

Pyroptosis in Neurodegenerative disease

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Abstract. Neurodegenerative diseases, typically, manifest in the elderly. It is becoming a new epidemic disease over the centuries and causes severe symptom as well as high public cost. Thus, finding the cure of neurodegenerative disease is in urgent need. There has been a lot of interest lately in the neuroinflammation-mediated neuronal death pathway. Aberrant activation of programmed cell death is observed in neurodegenerative disease, leading in undesired loss of neuronal cells and function. Among these, research currently on the pyroptosis, which serves a key function in regulating homeostasis and eliminating unwanted cells, has drawn much attention. Comparing pyroptosis within apoptosis, the unique features of pyroptosis made it possible to be cure of the neurodegenerative disease. Due to its mechanism, it can function differently in different neurodegenerative disease. This review focuses on the characteristics and molecular mechanism of pyroptosis, in addition, its role in neurodegenerative disease has also been discussed.

Keywords: Pyroptosis, Neurodegenerative disease, Parkinson's disease, Multiple sclerosis, Alzheimer's disease.

1. Introduction

Protein aggregation, immunological dysregulation, and aberrant cell death are all symptoms of neurodegenerative disorders, which are defined by losing of neurons in the brain or system of peripheral nervous [1]. Among people over the age of 80, neurodegenerative diseases' popularity has unexpectedly increased during the past century [2]. Around the world, neurodegenerative disease accounts for 4% of all fatalities and 5% of non-communicable disease disability-adjusted life years [3]. With 276 million disability adjusted life years, or DALYs, by age and 11.6% of all DALYs worldwide, neurodegenerative diseases are the main causes that could lead people to become disable and the second biggest reason of death in the GBD, behind heart disease [4]. Neurodegenerative diseases are typically incurable. As a result, a neurodegenerative disease diagnosis can be disastrous [5]. There may be incontinence, immobility, gait abnormalities and falls, dementia, and confused symptoms associated with neurodegenerative disorders. These disorders are significant contributors to the need for institutional care and loss of independence [2]. There will be a significant burden on societies and their healthcare systems as the number of persons with NCDs rises. Because each country's health-care systems are different, as are the neurological disorders, in their ability to meet this growing need. Therefore, it is crucial to comprehend illness mechanisms and create disease-modifying approaches [6]. Pyroptosis is a unique programmed pattern of cell death as well as an innate immune response triggered by infections or non-infectious causes. It eliminates the microenvironment that pathogens need to survive, attracts immune cells by releasing inflammatory factors and cell contents, and activates the immune system to get rid of pathogenic microorganisms in the body. However, it can also cause tissue and organ damage due to over-activation of the inflammatory response. As a consequence of the continuous study of the gasdermin (GSDM) and its protein family, and the continuing study on other caspase molecules over the pass few years, pyroptosis is now known to be a distinct kind of programmed that will cause cell to be dead. Pyroptosis and the development and incidence of neurodegenerative illnesses have been linked in a significant body of research. This review examines pyroptosis' characteristics, molecular basis, and connection to neurodegenerative illnesses [6].

2. Proptosis

2.1. Characteristics of pyroptosis

Inflammatory proteases have enzymatic activity. Thus, proteases are members of the cysteine-dependent aspartate-specific protease (caspase) family, which is necessary for regulation of cell death process known as pyroptosis by pro-inflammatory [7].

Apoptosis and pyroptosis have some characteristics, such as DNA damage and chromatin condensation (Table 1). Before the pyroptotic cells exploded, numerous protrusions that resemble bubbles appeared within the cellular membrane's outer layer, which is an interesting phenomenon. Caspase-3 is required for the process of apoptosis, which also results in membrane blebbing. It's interesting to note that pyroptotic cells can be stained by Annexin V, which are not only comparable to apoptotic cells, but also are comparable to the dye attaches to PS, which is also known as phosphatidyl serine. As a result, Annexin V is unable to distinguish between apoptotic and pyroptotic cells. Additionally, pyroptotic bodies are produced during pyroptosis, whereas apoptotic bodies are produced during apoptosis. It's interesting to note that pyroptotic bodies and apoptotic bodies both have diameters between 1 and 5 μ m. Additionally, caspase activity is linked to both apoptosis and pyroptosis. Previously, it was recognized that pyroptosis was a kind of caspase-1-related cell death. It is crucial to keep in mind that current research has revealed that additional caspases, such as caspase-3/4/5/6/8/9/11, are also responsible for inducing pyroptosis in several cell types and are crucial for the development of tumors. Caspase-3 was originally assumed to be the catalyst for apoptosis, but it has been proposed that by cleaving GSDME, caspase-3 can also trigger pyroptosis. More unexpectedly, pyroptosis can also be induced directly by the apoptosis-related protein caspase-8 by cleaving GSDMD. Additionally, via cutting and turning on caspase-3 and mediating the cleavage of GSDMC through caspase-6, caspase-9 is also engaged in pyroptosis [6].

However, pyroptosis' distinctive morphological traits clearly vary from those of apoptosis (Table 2). Apoptosis is typically thought to be a harmless kind of death, however pyroptosis, which is triggered with the use of extracellular or intracellular stimulation such bacteria, viruses, toxins, and chemotherapeutic medications, can induce inflammation. In actuality, leaking of the membrane of the plasma will lead to the result that pyroptosis will be causing the cytoplasm to become flatten, as opposed to the necrosis-related explosive rupture. The N-terminal of gasdermin oligomerizes due to the caspase activation or granzyme release and forms a channel (between 1 to 2 meter in diameter) in the membrane of plasma, allowing mature IL-1/IL-18 to have a diameter that is 4.5 nanometer and caspase-1 to have a diameter that is 7.5 nanometer to cross. As a result of cell enlargement and osmotic lysis brought on by water entering through the pores, the plasma membrane ruptures, releasing IL-1 and IL-18. Because these dyes have a low molecular weight, the pyroptotic cells can pass through 7-AAD, which is also known as 7-aminoactinomycin, PI, which is also known as propidium iodide, and EtBr, which is also known as ethidium bromide. Apoptotic cells, in contrast to pyroptotic cells, preserve membrane integrity, making them resistant to staining by these dyes. Additionally, there is a unique type of DNA damage that is distinct from apoptosis and exhibits positive TUNEL with full name, dUTP nick-end labeling, at early-stage when staining of pyroptosis has happened. Damaging DNA in pyroptotic cells is less severe than it is in apoptotic cells. Pyroptosis results in random DNA fragmentation, while apoptosis results in ordered DNA fragmentation and nucleus fragmentation. Despite the fact that current research have indicated that caspase-1, caspase-4/5/11, and caspase-2, 7, 10 are exclusively connected to apoptosis, future detailed studies may reveal even more evidence to show pyroptosis is closely related to caspases, and also more evidence to show apoptosis is closely related to caspases. The amount of ATP influences apoptosis, and the PARP gene is activated during apoptosis, which depletes ATP. The gasdermin family23, however, is home to the pyroptosis effector proteins (Table 1, 2) [6].

Table 1. Similarities when comparing pyroptosis to apoptosis

Features	Apoptosis	Pyroptosis
Caspase-3 activation	✓	✓
Caspase-6 activation	✓	✓
Caspase-8 activation	✓	✓
Caspase-9 activation	✓	✓
TUNEL staining	✓	✓
Annexin V staining	✓	✓
Membrane blebbing	✓	✓
The diameters of pyroptotic bodies and apoptotic bodies (1–5 µm)	✓	✓
DNA damage	✓	✓
Programmed cell death	✓	✓
Chromatin condensation	✓	✓
PS exposure	✓	✓

“✓”, Yes.

Table 2. Differences when comparing pyroptosis to apoptosis

Features	Pyroptosis	Apoptosis
Inflammation	✓	-
Apoptotic bodies	-	✓
Pyroptotic bodies	✓	-
Intact nucleus	✓	-
Pore formation	✓	-
Cell swelling	✓	-
Cell shrink	-	✓
Osmotic lysis	✓	-
Membrane integrity	-	✓
7-AAD staining	✓	-
PI staining	✓	-
EtBr staining	✓	-
Caspase-1 activation	✓	-
Caspase-4 activation	✓	-
Caspase-5 activation	✓	-
Caspase-11 activation	✓	-
Caspase-2 activation	-	✓
Caspase-7 activation	-	✓
Caspase-10 activation	-	✓
PARP cleavage	-	✓
Gasdermin cleavage	✓	-

“✓”, Yes; “-”: blank also as No.

2.2. Introducing the mechanism of pyroptosis

Members of the gasdermin protein family have very preserved structures. All gasdermins—aside from DFNB59—include C-terminal domains and N-terminal domains, with the N-terminus serving

as an executioner of the pyroptosis. In the past research, gasdermin could not make pyroptosis to happen by using the help from apoptosis-related caspases (like caspase-3 and caspase-8), but later on, more research has shown that within the help from caspase-3-mediated GSDME cleavage, highly GSDME expression could be happened in tumor cells when chemotherapeutic drugs are involved, which could be found in N-GSDME terminus as well as pyroptosis. Furthering our understanding of pyroptosis is the discovery that during *Yersinia* infection, the effector protein YopJ will have three effects. The first effect is to inhibit TGF. The second effect is to activate kinase 1 (TAK1). The third effect is to let the caspase-8-related cleavage of GSDMD happening in mouse macrophages. It's interesting to note that breast cancer has an apoptosis, which is called TNF-mediated, can be changed by PD-L1 into pyroptosis. Under hypoxic conditions, p-Stat3 encourages PD-nuclear L1's translocation, and their combined actions improve GSDMC's transcription. Within stimulating Caspase-8 by using TNF-, it can lead to cleavage of GSDMC in order to produce N-GSDMC and also allow membrane pores to occur that will able pyroptosis happen in cells. Three important features that are necessary for tumor pyroptosis caused by macrophage-derived TNF in vivo is Nuclear PD-L1, caspase-8, and GSDMC. Aside from, Antibiotic chemotherapeutic agents may can cause not only caspase-8 and GSDMC-mediated thermal thawing death in breast cancer cells [6].

Human caspase-4/5 (the mouse ortholog of caspase-11) can be immediately driven to connect with LPS, which full name is intracellular lipopolysaccharide, via an N-terminal CARD owing that the upstream sensory complexes are lacking in pyroptosis pathway, which the pathway is non-canonical. It is essential to remember that the TLR4 agonist oxPAPC, also known as 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine, competes with LPS for the binding of caspase-4 and caspase-11 and inhibits the inflammasomes in macrophages but could not inhibit the inflammasomes in dendritic cells. Additionally, GSDMD can be broken down by activating caspase-4/5/11 into N-GSDMD, which oligomerizes and is subsequently transported to membrane of cell to generate pores that could be found on plasma membrane. Caspase-4, Caspase-5 and Caspase-11, however, can mediate the maturation along with secretion of both IL-1/18 in some cells through the NLRP3/caspase-1 pathway even if they are unable to cleave pro-IL-1/18. Additionally, caspase-4/5/11 cleaves GSDMD and thus causing K⁺ to be efflux, causes the NLRP3 inflammasome to assemble, and ultimately results in pyroptosis. Notably, one of the essential proteins that can control cell death that is pyroptotic is Pannexin-1, which is in the unconventional route triggered by caspase-11. Shearing and altering Pannexin-1 in response to LPS stimulation can be accomplished by activating caspase-11. This results in the release of pyroptosis and cellular ATP, which is mediated by the ion channel P2X7 receptor. It's significant to note that P2X7 independent K⁺ efflux and NLRP3 inflammasome-mediated caspase-1 cleavage was also possible in murine BMDMs with Pannexin-1 loss. Additionally, endotoxin shock is protected in mice with Pannexin-1 knockouts, indicating that specific K⁺ channels regulate non-canonical NLRP3 activation [6].

3. Pyroptosis in different neurodegenerative disease

3.1. Pyroptosis in Alzheimer's disease

Alzheimer's disease (AD), which are the most common reason why dementia could be appeared, is characterized by disappearing of synapses, extracellular amyloid- (A β) peptide deposition, and death of neuron. Clinically, A gradual and permanent loss of cognitive abilities is a hallmark of AD. PS1, PS2, and APP, which is also known as amyloid precursor protein, or apolipoprotein E (ApoE) gene variants that cause disease, as well as elevated extracellular A β levels, are the main causes of A β accumulation. PS1 and PS2 could also be called as Presenilin 1 and 2. These mechanisms include excitotoxicity, oxidative stress, energy expenditure, inflammation, and apoptosis. The specific mechanisms behind the pathogenic character of degeneration of the A β -induced neuronal found in AD, however, are not that clear. Recent research has revealed a unique inflammasome signaling pathway, and brain as well as transgenic mice models of the disease both exhibit abnormal inflammasome-related protein expression. Inflammasome-related proteins, such as the NLRP1

inflammasome, have been linked to the abnormal expression of inflammation and pyroptotic death in AD patients' brains, according to mounting evidence. The NLRP1 inflammasome's role in the etiology of AD is still unknown, despite the fact that recent research has linked NLRP1 genetic variations with the disease. Cerebral NLRP1 levels increased in APPswe/PS1dE9 transgenic mice as a result [8].

3.2. Pyroptosis in Parkinson's disease

There many symptoms Parkinson's disease (PD) may have. However, the major clinical symptoms of PD are dyskinesia, balance issues, and tremor. Thinking of the major pathological aspect of PD is the irreversible destruction of dopamine neurons, which is located in the substantia nigra. Recent times have seen a lot of interest in the neuroinflammation-mediated neuronal death pathway. Neuroinflammation, which is an immune response that occurred when inborn, assists the brain and spinal cord in protecting against pathogen invasion and promotes nerve tissue healing by eliminating damaged tissues and pathogens in the CNS of a healthy organism. CNS is known as central nervous system. However, in some pathological circumstances, inflammatory response occurred in the CNS may lead to neuronal damage and worsen the progression of illnesses. The NLRP3 inflammasome's activation encourages the release of the pro-inflammatory cytokine IL-1, exacerbating neuroinflammation and advancing PD. In order to cause glial rupture but also release the additional inflammatory mediators subsequently, GSDMD (an executive protein of pyroptosis) is activated and transported to the membrane. It may develop into a promising treatment for PD by blocking the activation of NLRP3 in order to lessen the development of neuroinflammation [9].

3.3. Pyroptosis in multiple sclerosis

The cause of the progressive inflammatory demyelinating disease known as multiple sclerosis (MS), which is still incurable, is unknown. Proinflammatory cytokines IL-1 and IL-18 mature and are released via inflammasome-associated caspases, which also activate the gasdermin D pore-forming protein (GSDMD). Recently, it was demonstrated that GSDMD was also able to mediate pyroptosis [10].

4. Conclusion

Neurodegenerative diseases consist of Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and so on, currently, few or even no effective treatments are available for neurodegenerative diseases, which are commonly develop in irreversible ways and become a huge social and personal financial burden. Neuronal death caused by inflammatory cytokine-mediated neuroinflammation is being extensively studied nowadays. Pyroptosis is a type of cell death that eventually leads to a loss of plasma membrane integrity and is caused by the activation of so-called inflammatory body sensors. NLRP3, one type of inflammatory complexes found in microglia. Its activation promotes the secretion of the inflammatory cytokine interleukin-1 β /18 (IL-1 β /18) and induces cellular coke death as well as rupture microglia to further release IL-1 β . Even though the best cure of neurodegenerative disease is still unknown, but studies about pyroptosis has shown that it is one of the useful treatments that could be used in some different neurodegenerative disease. Cellular scorching has proven to be a very complex process, with different core players having the ability to break the fragile balance of the cellular environment from birth to death and from pro-inflammatory signals to anti-inflammatory signals. With more understanding of the complex regulatory mechanisms that control cytokinesis, pyroptosis has been a potential target for treating neurodegenerative diseases. The research that exited has proven the function of pyroptosis can be utilized to cure neurodegenerative disease. Yet, there are still points that are not cleared. But, if we could focus on pyroptosis in the ongoing research in the future, we could find the cure for neurodegenerative disease. This review pays attention to the characteristics and molecular mechanism

of pyroptosis, differences between pyroptosis and apoptosis have also been summarized. In addition, the role of pyroptosis in neurodegenerative disease has also been discussed.

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