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Pyroptosis and its therapeutic potential

Odintsova I.A., Chirsky V.S., Slutskaya D.R., Andreeva E.A., Berezovskaya T.I.

S.M. Kirov Military Medical Academy
6g, Akademika Lebedeva Str., Saint Petersburg, 194044, Russian Federation

ABSTRACT

The review examines present data on pyroptosis – a type of programmed cell death associated with infection with various pathogens. During pyroptosis. specific molecular complexes, inflammasomes, are formed, caspases are activated, and proinflammatory cytokines are produced.

We consider the mechanisms of pyroptosis activation, including canonical and non-canonical pathways, as well as methods for its detection in cells. The review substantiates the relevance of studying the role of pyroptosis in pathological processes in different tissues. We focus on the therapeutic potential of pyroptosis, including its role in the treatment of sepsis. Pyroptosis is involved in sepsis-induced tissue damage in various organs, so regulation of this type of cell death can serve as the basis for the development of innovative treatment methods.

Keywords: cell death, pyroptosis, gasdermins, inflammasome, caspases, therapy, sepsis

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Пироптоз и его терапевтический потенциал

Одинцова И.А., Чирский В.С., Слуцкая Д.Р., Андреева Е.А., Березовская Т.И.

Военно-медицинская академия (ВМА) им. С.М. Кирова
Россия, 194044, г. Санкт-Петербург, ул. Академика Лебедева, 6ж

РЕЗЮМЕ

В обзоре рассмотрены современные сведения о пироптозе – форме запрограммированной гибели клеток, связанной с инфицированием различными патогенами. При этом образуются специфические молекулярные комплексы – инфламмасомы, происходит активация каспаз и выработка цитокинов, опосредующих воспаление.

Рассмотрены механизмы активации пироптоза, включающие канонический и неканонический пути, а также методы его выявления в клетках. Обосновывается актуальность исследования роли пироптоза в патологических процессах в разных тканях. Акцентировано внимание на терапевтическом потенциале пироптоза, в том числе при лечении сепсиса. Пироптоз вовлечен в вызванные сепсисом повреждения тканей разных органов, поэтому регулирование этой формы клеточной гибели может служить основой для разработки инновационных методов лечения.

✉ *Slutskaya Dina R.,* vmeda_21@mil.ru

Ключевые слова: клеточная гибель, пироптоз, гасдермины, инфламмасома, каспазы, терапия, сепсис

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INTRODUCTION

The vital activity of cells includes a number of key processes, namely proliferation, differentiation, adaptation, reactive changes, etc. The terminal phase of cell life cycle is death, which is implemented by simultaneous or sequential involvement of certain biomolecules. The German researcher Karl Vogt was the first to mention cell death; he described the death of embryonic cells of the notochord in 1842 [1]. Since then, the understanding of cell death has expanded significantly. Scientists paid close attention to the study of forms of cell death only in the second half of the XX century, which contributed to the creation of the international Nomenclature Committee on Cell Death (NCCD).

Cell death occurs both under normal (physiological) conditions and during pathological histogenesis. It is one of the fundamental cytophysiological processes in all living organisms and is observed in embryonic development, during the normal functioning of tissues and organs, aging, immune (including autoimmune) responses, irreversible reactive changes, and various pathological processes. For a long time, experts considered non-programmed cell death (necrosis or necrobiosis) as the main form of cell death. Later, they discovered apoptosis, and more recently, autophagy-dependent cell death, neutrophil extracellular traps, ETosis, entotic cell death, ferroptosis, mitotic catastrophe, death through terminal differentiation, etc. [2–7].

One of the recently identified forms of proinflammatory cell death is pyroptosis, which occurs not only in leukocytes and macrophages, but also in other cells and affects the course of both normal and pathological histogenesis [8–10]. In recent years, its role in the pathogenesis of certain diseases has been discovered, and the possibilities of therapeutic effects on this process are under discussion [7, 11, 12].

HISTORICAL REFERENCE

The term “pyroptosis” takes its origin from the Greek roots “pyro” – fire, fever, and “ptosis” – fall. A. Zychlinsky et al. [13] described pyroptosis for the first time in the late XX century and revealed the death of macrophages infected with *Shigella flexneri*. In 1996, D.M. Monack et al. published a study describing the death of macrophages infected with *Salmonella enteric* (serotype *Typhimurium* – *S. typhimurium*) [14]. Due to some similarity in morphological manifestations and the absence of characteristic differentiation biomarkers discovered later, this form of cell death was mistakenly considered as apoptosis at that time.

Subsequently, scientists identified similarities and differences in the mechanisms of pyroptosis and apoptosis, which brought some clarity to the interpretation of the data obtained [15]. Further studies showed that this bacteria-induced cell death depends on the enzyme caspase-1 [16]. The work by S.M. Man and T.-D. Kanneganti [17] confirmed the importance of caspase-1 and also revealed that *S. flexneri* cannot induce pyroptosis in macrophages that have a knockout of this enzyme. In 2001, B.T. Cookson and M.A. Brennan [18], having discovered this form of programmed cell death in macrophages infected with *S. thyphimurium*, called it pyroptosis.

In 2002, special molecular intracellular protein complexes, inflammasomes, were discovered and it was found that caspase-1 is one of their components [19, 20]. Further studies of inflammasomes showed that these structures are of great importance in the development of pyroptosis. In 2008, S.L. Fink et al. [21] found that in pyroptosis, DNA was fragmented and the cell membrane was damaged, which was accompanied by a release of intracellular contents, initiating an inflammation. Laboratory mice are the

most common laboratory animals on which pyroptosis has been studied. In 2011, in an experiment on mice, N. Kayagaki et al. [22] found that caspase-11 can induce macrophage death in mice, and this process is similar to pyroptosis mediated by caspase-1 in humans. In contrast to pyroptosis, which involves caspase-1 (the so-called canonical pathway), the authors designated capase-11-dependent pyroptosis as non-canonical. Pyroptosis, which involves human caspase-4 and caspase-5, is also called non-canonical.

MECHANISMS OF PYROPTOSIS

The main goal of pyroptosis is to induce strong inflammatory responses that protect the body from bacterial infection [23]. Probably, for this reason, this phenomenon is best studied in cells whose main function is protective (for example, leukocytes and macrophages). It has been established that pyroptosis inhibits the intracellular replication of microorganisms and activates immune cells to destroy pathogens [24, 25]. Activation of pyroptosis occurs in response to a wide range of effects, primarily infection (contamination) with pathogenic microorganisms. Based on its mechanism, pyroptosis can be canonical and non-canonical. The differences between the two types are not significant, since both pathways result in the formation of transmembrane gasdermin pores in the plasma membrane and disruption of the salt and water homeostasis in the cytoplasm.

The formation of gasdermin pores in the cell disrupts the water and ion balance, ultimately leading to cell death [23]. With the discovery of the gasdermin group of proteins, which in humans includes six proteins, the scope of research on pyroptosis has expanded significantly. All gasdermins (with the exception of the gasdermin protein pejvakin) play different roles in pyroptosis [26, 27]. Nowadays, gasdermin D is the most studied one [23]. It has two domains, an N-terminal domain and a C-terminal domain (GsdmD-N and GsdmD-C, respectively), connected by a peptide linker.

Only the N-terminal domain is considered as an effector domain and can form transmembrane pores [23, 28–30]. Human caspase-1 (canonical pyroptosis pathway) or human caspase-4 and 5 and caspase-11 in mice (non-canonical pyroptosis pathway) split gasdermin D into two domains in the cytoplasm [31, 32]. Embedding into the cell membrane, GsdmD-N selectively binds to its lipids and forms a gasdermin transmembrane pore, releasing cellular contents, including proinflammatory cytokines and the so-called danger signals (alarm signals) [23, 33–37]. There is evidence that GsdmD-N can not only perforate the cell membrane, but also takes part in the activation of cytokines, such as interleukin (IL)-18 and IL-1β [31, 32].

Caspases are a family of evolutionary conserved cysteine proteases [38, 39], which can be divided into two main groups, namely caspases-I (caspases 1, 4, 5, 13, 14) and caspases-II (caspases 2, 3, 6, 10). Caspase-1 substrates include cytokine precursors IL-1β, IL-18, and IL-33 [7, 40, 41].

The canonical pathway of pyroptosis develops when pathogen-associated molecular patterns (PAMPs) and the so-called danger signals or damage-associated molecular patterns (DAMPs) affect the cell. PAMPs include, for example, bacterial, viral, and fungal substances. DAMPs are released from damaged cells into the extracellular matrix and serve as potent proinflammatory factors [42]. Fragments of damaged cells including DNA, ATP, RNA, heat-shock proteins, fatty acids, etc., can act as DAMPs. It is proposed to single out metabolic disorders called homeostasis-altering molecular processes (HAMPs) into a separate group of pyroptosis activators [43–45]. The intracellular lipopolysaccharides (LPS) of gram-negative bacteria [23] initiate the non-canonical pyroptosis pathway.

The key sensors of PAMPs, DAMPs, and HAMPs are cellular receptors, which are called pattern recognition receptors (PRRs). In particular, these include toll-like (TLR), NOD-like (NLR), and Rig-1-like (RLR) receptors [11]. TLR are the most diverse. They are located both on the cell surface and in the cytoplasm and are represented on cells of different cell lineages. Known TLR ligands include various bacterial and fungal components, including LPS for TLR4, flagellin for TLR5, etc. [46]. Products of necrotic cells, heat-shock proteins HSP60 and HSP70, are the ligands of TLR2 and TLR4 [46]. It is known that human HSP60 acts on TLR4 to subsequently stimulate tumor necrosis factor (TNF) α and NO [47]. The mechanism of TLR action is to transmit a signal to the cell nucleus and activate nuclear factor (NF-kB), leading to the production of proinflammatory cytokines and chemokines (IL-1 α, IL-1β, IL-6, and other inflammatory mediators) [46, 48–50].

Activation of PRRs due to interaction with a pathogen causes the assembly of inflammasomes, which are necessary not only for pyroptosis, but also for the production of active forms of proinflammatory cytokines [7, 23]. The main components of

inflammasomes are PRRs, ASC (apoptosis-associated speck-like protein), and procaspase-1 [23]. Formation of inflammasomes ultimately leads to the maturation (activation) of caspase-1 (canonical pathway) or caspase-4, -5 (in humans) and caspase-11 (in mice) (non-canonical pathway). These enzymes cleave the gasdermin D protein, releasing its N-terminal domain.

The analysis of the literature indicates that it is inflammasomes that play a key role in the development of pyroptosis. Currently, we know more than 20 varieties of inflammasomes. Modern reviews by E.E. Garanina et. al (2020) and V.V. Klimov et al. (2023) [7, 11] describe in detail their molecular structure, mechanisms of activation, features of functioning, and regulation methods. It is emphasized that the mechanisms of component activation and assembly of inflammasomes need to be clarified and studied further.

METHODS FOR DETECTING PYROPTOSIS IN CELLS

It is known that different molecular mechanisms regulate cell death, which are accompanied by various changes at the morphological level [51]. Pyroptosis activates caspase-1- dependent nuclease, which leads to chromosome condensation [52]. We can observe enhanced pore formation in the cell membrane, but there is no disruption of the integrity of the mitochondrial membrane, which can be detected by electron microscopy [53]. Low-molecular-weight dyes, such as propidium iodide and ethidium bromide, can be used to detect pyroptosis [42]. Normally, the cell membrane is impermeable to these dyes, but during pyroptosis, these dyes penetrate through the damaged cell membrane are found in the cytoplasm.

Pyroptosis can also be detected by staining preparations with annexin V, but it does not make it possible to clearly distinguish pyroptosis from apoptosis [42]. To detect pyroptosis, it is advisable to use methods, such as flow cytometry, immunofluorescence staining of proteins of the gasdermin family, and determination of lactate dehydrogenase in the extracellular environment by Western blotting. The work by T.F. Sergeeva et al. (2015) proposes various methods for detecting caspase activation and DNA fragmentation [54]. In particular, the authors [54] propose methods for studying the caspase activation *in vitro*: immunohistochemistry, enzyme-linked immunosorbent assay, flow cytofluorometry, fluorescence imaging, fluorescence spectroscopy, FRET/FLIM imaging without a detailed explanation.

Characterizing the methods proposed by researchers for detecting pyroptosis, it should be noted that many of them are not strictly specific to this form of cell death, and we should continue the search in order to detect more accurate signs of differentiation.

PATHOLOGY AND THERAPEUTIC POTENTIAL OF PYROPTOSIS

In the process of studying pyroptosis, it became clear that this phenomenon has a dual meaning and can be both positive and negative [42, 51, 55, 56]. The positive value of pyroptosis is associated with the possibility of release of proinflammatory cytokines from the cells that produce them (macrophages and neutrophil granulocytes) through the transmembrane gasdermin pores of the cell membrane. Oligomerization of the N-terminal domains of gasdermin leads to pore formation, cell swelling, and release of cytoplasmic contents, including IL-1β, IL-33, and IL-18, which trigger the host inflammatory response associated with the inflammasome. Immunocytes recognize and eliminate bacteria that remain viable.

It has been shown that activated gasdermin can induce the formation of transmembrane pores not only in the cell membrane of human cells, but also in the membranes of bacterial cells, causing the death of microorganisms, such as *E. coli*, *L. monocytogenes*, *S. aureus* [34]. Therefore, pyroptosis has a protective function at an early stage of infection. Even though we considered pyroptosis as an exclusively pathological form of cell death, further research has shown that pyroptosis is a protective mechanism of the body that promotes the elimination of pathogens.

Along with the positive effect of pyroptosis, we should also take into account its role in the development of excessively pronounced inflammation and other pathological conditions. The discovery of inflammasomes, mediators of pyroptosis, and experimental confirmation that they are regulators of the secretion of proinflammatory cytokines made it possible to substantiate the leading role of inflammasomes in the development of many diseases [7]. Studies have shown that although pyroptosis can protect the body from microbial agents, its dysregulation leads to the development of autoimmune and autoinflammatory conditions [57, 58].

It is known that an excessive proinflammatory response or immunosuppression can lead to organ dysfunction or the development of secondary infection during the development of sepsis [59]. Although IL-1β, IL-18, and IL-33 are the only

known proinflammatory cytokines generated directly as a result of inflammasome activation, *in vivo* activation of the inflammasome can indirectly lead to the production of numerous other proinflammatory cytokines, including TNFα and IL-6, which causes the so-called cytokine storm and tissue damage to vital organs [60].

X. Zheng et al. [61] emphasize that excessive activation of pyroptosis will inevitably cause uncontrolled inflammation, which significantly accelerates the onset and development of sepsis, which indicates a poor prognosis. It has been shown that pyroptosis participates in septic damage to various cells: neurons and astrocytes of the brain [62], renal tubular epithelial cells [63], hepatocytes [64]. Elevated levels of IL-18 in the blood serum indicate severe sepsis and correlate with a poor prognosis [65, 66].

Many studies demonstrate that overactivated pyroptosis causes organ damage, and A. Sarkar et al. (2006) believe that in sepsis, pyroptosis can contribute to the development of another form of programmed cell death – apoptosis, thereby exacerbating inflammation and clinical manifestations of multiple organ dysfunction [67]. There are indications that pyroptosis is closely associated with atherosclerosis and diabetic nephropathy [31]. Cardiovascular diseases, especially atherosclerosis and myocardial infarction, are often accompanied by cell death and acute or chronic inflammation. The research by L. Wang et al. (2021) revealed that exosomes obtained from monocytes can contain the TXNIP-NLRP3 complex and transport it to macrophages of the myocardial connective tissue, subsequently promoting IL-1β and IL-18 production by them and aggravating inflammation [68].

An increasing number of studies are devoted to studying the role and molecular mechanisms of pyroptosis in sepsis-induced myocardial dysfunction (SIMD), which is a devastating complication of sepsis with a mortality rate of more than 50%. A small molecule called PSSM1443 can reduce the protein levels of active caspase-1, IL-1β, and IL-18 in SIMD mice by disrupting the TXNIP-NLRP3 interaction [68]. This indicates that inhibition of NLRP3 inflammasome activation is beneficial for the treatment of this cardiac pathology.

Proinflammatory caspases take part in endothelial cell pyroptosis, and caspase-11 takes part in the pathogenesis of sepsis-induced lung injury. In the experiment, mice with caspase-11 showed a decrease in inflammation and lung damage within 12 hours compared to mice in the control group, indicating the involvement of this caspase in the pathogenesis of sepsis-induced lung injury [69].

M. Kalbitz et al. (2016) found that number of the NLRP3 inflammasomes and the concentration of IL-1β were significantly increased in left ventricular cardiomyocytes in mice with experimental peritonitis [70]. At the molecular level, IL-1β matures through activation of the NLRP3 inflammasome, which can further cause atrophy and impair cardiomyocyte contractility and relaxation [71]. Analysis of the literature allows us to conclude that currently much attention is paid to the study of diseases associated with inflammasomes [7, 9, 42]. There is information in the literature about the role of pyroptosis in the tumor process. The induction of pyroptosis in tumor cells occurs with the activation of both innate and acquired immunity [42]. In this case lysis of the tumor cell and release of its contents into the intercellular space take place, and local inflammation occurs with the production of IL-1β and IL-18 by neutrophil granulocytes and macrophages, which helps attract immune system cells to the area of the primary tumor.

An extremely urgent task is to find effective ways to eliminate the adverse effect of pyroptosis in the development of pathological conditions. There is evidence that administration of certain substances can enhance or, conversely, suppress pyroptosis. Thus, in an experiment with the administration of the glutamine, pyroptosis of hepatocytes increased within 24 hours after experimental modeling of sepsis, but suppression of pyroptosis was observed after 72 hours [64]. The authors concluded that the regulation of pyroptosis cell death can serve as a basis for the development of treatment methods for certain diseases.

Based on the study of inflammasomes and pyroptosis, various research teams are developing innovative therapeutic approaches [9, 55]. In recent years, researchers have considered the possibility of using pyroptosis as a potential strategy for treating tumors and developing new anticancer drugs [72]. It is assumed that the activation of pyroptosis in tumor cells may be justified in the treatment of malignant neoplasms [42].

Recent studies have shown that $CD8^+$ T lymphocytes can suppress tumor growth by inducing pyroptosis and ferroptosis. R. Tang et al. (2020) concluded that pyroptosis, along with necroptosis and ferroptosis, represents a potentially new mechanism of immunogenic cell death [73]. Currently, promising

gasdermin D inhibitors are being developed for the treatment of a number of inflammatory diseases [23]. There is information about the effectiveness of drugs that are inflammasome inhibitors for the treatment of certain diseases [7]. One of them is rilonacept, which can bind IL-1α and 1β. C. Liu et al. (2021) found that Gly-Pro-Ala (GPA) peptide could significantly attenuate lung tissue damage in mice [74]. *In vitro* experiments showed that GPA peptide can protect alveolar macrophage from caspase-1-dependent pyroptosis.

CONCLUSION

The analysis of modern scientific literature indicates significant interest in studying the molecular mechanisms of pyroptosis and its therapeutic potential. Nowadays, we know the main manifestations of this type of programmed cell death, pattern recognition cell receptors, the structure and significance of various types of inflammasomes, and proteins of the gasdermin family. At the same time, many questions remain poorly researched, and the available answers to them are contradictory.

Pyroptosis in immunocompetent cells, neutrophil granulocytes, and macrophages has been studied quite well. Much less attention is paid to other cells, especially to representatives of the main cell lineages in the tissues of vital organs. Methods of pyroptosis detection in experimental and clinical conditions require further development. An effective solution to these issues is possible only through the interaction of specialists in different fields, namely morphologists, molecular biologists, biochemists, physiologists, pathologists, microbiologists, clinicians, etc.

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Authors' contribution

Odintsova I.A. – conception and design, drafting of the manuscript, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Chirsky V.S. – drafting of the manuscript, editing of the manuscript, final approval of the manuscript for publication. Slutskaya D.R. – search and analysis of literature on the mechanisms of pyroptosis. Andreeva E.A. – search

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Authors' information

Odintsova Irina A. – Dr. Sci. (Med.), Professor, Head of the Department of Histology with a Course in Embryology, S.M. Kirov Military Medical Academy, Saint Petersburg, vmeda_21@mil.ru, https://orcid.org/0000-0002-0143-7402

Chirsky Vadim S. – Dr. Sci. (Med.), Professor, Head of the Department of Pathological Anatomy, S.M. Kirov Military Medical Academy, Saint Petersburg, vmeda_21@mil.ru, https://orcid.org/0000-0003-3215-3901

Slutskaya Dina R. – Cand. Sci. (Biology), Associate Professor, Department of Histology with the Course in Embryology, S.M. Kirov Military Medical Academy, Saint Petersburg, vmeda_21@mil.ru, https://orcid.org/0000-0003-3910-2621

Andreeva Elena A. – Cand. Sci. (Med.), Associate Professor, Department of Pathological Anatomy, S.M. Kirov Military Medical Academy, Saint Petersburg, vmeda_21@mil.ru, https://orcid.org/0000-0003-1973-9211

Berezovskaya Tatyana I. – Lecturer, Department of Histology with a Course in Embryology, S.M. Kirov Military Medical Academy, Saint Petersburg, vmeda_21@mil.ru, https://orcid.org/0009-0009-1591-9152

(✉) **Slutskaya Dina R.,** vmeda_21@mil.ru

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