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Research Progress of Pyroptosis in Ophthalmic Diseases

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Abstract

Pyroptosis, also known as cell inflammatory necrosis, is a new way of programmed cell death discovered and confirmed in recent years, which is characterized by dependence on inflammatory caspase and the release of a large number of pro-inflammatory factors. GSDMD plays an irreplaceable role in the process of pyroptosis. Studies have shown that pyroptosis is widely involved in the development of infectious diseases, nervous system-related diseases and atherosclerotic diseases, and plays an important role. Recent studies have shown that cell death is involved in the central link of many eye diseases, especially dry eye, senile cataract and glaucoma. Therefore, an in-depth understanding of the pathogenesis of cell death in eye diseases will help to provide new ideas for clinical prevention and treatment of eye diseases. The purpose of this paper is to explain the mechanism of cell death and its related role in some eye diseases.

Keywords

Pyroptosis, Caspase, GSDMD, Ophthalmopathy, Dry Eye, Glaucoma, Cataract

1. Introduction

Pyroptosis, also known as inflammatory cell death, comes from the Greek root pyro, meaning "fire", and to-sis means "fall" to describe pro-inflammatory programmed cell death [1]. Pyroptosis is usually related to the secretion of IL-1β and IL18, thus mediating a strong pro-inflammatory effect [2]. Inflammatory caspase cleaves gasderminD protein (GSDMD) to trigger pyroptosis. The membrane pore-forming activity of the GSDMD-N domain of GSDMD is responsible for the execution of pyroptosis [3] [4] [5]. The 2018 Cell death Nomenclature Committee recommended that pyroptosis be defined as a form of regulatory cell

death (RCD) that depends on members of the gasdermin protein family to form plasma membrane pores, usually but not always activated by inflammatory caspase [6].

2. Cysteine-Aspartic Protease (Caspase) and Pyroptosis

Cysteine-aspartic protease (caspase) is a proteolytic enzyme, which is mainly used to control cell death and inflammation. According to their functions, Caspase-2, -3, -7, -8, -9 and -10 are involved in apoptosis, caspase-1, -4, -5, -11 and -12 are involved in inflammation [7]. The recognition and cleavage of GSDMD by caspase-1, caspase-4, caspase-5 and caspase-11 are important steps to initiate pyroptosis after inflammasome activation. Caspase-1 mediates classical pyroptosis pathway, while caspase-4, caspase-5 and caspase-11 mediate non-classical pyroptosis pathway [8]. Caspase-1, as the first member of Caspase family, plays an important role in cell apoptosis without inflammatory corpuscles. Inflammatory corpuscles are a group of intracellular multimeric protein complexes that activate caspase-1. Among them, NLRP3 inflammatory corpuscles are the most deeply studied in the past decade, which can cleave pro-caspase-1 into active caspase-1 [9], Activated caspase-1 further leads to the maturation and release of pro-inflammatory cytokines IL-1β and IL-18 [1]. For a long time, pyroptosis has been considered to be related only to the death of monocytes or macrophages that mediate the activation of typical caspase-1. With the discovery that caspase-11 in mice and its corresponding caspase-4/5 in human body are directly activated by lipopolysaccharide, pyroptosis is induced, which expands the role of caspase in pyroptosis [10]. Besides inflammatory caspase, caspase-8 also plays a role in pyroptosis. Studies have shown that besides the role of Caspase-8 in cell apoptosis and necrosis, caspase-8 can be used as scaffold protein to induce cytokine production, and this effect is independent of its enzyme activity [11]. The scaffold function of Caspase-8, but not its enzyme activity, has also been proved to be involved in the activation of NLRP3 inflammasome in macrophages induced by double-stranded RNA(dsRNA) [12]. Recently, Zhang *et al.* also found that α-ketoglutarate (α-KG), a metabolite, activates caspase-8 through death receptor 6(DR6) to induce cell death [13].

3. GSDMD and Pyroptosis

GSDMD is one of the collateral homologous genes of human beings in Gasdermin gene family. The other five are GSDMA, GSDMB, GSDMC, GSDME (also known as DFNA5) and PJVK (also known as DFNB59) [14]. SHI *et al.* [5] found that GSDMD was co-expressed with inflammatory caspase for the first time, which confirmed that GSDMD was the direct substrate of inflammatory caspase, and the cleavage of GSDMD by inflammatory caspase determined pyroptosis by releasing GSDMD-N domain. His finding redefines the concept of pyroptosis, that is, programmed necrosis mediated by gasdermin. Ding *et al.* [3] further found that GSDMD has two important domains, namely, N-terminal effector

domain and c-terminal inhibitory domain. When it is not cleaved by activated inflammatory caspase, the C-terminal domain has self-inhibitory effect on the N-terminal domain. When pyroptosis occurs, GSDMD can be cleaved by activated caspase-1/4/5/11 to form two independent domain fragments, N-terminal and C-terminal. Among them, the N-terminal domain of GSDMD-N can migrate to the cell membrane and combine with phospholipids on the cell membrane, which makes the cell membrane form pores and then leads to the release of cell contents and then activates a strong inflammatory reaction. LorenzoSborgi [4] also confirmed the pore-forming activity of GSDMD-N terminal domain, they found in the function of GSDMD in living cells and *in vitro* that the N-terminal fragment of GSDMD cleaved by caspase-1 can quickly target the membrane part of macrophages in vivo and induce the formation of plasma membrane pores, *in vitro*, the N-terminal fragment of recombinant GSDMD cleaved by caspase-1 closely combined with liposome and formed a large permeable hole, when the GSDMD encapsulated by liposome was displayed with nanometer resolution by cryoelectron microscope and atomic force microscope, an annular hole with a diameter of about 20 nm could be seen. It can be seen that GSDMD is the direct and final executor of pyroptosis, and it occupies an irreplaceable position in the occurrence of pyroptosis.

4. Pyroptosis and Ophthalmopathy

4.1. Pyroptosis and Dry Eye

Among ocular surface diseases, dry eye is the disease that most affects vision and quality of life. It is a chronic ocular surface disease caused by many factors, which is the instability of tear film or the imbalance of ocular surface microenvironment caused by the abnormal quality, quantity and dynamics of tears, which may be accompanied by inflammatory reaction, tissue damage and neurological abnormalities, resulting in various uncomfortable symptoms and/or visual dysfunction [15]. An important mechanism of dry eye is the relationship between the increase of tear osmotic pressure and the severity of inflammation, and the inflammatory reaction is accompanied by the occurrence and development of dry eye [16]. The process of pyroptosis is accompanied by the release of cytokines that promote inflammatory response, so pyroptosis dependent on GSDMD also plays a certain role in the occurrence and development of dry eye, which provides a new target for the treatment of dry eye. In 2014, Zheng, Q and other researchers found that ROS-NLRP3-IL-1b signaling pathway may play a starting role in the development of mouse dry eye model induced by environment [17]. In their subsequent research, it was also found that pyroptosis triggered by the increase of reactive oxygen species (ROS) mediated by NLRP3 also induced inflammation in human corneal epithelial cells (HCECs) under hyperosmotic stress [18]. The research findings of Chi *et al.* also confirmed that NLRP3-ASC-caspase-1 was significantly activated in human corneal epithelium exposed to high osmotic pressure and in the eye surface of mouse model in dry environ-

ment. In addition, they found that caspase-8 not only activated NLRP3 inflammasome, but also inhibited the production and activity of NLRP6 with anti-inflammatory function in these two models [19]. The activation of caspase-8 (CASP8) induced by TLR4 in response to dry stress in corneal epithelium induced NLRP12 and NLRC4 inflammasome to initiate GSDMD-dependent pyroptosis, which also provided strong evidence for its role in dry eye [20]. The related research on the treatment of dry eye through cell death has also emerged. The combination therapy of carboxymethyl cellulose (cmc) and α-melanocyte stimulating hormone (α-msh) can improve ocular surface lesions and restore ocular surface function in mice by reducing ros level and inhibiting nlrp3 signaling pathway [21]. *In vitro* studies have shown that calcitriol can effectively alleviate the injury of human corneal epithelial cells induced by hyperosmotic stress by inhibiting the pyroptosis pathway of NLRP3-ASC-caspase-1-GSDMD [22]. The latest research found that dexamethasone inhibited the activation of NF-κB, and effectively inhibited pyroptosis induced by hyperosmotic stress (HS) through KCNQ1OT1/miR-214/caspase-1 signal axis [23]. This provides a new mechanism for dexamethasone as an anti-inflammatory drug in dry eye. Long noncoding RNAMIAT has also been reported to regulate corneal epithelial cell damage induced by hyperosmotic stress by inhibiting Caspase-1-dependent corneal epithelial cell pyroptosis [24].

4.2. Pyroptosis and Glaucoma

Glaucoma is a neurodegenerative disease that causes irreversible vision loss [25]. It is estimated that by 2040, the number of patients will reach 112 million worldwide [26]. Glaucoma is a disease affected by the interaction of many genes and environmental factors. Studies have found that inflammation may also participate in the pathogenesis of glaucoma [27]. Progressive death of ganglion cells (RGC) is a characteristic manifestation of glaucoma. More and more evidences show the potential role of pyroptosis in ocular hypertension [28] [29] [30] [31]. WeiChi found that during the development of acute glaucoma, HMGB1 responded to the sharp increase of intraocular pressure. In the IR injury of retina, HMGB1/Caspase-8 pathway induced the activation of NLRP3 and the production of IL-1β through NF-β B pathway [28]. In their subsequent studies, it was also confirmed that Caspase-8 promoted the inflammasome activation of NLRP1/NLRP3 and the production of IL-1β in acute glaucoma [30]. HuiChen and other researchers found that mice with GSDMD gene knocked out can significantly reduce the death of RGCs and the severity of retinal ischemia injury in mice, which indicates that cell death plays a vital role in the development of acute glaucoma, in their research, it was also found that IL-1β with biological activity can positively accelerate the occurrence of pyroptosis, which plays a key role in amplifying pyroptosis and neuroinflammation in the occurrence and development of acute glaucoma [31]. IL-1β closely related to the dysfunction of trabecular meshwork cells [32]. IL-1β is an important effector of cell focal death.

Further study on whether trabecular meshwork cells in glaucoma patients have focal death will be a new direction in the occurrence and development of focal death.

4.3. Pyroptosis and Cataract

Cataract is the main eye disease leading to blindness and visual impairment of the elderly in the world, and its prevalence and incidence are at a high level, which will continue to be a major public health problem in the next few decades [33]. The pathogenesis of cataract is very complicated, among which oxidative stress is generally considered as the main cause in the medical field [34]. pyroptosis is also closely related to oxidative stress [35]. In the research of Jin *et al.*, it was found that the mRNA and protein expressions of caspase-1 and IL-1β in human lens epithelial cells treated with hydrogen peroxide (H_2O_2) were significantly higher than those in control cells, so they thought that pyroptosis might play an important role in human lens epithelial cells under oxidative stress [36]. With the invention and popularization of blue light-emitting diode (LED), our eyes are exposed to more short-wavelength blue light than in the past. Studies have shown that after short-wavelength blue light irradiation, the expressions of pyroptosis markers caspase-1, caspase-11 and GSDMD in rat lens epithelial cells and human lens epithelial cells cultured *in vitro* increase [37] [38]. Many studies have shown that the incidence of cataract in patients with type 2 diabetes is high [39]. Pyroptosis is also closely related to the progression of diabetes [40]. Therefore, we guess that compared with age-related cataract, caspase-1-mediated pyroptosis of lens epithelial cells and the release of inflammatory mediators caused by pyroptosis may play a more important role in the occurrence and development of diabetic cataract. The therapeutic strategy to prevent lens epithelial Pyroptosis can inhibit the expression of related cell apoptosis factors, and may be beneficial to the treatment of age-related cataract and the prevention of the most common complication after cataract surgery. However, the specific mechanism of pyroptosis and its inhibitor in human lens epithelial cells needs to be explored in detail.

5. Summary and Prospect

Pyroptosis is a newly discovered form of regulatory cell death in recent years, which is different from other forms of cell death in that it is accompanied by the release of pro-inflammatory response factors. It can participate in the occurrence and development of various ophthalmic diseases through classical focal pyroptosis pathway and non-classical focal pyroptosis pathway, including dry eye, glaucoma, cataract and other ophthalmic diseases, and it is also involved in the occurrence and development of retinal-related diseases [41] [42] [43] [44]. At present, there have been studies on RLRP3 inflammatory corpuscles and GSDMD-related inhibitors used to inhibit the occurrence of pyroptosis [45] [46] [47], and inhibit the occurrence and development of related diseases. This also

provides a new target for the treatment of related eye diseases. The study of pyroptosis in eye diseases has just started. Further study on which activation signals can start pyroptosis will be more helpful to clarify its mechanism and provide new ideas for clinical treatment of related eye diseases.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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