GPX consists

in neutralization of ROS (superoxide anions, hydrogen peroxide and hydroxyl radicals) and regulation of redox homeostasis in the cell [139–142]. GPX1, one of the important antioxidant enzymes in the body, is involved in the regulation of the NRF2/ARE signaling pathway; this enzyme can reduce accumulation of pro-inflammatory factors and increase the antioxidant defense of the body [142–144].

Studies have shown that selenium-containing dietary supplements can increase the activity of antioxidant enzymes, reduce malondialdehyde (MDA) levels, and reduce DNA damage and cell apoptosis caused by oxidative stress [139, 142]. However, it was previously reported that selenium deficiency serves as a risk factor for increased apoptosis through a simultaneous increase in the level of caspase-2, -3, -7, -8, and -9 mRNA and a decrease in the activity of the main cytoprotective and antioxidant enzymes (SOD, CAT, GPX, GST, and GR). In addition, selenium-dependent enzymes are involved in the regulation of redox-sensitive components in the signaling cascades of inflammation and cell death (MYD88, ASK1, IKKα/β, NF-κB, AP-1, caspase-3, -8, -9) [145], and also increase the expression of DNA methyltransferase 1 DNMT1 and block oxidative DNA damage [146].

During oxidative stress, NRF2 dissociates from the Keap1 protein, enters the nucleus and binds to AREs, activating the NRF2/ARE pathway and enhancing expression of cytoprotective genes, including the selenium-dependent enzymes GPX and TRXR (see sections 3.4–3.7). Selenium-containing proteins and enzymes help reduce the expression of inflammatory factors, reduce the level of phosphorylation of IκK, IκBα, and NF-κB P65, inhibit the production of the pro-inflammatory factor NO and attenuate the pro-inflammatory response caused by oxidative stress. The role of selenium and selenoenzymes in the redox regulation of inflammation and pyroptosis is schematically shown in Figures 5 and 6.

In a large-scale study performed almost 30 years ago, the blood concentrations of selenium ranged from 39.37 μg/l to 196.85 μg/l were considered as normal [147]. According to recent data, the normal range of selenium in the blood for adults is 70–130 μg/l, and the daily selenium intake threshold should not exceed 400 μg, since high doses of selenium can be toxic [148].

It was reported in [149] that a suboptimal selenium concentration in the blood of 0.86 μM (68 μg/l) or less significantly changed the expression of more than two hundred and fifty genes compared with the optimal selenium concentration in the blood of 1.43 μM or 113 μg/l.

Thus, the concentration of selenium in the blood serum can be considered as a marker for determining both the selenium status and the redox status of the whole body [150, 151]. In this regard, an adequate supply of selenium (the optimal selenium concentration in the blood is 1.43 μM or 113 μg/l) is necessary not only for the full functioning of the antioxidant system, but also as an important indicator of the body's anti-inflammatory defense. At the same time, selenium deficiency and/or a selenium concentration in the blood of 0.86 μM (68 μg/l) or less can be used to assess the risk of inflammatory processes [142, 152–160].

CONCLUSIONS

Various molecular structures of endogenous and exogenous origin (DAMPs, PAMPs, and LAMPs) initiate inflammatory signaling cascades in the cell, inflammasome assembly, caspase-1 activation and the formation of GSDM pores, through which mature interleukins IL-1β and IL-18, and also potassium ions leave the cell. The large number of GSDM pores, loss of membrane potential and cell swelling cause PM ruptures. These events about 20 years ago were called pyroptosis. It is now known that by the time the PM ruptures, the cell is already dead, since pyroptosis damages all intracellular structures (nucleus, mitochondria, ER, lysosomes, and Golgi complex). Mitochondria play the central role in triggering pyroptosis. The NLRP3 inflammasome assembly occurs on the outer mitochondrial membrane followed by subsequent activation of caspase-1 and gasdermins. In addition, mitochondrial damage is associated with the production of mtROS, causing oxidative stress in the cell and oxidation of redox-sensitive molecules. These molecules include NEK7, NLRP3, NF-κB, NRF2, Keap1, p62, TXNIP, Ninj1, TMEM16, caspase-1, and GSDMs. Redox regulation of these structures requires selenium-dependent enzymes GPX and TRXR [142]. Selenocysteine is a proteinogenic acid encoded by the UGA codon. In the case of selenium deficiency, the synthesis of selenoproteins at this codon is terminated and UGA acts as a stop codon [136–138]. In this regard, we propose to consider selenium as an important indicator of redox homeostasis in the cell, and its suboptimal concentration in the blood (0.86 μM or 68 μg/l or less) and/or selenium deficiency conditions to be used to assess the risk of developing inflammatory processes [142, 152–160].

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COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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РЕДОКС-РЕГУЛЯЦИЯ NLRP3-ОПОСРЕДОВАННОГО ВОСПАЛЕНИЯ И ПИРОПТОЗА

Н.Ю. Русецкая*, Н.Ю. Логинова, Е.П. Покровская, Ю.С. Чесовских, Л.Е. Титова

Саратовский государственный медицинский университет им. В.И. Разумовского,
410012, Саратов, ул. Б. Казачья, 112; *эл. почта: meduniv@sgmu.ru

Представлены современные данные о механизмах активации и редокс-регуляции инфламмасомы NLRP3 и гасдерминов, а также о роли селена в этих процессах. Активация инфламмасомы и пироптоз представляют собой эволюционно консервативный механизм защиты организма от патогенов, описанный для различных типов клеток и тканей (макрофагов и моноцитов, клеток микроглии и астроцитов, подоцитов и паренхиматозных клеток почек, тканей периодонта, остеокластов и остеобластов, а также клеток органов пищеварительной и урогенитальной систем и др.). В зависимости от особенностей редокс-регуляции участников NLRP3-воспаления и пироптоза можно условно разделить на 2 группы. Представители первой группы блокируют митохондриальную цепь переноса электронов, способствуют образованию активных форм кислорода и развитию окислительного стресса. К этой группе относятся гранзимы, митохондриальный антивирусный сигнальный белок MAVS и другие. Вторую группу образуют белок, взаимодействующий с тиоредоксином (TXNIP), ядерный фактор-2 эритроидного происхождения (NRF2), Kelch-подобный белок 1, ассоциированный с ECH, (Keap1), нинджурин (Ninj1), скрамблаза (TMEM16), регуляторная протеинкиназа инфламмасомы NLRP3 (NEK7), каспаза-1, гасдермины GSDM B, D и другие, имеющие редокс-чувствительные домены и/или остатки цистеина, которые подвергаются редокс-регуляции, глутатионилированию/деглутатионилированию или иным видам регуляции. Подавление окислительного стресса и редокс-регуляция участников NLRP3-воспаления и пироптоза зависит от активности антиоксидантных ферментов глутатионпероксидазы (GPX) и тиоредоксинредуктазы (TRXR), содержащих в активном центре остаток селеноцистеина Sec. Экспрессия GPX и TRXR регулируется NRF2 и зависит от концентрации селена в крови. Вместе с тем, дефицит селена вызывает неэффективную трансляцию кодона Sec UGA, терминацию трансляции, а, следовательно, синтез неактивного селенопротеина, что может вызвать различные типы запрограммированной гибели клеток: апоптоз нервных клеток и сперматазоидов, некроптоз предшественников эритроцитов, пироптоз инфицированных клеток миелоидного ряда, ферроптоз Т- и В-лимфоцитов, клеток почек и поджелудочной железы. Кроме того, субоптимальная концентрация селена в крови (0,86 мкМ или 68 мкг/л и меньше) значительно изменяет экспрессию более двухсот пятидесяти генов по сравнению с оптимальной концентрацией селена (1,43 мкМ или 113 мкг/л). На основании вышеизложенного мы предлагаем рассматривать концентрацию селена в крови как важный показатель редокс-гомеостаза в клетке, а его субоптимальную концентрацию в крови (или селенодефицитные состояния) использовать для оценки риска развития воспалительных процессов.

Полный текст статьи на русском языке доступен на сайте журнала (http://pbmc.ibmc.msk.ru).

Ключевые слова: инфламмасома NLRP3; пироптоз; редокс-регуляция; тиоредоксин; глутатионпероксидаза; селен

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