

# Pyroptosis and neurological diseases

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## ABSTRACT

Pyroptosis is a new process of programmed cell death, which has been discovered and confirmed in recent years. Its cardinal features include activation of caspase-1 and a massive release of inflammatory cytokines (interleukin (IL)-1 $\beta$ , IL-18), *etc.* The morphological characteristics, occurrence and regulatory mechanisms of the pyroptosis greatly, differ from other cell death mechanisms such as apoptosis and necrosis. It has already been proven that pyroptosis participates and plays an important role in a wide range of neuronal diseases. Here, we review the current understanding of the pyroptosis and its roles in neurological diseases.

**Key words:** Caspase-1, inflammasome, interleukin-1 $\beta$ , interleukin-18, neurological diseases, pyroptosis

## INTRODUCTION

Cell death is a critical and inevitable phase common to all cell types. A deeper understanding of cell death in its form and nature is critical to shed new light on the emergence, development and treatment of diseases. Many different types of cell death patterns have been discovered in the last years; among that pyroptosis is one of the most recent. It is now widely accepted that this mechanism contributes to the development of neurological diseases. In this review, we first describe the definition of the pyroptosis and its basic mechanisms and discuss how pyroptosis and its relevant molecules participate in neurological diseases and their progression.

## THE HISTORY OF PYROPTOSIS AND ITS CHARACTERISTICS

The understanding of cell death has changed a lot through decades. Nowadays we believe that cell death can be roughly divided into necrosis and programmed cell death, the latter one, including apoptosis, oncosis, autophagy, *etc.*, as well as pyroptosis that will be discussed in this review.

Pyroptosis was first observed in 1992 when Zychlinsky *et al.* described that *Shigella flexneri* can induce programmed cell death in macrophage, but this process was mediated by a caspase-1, and the iconic molecule in apoptosis, caspase-3, was not apparently involved. This observation suggested that such programmed cell death was different from apoptosis.<sup>[1]</sup> Subsequent studies confirmed that in *S. flexneri* specific caspase-1 blocker Ac-YVAD-CHO inhibited programmed cell death of macrophages, whereas caspase-1 knockout could protect macrophages from death following *S. flexneri* infection.<sup>[1,2]</sup> In contrast, caspase-3 specific blockers and caspase-3 knockout macrophages did not show any effects.<sup>[3]</sup> Then, in 2001, Cookson and Brennan found a type of caspase-1 dependent cell death in *Salmonella* infected macrophages, and for the first time named it "pyroptosis", its meaning deriving from the Greek root pyro (fireworks) and ptosis (to-sis) (death).<sup>[4]</sup>

In the process of the pyroptosis, activated caspase-1 mediates massive generation of pro-inflammatory cytokines, interleukin (IL)-1 $\beta$ , IL-18,<sup>[5]</sup> leading to cell morphological changes similar to apoptosis, such as nucleus pycnosis, DNA fragmentation and TUNEL staining positivity, *etc.* However, in contrast to apoptosis, in pyroptotic cell, the integrity of the cell membrane is not preserved and micro-pores with diameter about 1-2 nm are formed on it, resulting in potassium efflux, intracellular and extracellular ion imbalance, cell swelling and rupture. Meanwhile, the pro-inflammatory cytokines and cytoplasmic components are released to the extracellular space, causing focal inflammation and cell death.<sup>[6]</sup>

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Lately, researchers realized that a variety of bacterial and nonbacterial stimuli (e.g. substance related to autoimmune diseases and cardiovascular and cerebrovascular diseases<sup>[7-9]</sup>) can drive programmed cell deaths similar to pyroptosis. Meanwhile, in addition to macrophages, there are a variety of cells (such as dendritic cells, *etc.*) undergoing programmed death involving caspase-1 activation, thereby different from caspase-3 mediate apoptosis. Moreover, cells undergoing pyroptosis exhibit a series of cellular changes from complete necrosis to complete the apoptosis.<sup>[10-12]</sup>

## MECHANISMS OF PYROPTOSIS

Pyroptosis and caspase-1 are closely associated. Caspase family is a group of proteases with high homology, and it can be divided into two categories according to its relationship with apoptosis and pyroptosis. One includes apoptosis-related proteases, for instance caspase-3, the executor of apoptosis, and also caspase-2, 6, 7, 8, 9, 10 *etc.* Caspase-3 is activated by co-action of caspase-2, 6, 7, 8, 9, 10 *etc.*, and activated caspase-3 could induce DNA dissolution, proteolysis, and downstream events leading to apoptosis. The second is inflammation-associated proteases, including caspase-1 and caspase-4, 5, 11, 12, 13, 14 *etc.*, taking part in cytokines-mediated inflammatory response.<sup>[13]</sup> Caspase-1 is not involved in apoptosis, but represents the key factor in pyroptosis. Caspase-1 is an IL-1 $\beta$  converting enzyme. Pro-caspase-1 does not have biological activity when produced. Its molecular weight is 45 kDa, constituted by the three domains, including the caspase activation and recruitment domains (CARD) structure in NH<sub>2</sub>-terminal, a large subunit about 20 kDa, and a small subunit about 10 kDa. Then, pro-caspase-1 is converted into heterodimer in the cytoplasm, and further assembled into biologically active tetrameric caspase-1.<sup>[13]</sup> This activation process is regulated by a multi-protein complex in the cytoplasm named inflammasome.<sup>[14]</sup>

Inflammasome is a multi-protein complex composed by NOD-like receptors (NLRs), proteins containing NATCH, leucine-rich repeat and PYD domains (NLRP1 NLRC4 NLRP3 NAIP5 and NLRC5), or absent in melanoma 2 (AIM2), or Caspase-1 *etc.* Some of the inflammasomes also contain apoptosis-associated speck-like proteins containing CARD (ASC). Recent studies have confirmed that retinoic acid-inducible gene I (RIG-I), one of the receptors of some RNA viruses, can form inflammasome with ASC, without the participation of NLRs.<sup>[15]</sup> Under the regulation of inflammasome, pro-caspase-1 is activated, promoting the processing and maturation of pro-inflammatory factors such as IL-1 and IL-18.

NOD-like receptors are one of the pattern recognition receptors (PRR); they can be assembled into inflammasome under the stimulation of pathogens or other dangerous signals. According to different NLRs, the inflammasome can be classified into four types, NLRP-1, 3, 4 Ice Protease-Activating Factor (IPAF), 5. During pathogen stimulation, effector domains of NLRs are exposed to activating caspase-1 through CARD-CARD and PYD-PYD interactions or with the help of ASC directly. Different types of NLRs respond to different stimuli. NALP3 is sensible to perforin, extracellular adenosine triphosphate (ATP), urate crystals, DNA and RNA in virus and ultraviolet. IPAF is sensible to extracellular pathogens, such as *Pseudomonas*, and intracellular pathogens such as *Salmonella*, *Listeria*, *Shigella*, *Legionella bacteria*. *Legionella* also needs the help of NALP5-5 to activate caspase-1.<sup>[16,17]</sup> AIM plays an important role in viral infections; its function is to identify DNA cytoplasm. It is a cytoplasmic DNA transducer, one of PRRs sensible to extrinsic DNA. It belongs to HIN-200 family, with a PYD domain in amino-terminal and an HIN-200 domain in carboxy-terminal.<sup>[18]</sup> In virus-infected cells, AIM2 and caspase-1 can form inflammasome to induce innate immunity and resist intracellular bacteria and DNA viruses.<sup>[19]</sup> RIG-I also binds to the adaptor ASC to trigger caspase-1-dependent inflammasome activation by a mechanism independent from CARD and NLRP3 in RNA infection.<sup>[15]</sup> The effects of ASC are to combine caspase-1 and NLRP1, NLRP3, AIM2, RIG-I together. The mechanism is mediated by the PYD domain in the carboxyl terminus of ASC combined with PYD domain in NLRP1 NLRP3 and AIM, with the CARD domain in N-terminal of ASC combined with pro-caspase-1's CARD domain. In addition, ASC can be assembled into ASC dimer without the participation of NLRs, and ASC dimer can activate caspase-1 directly. This ASC dimer has been named Pyroptosome recently.<sup>[20]</sup>

The activators of the inflammasomes can be divided into two categories: pathogen associated molecular patterns activate a host-defense reaction, and damage associated molecular patterns activate a self-defense mechanism in response to danger signals.<sup>[21]</sup> Activators include bacteria, virus, fungus, protozoa, microbial proteins, crystalline urea, RNA, Alum, ATP, potassium efflux, fatty acids, A $\beta$ , and most recently, degraded mitochondrial DNA.<sup>[22-24]</sup> Overall the assembly and activation of inflammasomes are cell-type and stimulus-specific.<sup>[25,26]</sup>

With inflammasome, pro-caspase-1 is activated to caspase-1. Its function includes conversion of the pro-IL-1 $\beta$  and pro-IL-18 into active IL-1 $\beta$  and IL-18. When bound to their receptors, IL-1R and IL-18R, they lead to nuclear factor- $\kappa$ B dependent gene transcription.<sup>[27,28]</sup> IL-1 $\beta$  is a key molecule in inflammasome initiation and IL-18 can

regulate the function of interferon- $\gamma$  in T-cell and natural killer cell.<sup>[27,28]</sup> Finally, they can recruit and activate other immune cells and induce the synthesis of other inflammatory cytokines, chemokines, and adhesion molecules, expanding local inflammation response.<sup>[13]</sup> Moreover, cell membrane integrity is destroyed by micro-pores formation on it, which is caused by caspase-1, IL-1 $\beta$  and IL-18. These micro-pores lead to a series of pyroptotic processes such as cytoplasm release, cell osmotic lysis and inflammatory reaction.<sup>[13,29]</sup> In addition, during the process of the pyroptosis, caspase-1 is involved in chromosomes and DNA degradation. A specific endonuclease is activated by caspase-1. Once activated, this endonuclease can mediate degradation of DNA, which differs from the DNA degradation occurring in apoptosis.<sup>[29]</sup> More experiments have confirmed that the degradation of cytoskeletal proteins is also associated with pyroptosis and that this process is related with treatment and processing of substrates by caspase-1.<sup>[30]</sup>

## PYROPTOSIS AND NEUROLOGICAL DISEASES

Pyroptosis is closely related to neurological diseases. Pyroptosis and its relative mechanisms participate in acute and chronic aseptic inflammation in the nervous system. Our immune system could recognize disease-associated molecules through PRR. In the central nervous system (CNS), PRR are expressed mainly on microglial, macrophages and astrocytes. They are distributed on the surface of membranes to recognize extracellular signals (i.e. toll like receptors), or in the cytoplasm to transmit intracellular signal (i.e. NLR receptor).

There are several NLRP1 and NLRP3 inflammasomes expressed in the nervous system.<sup>[31]</sup> Mouse microglial cells could express NLRP3 and NLRP4 inflammasome, and they can respond to stimulation of dangerous signals.<sup>[32-35]</sup> Additional evidences indicate that inflammasomes can be expressed in nonmyeloid cells of the nervous system. Meanwhile, many studies have proven that caspase-1, IL-1 $\beta$  and IL-18 could be activated and NLRs inflammasomes can be assembled in neurons under stress conditions.<sup>[36-40]</sup> In addition, recent studies have also shown that NLRP2 inflammasomes can be expressed in astrocytes.<sup>[41,42]</sup> In the CNS, microglia, astrocytes and neurons can all undergo pyroptosis and express its related downstream molecules and receptors, thus taking part in the immune reaction to local inflammation.<sup>[27,28,43]</sup> In fact, in diseases such as viral encephalitis, stroke, Alzheimer's disease (AD) and multiple sclerosis (MS), many studies have shown massive expression of IL-1 $\beta$  and IL-18 *etc.*, in the nervous system.<sup>[39,44-46]</sup> However, further investigation is required to elucidate mechanisms.

## Pyroptosis and infection diseases in the nervous system

Pyroptosis and its related molecules may participate in the development of nervous system encephalitis and meningitis. These phenomena have a different prognosis in bacterial and virus infection. For example, in *Streptococcus pneumoniae* meningitis participation of NLRP3 inflammasome aggravate the damage caused by the disease. IL-1 $\beta$  and IL-18 are not involved in growth inhibition of bacteria, but contribute to exacerbate the inflammatory response in the nervous system.<sup>[47-49]</sup> Some studies indicate that mouse microglia and peripheral macrophages infected with *Staphylococcus aureus*, *Mycobacterium tuberculosis* and *Legionella pneumophila* *in vitro* may activate the NLRP3 or NLRP4 inflammasome thus inducing pyroptosis.<sup>[32,50,51]</sup>

However, in viral encephalitis caused by West Nile virus (WNV), influenza A virus, and herpes simplex virus, IL-1 $\beta$  and IL-18 can increase survival rate of neurons by inhibiting viremia.<sup>[39,52-54]</sup> In WNV encephalitis, it was observed that the production and release of IL-1 $\beta$  increased in neurons, and IL-1 $\beta$  inhibited the replication of WNV. The survival rate decreased in NLRP3 and ASC knockout mice infected by WNV. ASC knockout mice can experience excessive immune response after WNV infection, and this will contribute to neuronal damage.<sup>[39]</sup> Japanese encephalitis virus can activate NLRP3 inflammasome in microglia, promote the release of IL-1 $\beta$  and IL-18.<sup>[34]</sup> In CMV retinitis, it was also observed microglia death through pyroptosis pathway.<sup>[55]</sup> But their influence on prognosis is not yet clear.

## Pyroptosis and acute aseptic disease in the nervous system

In acute aseptic nervous system damage (such as stroke or traumatic brain injury), local autoimmune activation can cause nerve injury. Studies have demonstrated that mice with caspase-1 defection may have a certain resistance to stroke, which indicated that pyroptosis and its relative mechanisms exacerbate brain damage in stroke.<sup>[56]</sup> IL-18 knockout mice didn't show any kind of protective effects in stroke. In contrast, some IL-1 receptor antibodies could still have a protective effect(s) to neurons, even after the occurrence of stroke. This suggests that the protective effect is not only dependent on IL-1 $\beta$ , but also IL-1 $\alpha$ . IL-1 $\beta$  and IL-1 $\alpha$  defected mice have a better resistance to stroke.<sup>[57]</sup> Although IL-1 $\alpha$  and caspase-1 do not have a direct relationship, caspase-1 may have an indirect protective effect (s) by influencing IL-1R2 and caspase-1 dependent nonclassical secretion system.<sup>[58,59]</sup> Meanwhile, inflammasome also been observed in a study of excitotoxic injury in kainate model.<sup>[38]</sup>

Similarly, in the rodent model, antibodies for ASC or NLRP1 can reduce injury of brain trauma or stroke.<sup>[60,61]</sup>

A study demonstrated that MCAO could induce NLRP1 and NLRP5 inflammasome expression in rat neurons.<sup>[62]</sup> Traumatic brain injury patients with higher NLRP1 level in cerebrospinal fluid may have a worse prognosis.<sup>[63]</sup>

### Pyroptosis and chronic aseptic disease in the nervous system

Chronic aseptic diseases have a great influence on the structure and function of CNS. MS is a typical one. In MS, T cells and macrophages move into CNS. A study of NLRP3 and ASC knockout mice found that autoimmune encephalitis depends on the NLRP3 inflammasome.<sup>[64,65]</sup> Inhibition of NLRP3 expression and subsequent reduction of IL-1 $\beta$  and IL-18 secretion can restrain the activation of T cell and its migration into CNS, so as to mitigate the autoimmune encephalitis.<sup>[64-66]</sup>

In cuprizone-induced CNS autoimmune inflammation and demyelination model, IL-1 $\beta$  and IL-18 play a different role in demyelination. IL-1 $\beta$  knockout mice have a similar MS phenotype to wild-type animals, but the process of remyelination is delayed. This suggests that IL-1 $\beta$  may promote recovery from MS.<sup>[67]</sup> In contrast, in IL-18 knockout mice, the disease is reduced, and the speed of myelination is faster.<sup>[68]</sup> In NLRP3 knockout mice, the onset is delayed in cuprizone induced demyelination, but the extent of remyelination is identical to those of wild-type.<sup>[68]</sup> Therefore, the pyroptosis and its relative mechanisms are involved in the pathological process, and IL-1 $\beta$  and IL-18 have opposite effects on the recovery of the disease.

Besides, accumulating evidences suggest that the immune system participates in the process of amyotrophic lateral sclerosis (ALS), AD, Parkinson's disease and Huntington's disease.<sup>[69]</sup> Amyloid beta is the main components of senile plaques in AD, it is also one of the first molecules found to be involved in the relationship between chronic aseptic diseases and inflammasome.<sup>[33]</sup> LPS sensitized macrophages exposed to fibrillar amyloid-beta activate caspase-1 and induced the release of IL-1 $\beta$ . This process is dependent on NLRP3, endosomal rupture and cathepsin B release.<sup>[33]</sup> A similar phenomenon was found in  $\alpha$ -synuclein in Parkinson's disease and prion protein.<sup>[70,71]</sup> However, to elucidate the function of IL-1 $\beta$ , different studies have reached different conclusions. Some indicate that in IL-1 $\alpha$  knockout mice, injecting human amyloid beta into encephalocoele would activate microglia, so as to reduce neuron survival rate.<sup>[72]</sup> However, other experiments show that over-expression of IL-1 $\beta$  in hippocampus could reduce senile plaque formation by recruiting macrophage.<sup>[73]</sup>

In ALS, mutation of superoxide dismutase 1 (SOD1) leading to accumulation of toxic protein is one of the main pathogenic factors. Mutant SOD1 in cultured microglia

activates caspase-1 and the amount of subsequent IL-1 $\beta$  is proportional to the concentration of mutant SOD1 added. In this process, the activation of inflammasome requires endosomal rupture and participation of ASC. However, it is not clear which specific inflammasome is involved. Caspase-1 or IL-1 $\beta$  defect would improve the survival rate of mice expressing toxic SOD1, which indicates that pyroptosis and its relative mechanisms could exacerbate ALS.<sup>[74]</sup>

## CONCLUSION

Recent findings of the pyroptosis and inflammasome have provided insight into a new mechanism that may contribute to neuronal and glial cell death during neurological diseases. Multiple potential targets upstream and downstream of pyroptosis signaling and targeting its expression, assembly, activity and products, may pave the way for newly therapeutic drugs that may rescue inflammation in neurological diseases. However, it is important to note that although some aspects of the inflammatory response will not only exacerbate brain injury, it is also likely that other components will provide a beneficial contribution to brain recovery. Elucidating the role of these components will represent a challenge for future research. Unquestionably, still a lot needs to be done to clarify the role of the inflammasome during the recovery phase following neurological diseases.

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