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The Relationship Between Alzheimer's Disease and Pyroptosis and the Intervention Progress of Traditional Chinese Medicine

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease caused by multiple causes. The main pathological features of AD are β-amyloid (Aβ) deposition, hyperphosphorylation of Tau protein, and progressive neuronal loss. Pyroptosis is one of the main forms of neuronal death, which is mainly caused by the activation of Gasdermin protein by upstream signals and the release of its N-terminal domain on the cell membrane. Studies have shown that there is a close relationship between Alzheimer's disease (AD) and pyroptosis. Therefore, this paper summarizes the relationship between pyroptosis and its molecular mechanism and AD, as well as the related research of traditional Chinese medicine in the treatment of AD by regulating pyroptosis, in order to provide a new direction for the study of AD pathogenesis based on pyroptosis pathway.

Keywords: Alzheimer's disease, cell pyroptosis, inflammasome, traditional Chinese medicine

Introduction

Alois Alzheimer, a German psychiatrist from Bavaria, first described the pathological features of a neurodegenerative disease, which was later named Alzheimer's disease, also known as Alzheimer's disease, after him. Alzheimer's disease (AD) is a common neurodegenerative disease with insidious onset and progressive exacerbation. Symptoms are usually evident after 2–3 years of onset and the disease lasts for 5–10 years, resulting in loss of neurons and synapses or cerebral atrophy, which severely affects daily life and social function. The main clinical manifestations of Alzheimer's disease are progressive memory loss, cognitive and behavioral disorders.[1] According to the study, Alzheimer's disease ranks as the 6th leading cause of death among people over 65 years old in the United Kingdom and the 5th in the United States. China, as the world's largest country in terms of population, has an elderly population of more than 200 million, and according to a national cross-sectional study in 2020, there were 15.07 million cases of dementia among people aged 60 years and older in China, including 9.83 million cases of AD, 3.92 million cases of vascular dementia, and 1.32 million cases of other dementias. Meanwhile, another national study showed that the annual cost of treating AD patients in China was $167.74 billion in 2015, and the annual cost of patient care has been rising every year and is expected to be as high as $188.718 billion by 2050.[2] Alzheimer's disease, the main subtype of dementia, accounts for 60–80% of all dementia types. The global prevalence of Alzheimer's disease is expected to continue to rise as human life expectancy increases and the population ages.

Three typical pathological features of AD include amyloid plaques formed by deposition of extracellular β-amyloid (Aβ) aggregates, neurofibrillary tangles (NFTs) formed by intracellular hyperphosphorylated microtubule-associated proteins (Tau proteins), and neuronal loss.[3] Current research on brain neuronal cells focuses on apoptosis, autophagy, and cellular pyroptosis, in which both apoptosis and autophagy occur in the anterior and middle stages of the disease,

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whereas cellular pyroptosis, as a pro-inflammatory mode of programmed cell death, occurs in the prodromal stage of AD pathogenesis, and the neuroinflammatory response it mediates also plays an important role in the pathogenesis of AD.[4]

Pyroptosis

Summarize

The term pyroptosis, derived from the Greek roots "pyro" (fire or fever) and "ptosis" (fall), is a new form of non-apoptotic programmed cell death that is closely related to inflammatory responses and also Known as secondary necrosis.[5] It is primarily triggered by inflammatory vesicles and is executed by a family of caspases (Caspase-1/-3/-4/-5) and Gasdermin proteins. Physiologically, pyroptosis acts as an initiator of innate immunity by inducing the release of cytokines, including IL-1β and IL-18, as well as other molecules, following cell membrane rupture.[6] See Figure 1.

Pathways of Pyroptosis

Caspase (cysteinyl aspartate specific proteinase) is an endogenous cysteine-containing aspartic acid protein hydrolase, an important family of genes that are essential for organisms to maintain homeostasis through the regulation of cell death and inflammation.[7] Caspases have been broadly classified as apoptotic (Caspase-3 in mammals, Caspase-6, Caspase-7, Caspase-8, and Caspase-9) and inflammatory human Caspase-1, Caspase-4, Caspase-5, Caspase-12 and mouse Caspase-1, Caspase-11, and Caspase-129).[8] Cellular pyroptosis, on the other hand, occurs mediated by caspases, with the classical pathway of cellular pyroptosis mediated by Caspase-1 and the nonclassical cellular pyroptosis pathway mediated by Caspase-4, Caspase-5, and Caspase-11.

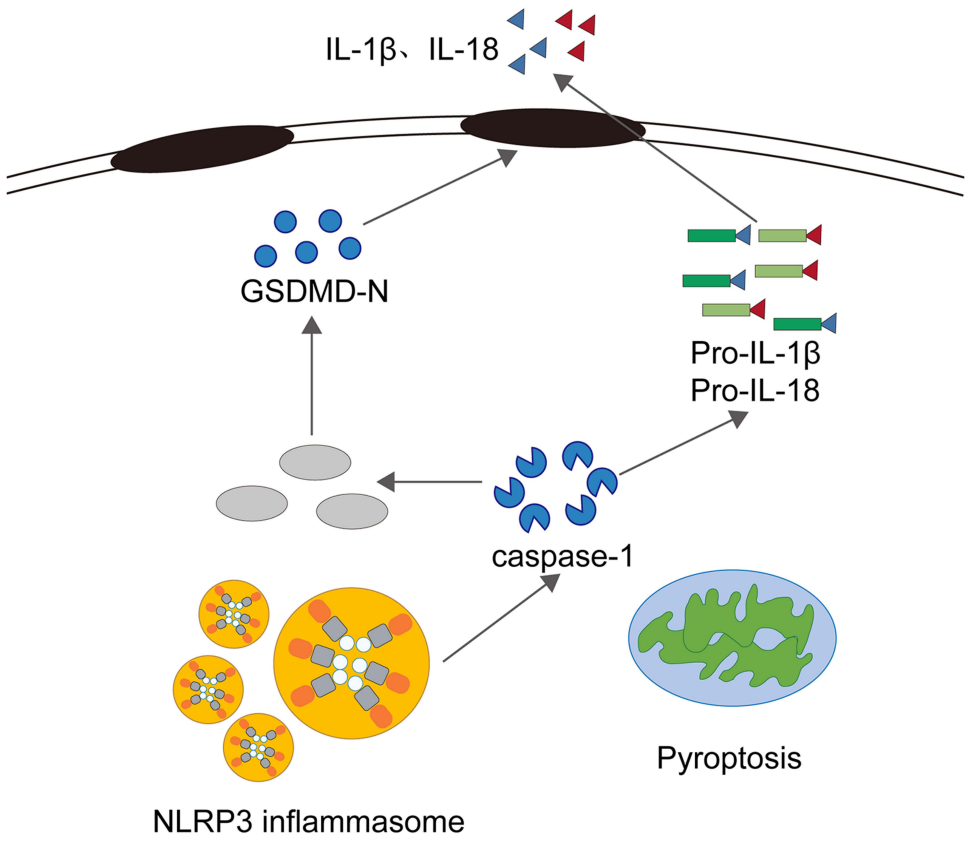

Figure 1 Mechanisms of initiation of pyroptosis. Pyroptosis is a non-apoptotic programmed cell death linked to inflammation, triggered by caspases and Gasdermin proteins, releasing cytokines like IL-1β and IL-18 after cell membrane rupture.

Canonical Pathway

In the canonical pyroptosis pathway, after the activation of inflammatory vesicles NLRP4, NLRP3, NLRP1, et cetera, Pro-Caspase-1 will be cleaved and the corresponding active Caspase-1 will be formed, and the structure of Caspase-1 is small catalytic subunit-large catalytic subunit-CARD from C-terminal to N-terminal in order, in which the CARD is the Caspase-1 recruitment domain. The CARD is the recruitment domain of Caspase-1, through which the related macromolecular complex recruits and activates Caspase, and then cleaves the GSDMD protein, causing it to split into GSDMD-N and GSDMD-C fragments, and then the separated GSDMD-N end will form a 10–15 nm diameter pyroptosis pore on the cell membrane, resulting in the death of the cell lysis.[9] At the same time, Caspase-1 can also cleave relevant inflammatory factor precursors such as pro-IL-1β, thus gradually forming biologically active inflammatory factors and releasing them outside the cell membrane for further expansion.[10]

Non-Canonical Pathway

In the non-classical pathway, inflammatory factors can enter directly into the cytoplasm without binding to the corresponding receptors. Upon stimulation by intracytoplasmic lipopolysaccharide (LPS), Caspase-4/-5/11 can link with specific structures of LPS and be activated, and activated Caspase-4/-5/11 can directly Activated caspase-4/-5/11 can directly cleave the GSDMD, thus triggering cell death. In addition, other related proteins can also induce the non-classical pathway of cell death. For example, GSDMB can directly activate caspase-4 and then cleave GSDMD to trigger cell death,[11] GSDME can participate in cellular pyroptosis through caspase-3, and GSDME is also able to convert caspase-3-mediated apoptosis into cellular pyroptosis. However, the mechanism of these two roles in cellular coking is still unclear and needs to be further explored. See Figure 2.

Pyroptosis and AD

AD is an irreversible neurodegenerative disease centered on impairment of memory and cognitive function, with plaques formed by extracellular β-amyloid deposition, fibrillar tangles formed by hyperphosphorylation of Tau proteins, and loss of neurons as the main pathological features. AD can cause overactivation of cellular death in the intrinsic immune cells of the CNS, which contributes to the aggravation of inflammatory responses by cytokines in the CNS, leading to neurodegeneration and tissue and organ damage. AD can cause overactivation of cellular death in CNS intrinsic immune

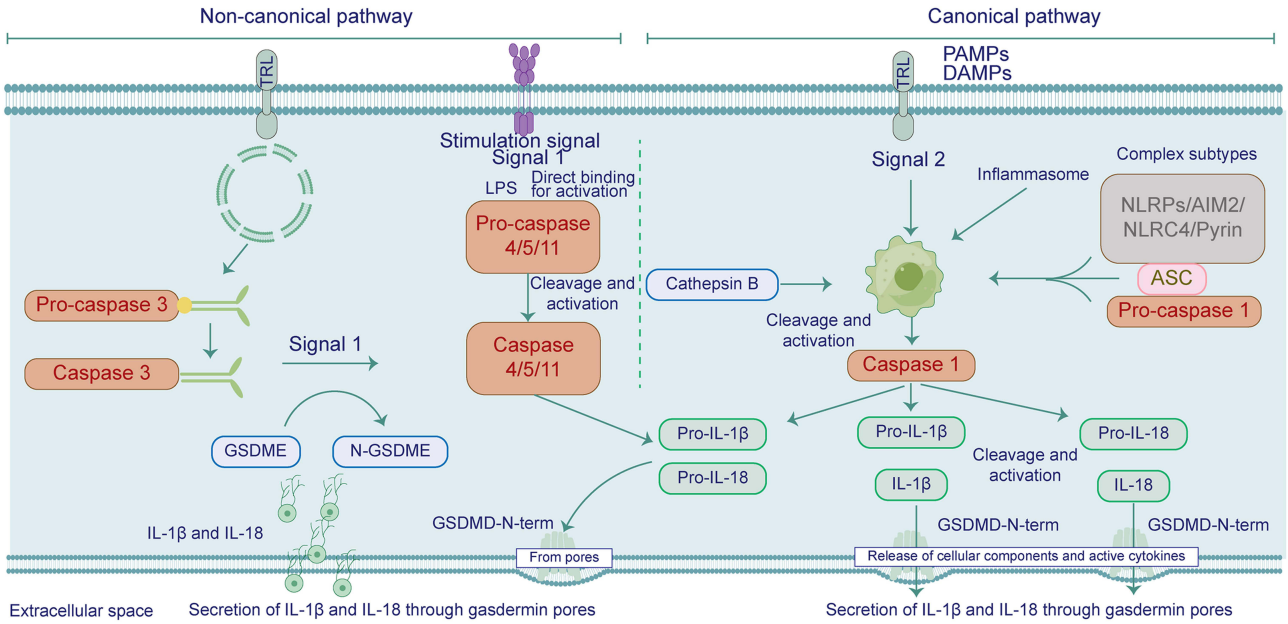

Figure 2 Canonical pathway/non-canonical pathway of pyroptosis. In the non-classical pathway, caspases-4/-5/11 and proteins like GSDMD and GSDME trigger pyroptosis by cleaving Gasdermins, though the detailed mechanisms remain unclear.

cells, which leads to cytokines that exacerbate the inflammatory response of the CNS, resulting in neurodegeneration and tissue damage.[12] Conversely, aberrant expression of inflammatory mediators can also play an inhibitory role in the pathologic process of AD.[13] In recent years, research on AD and cellular death has intensified, and there is a large body of evidence that suggests that the study of cellular death mechanisms is critical to the prevention and treatment of AD.[14] The following is a review of the pathological mechanisms of cellular death and AD, with a view to providing new ideas and directions for the diagnosis and treatment of AD in the future.

Pyroptosis and the Aβ Doctrine

The Aβ theory is one of the core mechanisms in the pathogenesis of AD, which suggests that excessive Aβ aggregation disrupts the dynamic balance of Aβ in the brain and leads to the deposition of amyloid plaques. Aβ exists in the form of soluble Aβ monomers and soluble Aβ oligomers, which bind to nerve cell receptors, disrupting the intracellular Ca2+ homeostasis and impairing the function of nerve cells. The soluble Aβ oligomers can bind to nerve cell receptors, thereby disrupting intracellular Ca2+ homeostasis and impairing neuronal function, and are involved in AD development.[15] In a transgenic AD mouse model (APP/PS1), chronic inflammation accelerates Aβ deposition in the brain by removing Aβ and reducing microglia uptake. In addition, as an initiator of NLRP3, Aβ induces cellular pyroptosis and activation of NLRP3, promoting its release of mature IL-1β, and under specific conditions, activated caspase-1 cleaves GSDMD, a key factor in downstream pyroptosis, thereby promoting microglia to undergo pyroptosis.[16] In contrast, NLRP3 was able to be activated not only by Aβ but also by low-molecular-weight Aβ oligomers, suggesting that Aβ-activated microglia begin the innate immune response in the CNS prior to Aβ deposition.[17] It follows that cellular pyroptosis reduces Aβ deposition and spreading and can serve as a potential target for the treatment of AD.

Pyroptosis and the Tau Protein Hypothesis

The primary pathogenesis of AD also includes hyperphosphorylation of Tau protein, a microtubule-associated protein whose phosphorylation is regulated by both kinases and phosphatases. The Tau protein hypothesis suggests that the steady state between the two enzymes is disrupted during disease states, which induces hyperphosphorylation of Tau protein,[18] This causes neuronal and synaptic damage and the production of NFTs, which in turn leads to the development of AD. Currently, in vivo experiments have demonstrated that inflammatory vesicles can activate the hyperphosphorylation of Tau proteins in the brain of AD rats and cause neurotoxicity, and that the inflammatory factors IL-1β and IL-18, which release caspase-1 from the pyroptosis pathway, can promote the hyperphosphorylation of Tau proteins. In addition, studies on the mechanism of Tau protein pathology have shown that genetic deletion of NLRP3 can ameliorate the hyperphosphorylation of Tau proteins through the regulation of the Tau kinase GSK-3β, suggesting that NLRP3 can modulate the disease process through the regulation of Tau. The above studies indicate that cellular pyroptosis is closely linked to Tau protein phosphorylation, and therefore, inhibition of cellular pyroptosis may be important for delaying the development of AD.

Pyroptosis and the Neuronal Correlation Doctrine

Neuronal loss is one of the typical pathologic features of AD, which may be related to factors such as Aβ accumulation and neuroinflammation.[19,20] Microglia around Aβ plaques contribute to Aβ accumulation, and the accumulated Aβ activates microglia, which produce pro-inflammatory mediators that cause progressive neuronal loss,[21] This in turn accelerates AD progression. Neuronal loss occurs primarily through the cholinergic pathway,[22] The cholinergic theory, on the other hand, suggests that the loss of cholinergic neuron function can have a direct impact on cognitive function. In addition, experimental studies have demonstrated that cognitive function can be improved by modulating proteins closely related to AD, reducing neuronal loss, and attenuating cholinergic inhibition. This further suggests that there is a close link between AD and neuronal loss. Therefore, stopping neuronal loss can be one of the effective ways to treat AD.

In summary, the 3 key pathogenic processes of AD are concurrent and interact with each other, and ultimately work together to induce AD, while cellular pyroptosis, as an important component of innate immunity, plays an important role in the deposition and spread of Aβ, phosphorylation, aggregation, and diffusion of tau proteins, as well as neuroinflammation. Thus, pharmacological inhibition of activation of cellular pyroptosis has emerged as a potential direction to ameliorate AD-related symptoms and slow down AD progression. Galanthamine, as a competitive and reversible inhibitor of cholinesterase, also modulates

neuronal nicotinic receptor (N-receptor) activity, and is better absorbed and has a longer duration of action, but its therapeutic effect is limited, and it does not improve all psychometric indicators in patients with AD. The NMDA receptor antagonist memantine, the only FDA-approved medication for the treatment of moderately-severe AD patients, slows down patients' As the only drug approved by the FDA for the treatment of patients with moderate-to-severe AD, memantine is the first-line drug for the treatment of moderate-to-severe AD. However, its curative treatment does not significantly alleviate the disease process, and its potential to induce seizures and other adverse effects have limited the application of memantine in the clinic. Nerve growth factor (NGF), which is currently receiving more attention, can stimulate nerve cells to produce and release Ach. Clinical trials have shown that the application of NGF analogs in early AD patients can reduce and reverse cognitive deficits. However, NGF does not easily cross the blood-brain barrier and is ineffective when administered orally or by injection. See Figure 3.

Exploring the Correlation Between AD and Pyroptosis Based on Chinese Medicine Theory

AD belongs to the categories of "epilepsy", "dullness" and "good forgetfulness" in Chinese medicine, and the first description of this disease can be found in Hua Tuo's Secret Biography of Divine Medicine,[23] The book points out that

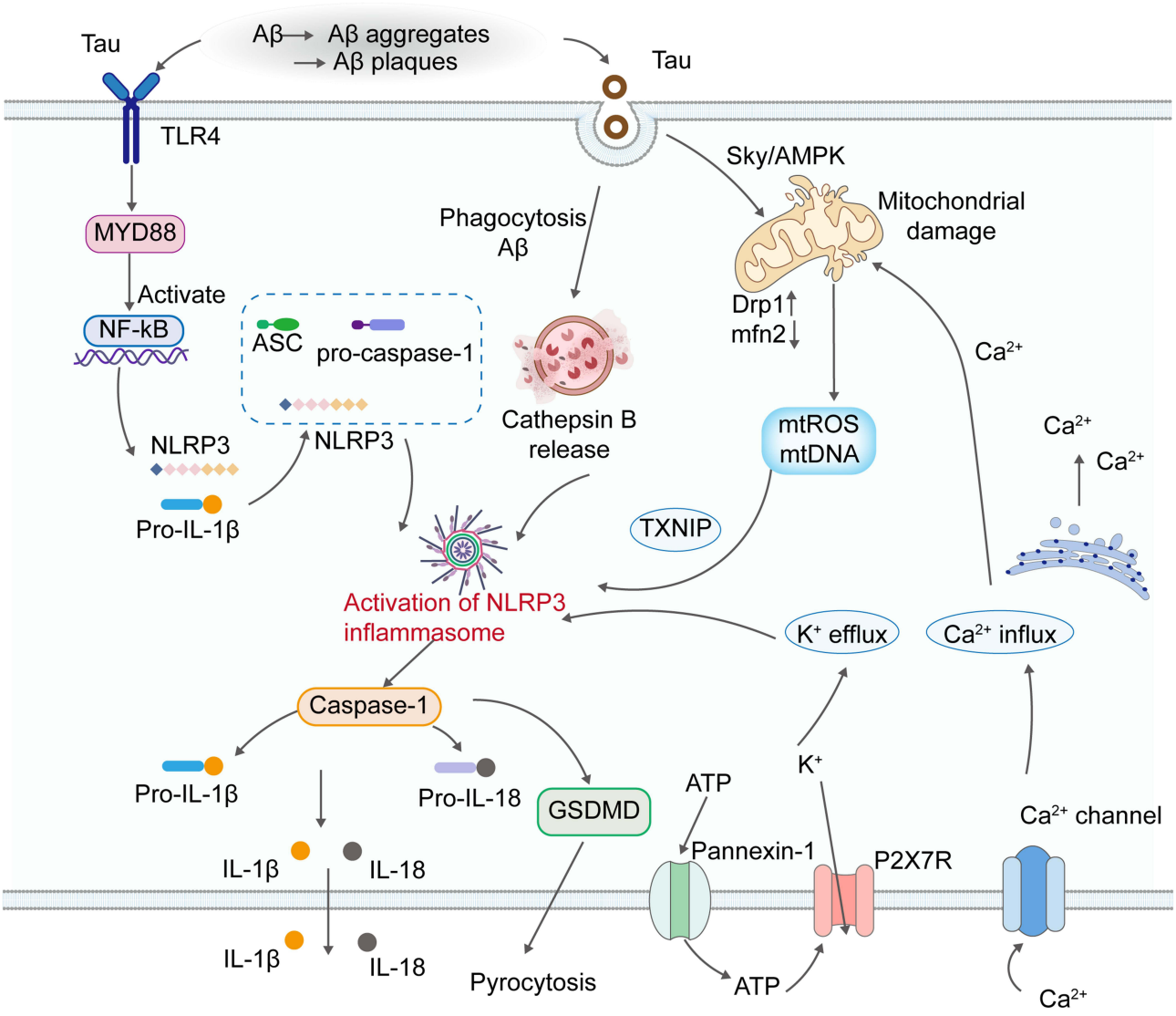

Figure 3 Mechanism of NLRP3 inflammatory vesicle activation in AD. The importance of cellular pyroptosis as an important component of innate immunity in Aβ proliferation and deposition, Tau protein phosphorylation, and neuroinflammation cannot be overstated. Therefore, inhibition of cellular pyroptosis activation should be considered as a potential direction to improve AD condition and slow down AD progression.

the mechanism of AD is depression and anger; Zhang Jiebin in Jingyue Quanshu – Miscellaneous Diseases Muo points out that this disease is mostly due to the depression of emotions and feelings, panic and fear.[24] AD is an evidence of deficiency and deficiency of kidney essence is the root cause of AD. The "Spiritual Pivot – Sea Theory" said: "Insufficient medulla oblongata, brain rotation tinnitus, shin soreness and dizziness, the eye is not able to see, slackness and lying down", the lack of kidney essence will lead to cerebral medulla oblongata, the loss of the use of God's mechanism, which will make the kidney yin generated by the generation of internal heat and false fire, refining liquid for phlegm, burning Jin for stasis, and ultimately forming a deficiency of renal yin for this, phlegm and stasis obstruction of collaterals for the label of the evidence of deficiency of the label of the real Characteristics. In the process of cell death, the inflammatory mediators released by the cells are involved, which should belong to the category of "poisonous evil" in Chinese medicine. Toxicity attacks and lies deep within, resulting in phlegm and dampness, which leads to fire and burns the fluid to form blood stasis, and then phlegm and blood stasis intertwine to paralyze the blood vessels and cause the onset of the disease. This inflammatory medium is the microcosmic manifestation of "phlegm-dampness" and "blood stasis". Therefore, from the perspective of Chinese medicine, it can be considered that cell death is mediated by "phlegm stasis", which is involved in the development of AD.

Intervention of Chinese Medicine in Pyrolysis

Intervention Effects of Herbal Monomers and Herbal Extracts on AD Based on Pyroptosis

Currently, there are studies proving that a variety of traditional Chinese medicines and herbal extracts can inhibit the activation and expression of relevant inflammatory vesicles and proteins by interfering with the progression of cellular pyrokinesis and reduce the inflammatory response, thus providing a therapeutic effect on AD. Radix Astragali has a variety of biological activities such as regulating immune function, anti-inflammation and neuroprotection,[25] which not only blocks the transcription of caspase-3,[26] It also inhibits aberrant activation of microglia and reduces pro-inflammatory mediators and apoptosis, thereby slowing the progression of AD.[27] Not only could the Isodon amethystoides reduce the serum levels of Caspase-1, IL-1β and IL-18 proteins in rats, but the transduction pathways it inhibited were also related to NLRP3/Caspase-1 signaling pathways. In addition, Formononetin not only inhibits the expression of NLRP3, counteracts the activation of Caspase-1 and reduces the levels of IL-1β and tumor necrosis factor-α (TNF-α), but also penetrates the blood-brain barrier and protects neurons and peripheral glial cells.[28] Polysaccharides of Lycium chinense, as the core component in Wolfberry, is a plant polysaccharide with a structure and its complexity, and its ability to reduce Aβ1-40-induced NLRP3 and IL-1β in rat brain,[29] And it has good biological efficacy for cognitive impairment. Dihydromyricetin extracted from Hovenia acerba Lindl is able to promote the transformation of microglia to the anti-inflammatory M2 type, not only that, dihydromyricetin has also been shown to inhibit the expression of the subunit of Caspase-1, which has great potential to stop the progression of AD.[30] In addition, Saponin, an important active component of ginseng, can reduce the expression of the inflammatory mediator IL-1β by inhibiting the activation of the NF-κB/STAT3 pathway in cells,[31] This in turn reduces the damage to the brain caused by the inflammatory response (Table 1).

Intervention Effects of Chinese Herbal Compounds and Proprietary Chinese Medicines on AD Based on Pyroptosis

The efficacy of treating AD from the perspective of pyroptosis using proprietary Chinese medicines and Chinese herbal compounds has been remarkable, and related studies are abundant. Clinical trials have shown that, add or subtract of Shu Yu Wan can reduce IL-1β/NF-κB/miR-146a in peripheral blood of AD patients.[32] Besides that, add or subtract of Shu Yu Wan was also able to decrease the expression levels of NLRP3, ACS, and Caspase-1 in the hippocampal region of AD mice, and induced microglia to polarize to M2 type and repair the neural function.[33] Hei xiaoyao powder can reduce the level of neuroinflammation, enhance the antioxidant capacity, and play a neuroprotective role by inhibiting the expression of NF-κB/NLRP3 signaling pathway and downstream related proteins.[34] Danggui Shaoyao Granules have been shown to inhibit NF-κB pathway signaling, accelerate the synthesis of antioxidant enzymes, prevent cellular lipid peroxidation, and protect hippocampal neurons in Aβ1-42-induced AD rats.[35] Also, Pill of six ingredients with rehmannia is able to protect

Table 1 Chinese Medicine Monomer/Chinese Medicine Extracts Target Pyroptosis Intervention in the Treatment of AD

Chinese Medicine Monomer/Chinese Medicine Extract	Therapeutic Target	Therapeutic Effect	Molecular Formula
Radix Astragali	Caspase-3	Blocking caspase-3 transcription, inhibiting aberrant microglia activation, and reducing pro-inflammatory mediators and apoptosis	C21H18O11
Isodon amethystoides	NLRP3/Caspase-1 signaling pathway, IL-1β, IL-18	Reduction of Caspase-1, IL-1β and IL-18 proteins in the serum of rats Inhibits the progression of cellular pyroptosis	C20H28O6
Formononetin	NLRP3, Caspase-1, IL-1β, TNF-α	Inhibits NLRP3 expression, counteracts caspase-1 activation and reduces IL-1β and tumor necrosis factor-α (TNF-α) levels, and also penetrates the blood-brain barrier to protect neurons and peripheral glial cells	C19H18O11
Polysaccharides of Lycium chinense	NLRP3, IL-1β	Reduction of Aβ1-40-induced NLRP3 and IL-1β levels in rat brain with favorable biological efficacy for cognitive deficits	C5H8O4
Dihydromyricetin	mtROS, Caspase-1, NLRP3	Promoting the conversion of microglia to the anti-inflammatory M2 type also inhibits the subunit expression of caspase-1 and blocks AD progression	C15H12O8
Saponin	NLRP3, ASC, IL-1β, NF-κB/STAT3 signaling pathway	By inhibiting the activation of the NF-κB/STAT3 pathway in cells, thereby reducing the expression of the inflammatory mediator IL-1β, and thus attenuating the brain damage caused by the inflammatory response	C36H62O9

Abbreviations: AD, Alzheimer's disease; Caspase-3, Cysteinyl aspartate specific proteinase-3; NLRP3, NOD-like receptor protein 3; Caspase-1, Cysteinyl aspartate specific proteinase-1; IL-1β, Interleukin-1beta; IL-18, Interleukin-18; TNF-α, Tumor necrosis factor-α; Aβ1-40, Abeta1-40; mtROS, mitochondrial reactive oxygen species; ASC, Apoptosis-associated speck-like protein; NF-κB, Nuclear factor kappa-B; STAT3, Signal transducer and activator of transcription 3.

neurons by down-regulating the TXNIP/NLRP3 inflammatory signaling axis, decreasing caspase-1 activity and IL-1β levels.[36] The main mechanism is to inhibit microglia activation and reduce the levels of inflammatory factors TNF-α and IL-1β, thus slowing down the damage to neurons by the inflammatory cascade. Dianxianqing granule has anti-cell death and anti-inflammatory effects, and can be combined with NLRP3 antagonists to further strengthen the inhibition of NLRP3, and significantly improve the impaired blood-brain barrier function.[37] Furthermore, the efficacy of Qiling Yinao Decoction, a self-proposed Chinese medicine compound, is equally significant in AD, it consists of Astragalus, Smilax glabra Roxb, Cassia Twig, Sichuan lovage rhizome and other traditional Chinese medicines. Qiling Yinao Decoction can reduce the stimulation of NLRP3 in the cortical area of the brain by decreasing the deposition of Aβ, thus slowing down cognitive impairments[38] (Table 2).

Acupuncture Intervention in AD Based on Pyroptosis

Acupuncture, as an important part of Chinese medicine, is able to play a significant role in the treatment of AD by modulating inflammatory factors of cellular pyroptosis signaling pathway and related factors of negative regulation. After acupuncture at Shenting and Baihui points in rats with mild cognitive impairment, it was found that the protein levels of Caspase-1, NLRP3, and IL-1β were decreased, and the degree of activity of microglia in the hippocampus decreased,[39] Acupuncture at Shenting and Baihui points has been shown to inhibit NLRP3 pathways and improve cognitive dysfunction. In addition, some studies have shown that acupuncture can reduce the expression of IL-1β and TNF-α in the rat hippocampus, block the activated NF-κB from entering the cell nucleus and inhibit the transmission of its signaling pathway, thus reducing the release of inflammatory factors and alleviating the damage of nerve cells.[40] Similarly, electroacupuncture of Taixi and Ashigaru points has been shown to cause a decrease in activation of frontal lobe and astrocytes, as well as a decrease in the expression of TNF-αmRNA and IL-1βmRNA, thereby inhibiting neuronal degeneration and necrosis.[41] In addition, the acupuncture points of Sanyinjiao, Hegu, and Shakuzawa in CIRI

Table 2 Targeted Pyroptosis Intervention with Compound Prescription of Chinese Medicine/Prepared Prescription for the Treatment of AD

Compound Prescription of Chinese Medicine/ Prepared Prescription (Chinese Medicine)	Drug Composition	Therapeutic Target	Therapeutic Effect
Shu Yu Wan	Common Yam Rhizome, Foxglove, Prepared Fleeceflower Root, Tangshen, White Peony Root, Chinese Angelica, Atractylodes, Poria cocos, Wolfberry, Acorus Tatarinowii, Polygalae Radix, Eucommia ulmoides, Sichuan lovage rhizome, Chinese Magnolcavine Fruit	NLRP3/ACS,/ Caspase-1 signal pathway	Reducing the levels of IL-1β/NF-κB/miR-146a in the peripheral blood of AD patients, it was also able to decrease the expression levels of NLRP3, ACS, and Caspase-1 in the hippocampal region of AD mice, and induced microglial cells to polarize towards the M2 type, repairing the neurological function
Hei xiaoyao powder	Rehmannia Glutinosa, Chinese Thorowax Root, Chinese Angelica, White Peony Root, Largehead Atractylodes Rh, Indian buead, Ginger, Prepared Liquorice Root, Wild Mint Herb	NF-κB/NLRP3 signaling pathway, NOX2, ROS, p-IKBα, MDA, IL-6, IL-8	Inhibits the expression of NF-κB/NLRP3 signaling pathway and downstream related proteins, reduces neuroinflammation levels, enhances antioxidant capacity, and exerts neuroprotective effects
Danggui Shaoyao Granules	Chinese Angelica, White Peony Root, Largehead Atractylodes Rh, Indian buead, Sichuan lovage rhizome, Alisma Orientale	p-AMPK/AMPK signaling pathway, SIRT1, PGC-1α, Mfn2	Inhibition of NF-κB pathway signaling expression accelerates the synthesis of antioxidant enzymes, prevents cellular lipid peroxidation and protects hippocampal neurons in Aβ1-42-induced AD rats
Pill of six ingredients with rehmannia	Asiatic Cornelian Cherry Fruit, Common Yam Rhizome, Alisma Orientale, Indian buead, Tree Peony Bark, Rehmannia Glutinosa	TXNIP/NLRP3 inflammatory response signaling axis, Caspase-1, IL-1β, TNF-α	It can down-regulate TXNIP/NLRP3 inflammatory response signaling axis, inhibit microglia activation, and reduce the content of Caspase-1, IL-1β and TNF-α, thus slowing down the damage of inflammatory cascade response to neurons, and achieving neuronal protection
Dianxianqing granule	Chinese Angelica, Sichuan lovage rhizome, White Peony Root, Rehmannia Glutinosa, Gambir Plant, Suberect Spatholobus Stem, Common Selfheal Spike, Sickle Senna Seed, Margarita, Corydalis Yanhusuo, Manchurian wildginger	Sigma1 receptor, VEGF, Cx43, occludin mRNA, NLRP3	The ability to combine with NLRP3 antagonists to further enhance the inhibition of NLRP3, with anti-cellular pyroptosis and anti-inflammatory effects, and a significant improvement in impaired blood-brain barrier function
Qiling Yinao Decoction	Milkvetch Root, Smilacis Glabrae Rhizoma, Cmnamomi Mmulus, Sichuan lovage rhizome	NLRP3, AβmRNA	Stimulation of NLRP3 in cortical areas can be reduced by decreasing Aβ deposition, thereby slowing cognitive impairment

mice were found to be able to inhibit caspase-1 pathway-mediated cellular pyrolysis, reduce the volume of cerebral infarction, and decrease the level of neuronal cell damage in CIRI mice by electroacupuncture.[42] In addition to this, it was found that the expression of NLRP1, ASC, IL-1β, and IL-18 in SAMP8 mice was significantly decreased by alternating left and right needling of the acupuncture points of Kidney Yu, Sea of Blood, and Diaphragm Yu in SAMP8 mice, suggesting that acupuncture can inhibit NLRP1-mediated cellular focalization and ameliorate cognitive deficits in AD.[43] However, the current acupuncture interventions on jiao death are all experimental studies, and most of them inhibit jiao death by down-regulating protein expression and inflammatory factors in the jiao death pathway. However, cellular death has a bidirectional effect, and the balance between inhibiting death and promoting death should be well

characterized. In addition, there is a need to analyze the targets of acupuncture intervention in cellular juxtaposition and apply effective targets in AD, so that they can play a key role in the development of acupuncture intervention in juxtaposition as well as in the clinical treatment of AD.

Summary and Outlook

At present, the prevention and treatment of AD has become a global medical and social problem that needs to be solved urgently. In this paper, we summarize the relationship between cellular pyroptosis and AD, as well as the research on the treatment of AD by modulating cellular pyroptosis in traditional Chinese medicine (TCM), and determine that inhibiting cellular pyroptosis through targeting can reduce the release of inflammatory factors and the damage of neural cells, which can improve the symptoms of AD and slow down the progression of AD. At the same time, this paper also clarifies that traditional Chinese medicine can play a large degree of anti-inflammatory role in the prevention and treatment of AD by down-regulating the expression level of inflammatory vesicles and inhibiting the activation of related pathways. However, although some progress has now been made in the study of AD and the mechanism of cellular pyroptosis, further in-depth studies are needed to explore the biological mechanisms by which TCM regulates cellular pyroptosis. Therefore, in the future, the characteristics and mechanisms of cellular pyroptosis and the potential therapeutic targets of clinically relevant diseases should be studied in depth to further elucidate the mechanism of action, provide theoretical support for the research and development of relevant therapeutic drugs, and bring a new direction for the prevention and treatment of AD.

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Disclosure

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