Regulation of neuroinflammatory signaling pathway in neurodegenerative diseases

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Abstract. Neuroinflammation directly drives neuronal damage through chronic inflammatory microenvironment, and plays a key regulatory role in neurodegenerative diseases (NDDs). Microglia perceive pathological stimuli through classical pathways such as TLR/NF-κB, NLRP3 inflammatory corpuscles and cGAS-STING, and release pro-inflammatory factors and reactive oxygen species, thus forming a vicious cycle of "inflammation-degeneration". Different NDDs present disease-specific activation patterns: Aβ activates NF-κB and NLRP3 pathways through TLR/TREM2 in Alzheimer's Disease (AD); In Parkinson's disease, α -synuclein triggers MAPK cascade through TLR2; Amyotrophic lateral sclerosis highlights the role of cGAS-STING pathway in sensing cytoplasmic DNA. Multi-channels construct a cooperative regulatory network through positive feedback loop and cross-dialogue, such as the self-strengthening cycle promoted by NF-κB and NLRP3, and the polarization of M1 microglia driven by metabolic reprogramming, which leads to uncontrolled and chronic inflammatory reaction.

Key words: neuroinflammatory signaling pathway; neurodegenerative diseases; TLR; NF-κB; NLRP3; TLR; TREM2.

1. Introduction

Traditionally, the core mechanism of Neurodegenerative Diseases (NDDs) is the abnormal aggregation of protein and oxidative stress caused by mitochondrial dysfunction. However, recent studies have revealed that neuroinflammation is not a simple secondary reaction, but directly participates in neuronal damage and disease progression through chronic inflammatory microenvironment, forming a vicious circle of "inflammation-degeneration" [1].

Microglia, as resident immune cells within the central nervous system (CNS), activate downstream signaling pathways via pattern recognition receptors upon sensing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs). They subsequently release pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS) in an attempt to eliminate pathological stimuli [2]. However, in NDDs, persistent abnormal protein aggregation or metabolites lead to microglia being activated for a long time, forming an "excessive inflammatory reaction", which in turn aggravates nerve damage. Clinical evidence also supports the correlation between neuroinflammation and disease progression. The levels of IL-6 and TNF-α in cerebrospinal fluid of patients with Alzheimer's Disease (AD) are negatively correlated with cognitive score [3]. The density of microglia in substantia nigra of AD patients is 3-5 times higher than that of healthy people, and it is positively correlated with the severity of motor symptoms [4]. Genome-wide association studies (GWAS) have revealed that polymorphisms in inflammation-related genes such as NLRP3 and TLR4 are significantly associated with the risk of developing AD and Parkinson's disease (PD) [5].

The regulatory network of neuroinflammation is highly complex, involving the coordination and antagonism of multiple signal pathways. Among them, TLR/NF-κB pathway, as a classical inflammatory signal axis, induces the expression of proinflammatory factors by recognizing pathological stimuli such as Aβ and α-syn, and plays a key role in both AD and PD [6]. NLRP3 inflammatory corpuscles are used as cytoplasmic danger signal sensors, which form mature cytokines by cutting IL-1β precursors and drive chronic inflammation and neuronal focal death. The cGAS-STING pathway, discovered in recent years, activates IFN-I signal by sensing cytoplasmic DNA, and forms a "virus simulation" state in aging-related NDDs, which aggravates microglia aging and

neurotoxicity [7]. In addition, non-classical pathways play a neuroprotective role by regulating the balance between inflammation, antioxidation and autophagy. In this study, the regulatory role of neuroinflammatory signaling pathway in NDDs was systematically analyzed. By integrating single cell sequencing, spatial transcriptomics and animal models, the activation mode of disease-specific pathway, multi-channel collaborative network and key regulatory nodes were revealed, which provided theoretical basis for developing precise therapeutic strategies targeting neuroinflammation.

2. The core mechanism of neuroinflammatory signaling pathway

2.1 Classical signal path analysis

Neuroinflammation is an important pathological feature of NDDs, and its core mechanism involves the activation of microglia and astrocytes and the downstream inflammatory cascade [8]. Classic signaling pathways centered on nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) initiate inflammatory cytokine expression by sensing endogenous danger signals such as Aβ and α-synuclein or exogenous stimuli like pathogen-associated molecular patterns [9].

(1) TLR/MyD88/NF-κB pathway

Upon recognizing DAMPs, Toll-like receptors (TLR2/4) on the surface of microglia recruit the adaptor protein MyD88, activate IκB kinase (IKK), and trigger degradation of the NF-κB inhibitor (IκB). NF-κB promotes the transcription of TNF-α, IL-1β, IL-6 and other pro-inflammatory factors, and aggravates neuronal damage.

(2) MAPK pathway

Including p38, JNK and ERK subfamilies, which activate transcription factors through phosphorylation and cooperatively regulate the expression of inflammatory genes. For example, p38 MAPK is activated by Aβ in AD model, which induces iNOS expression and promotes oxidative stress [10].

(3) NLRP3 inflammatory corpuscle pathway

ATP and crystalline substances trigger NLRP3 to assemble into polymer complex, activate caspase-1, cleave pro-IL-1β into mature IL-1β, induce pyroptosis and release a large number of inflammatory mediators. This pathway is closely related to α -synuclein aggregation in PD [11].

2.2 Non-classical signal path and cross regulation

In addition to classical pathways, neuroinflammation also depends on non-classical pathways and dynamic interaction between multiple pathways, forming a complex regulatory network.

(1) Complement system and C5a receptor (C5aR) pathway

Complement C3/C5 cleavage products bind to C5aR on microglia surface, activate PI3K/Akt and NF-κB, enhance phagocytosis and amplify inflammatory response [12]. In Huntington's disease model, C5aR antagonists can significantly reduce neurotoxicity.

(2) JAK/STAT pathway

Cytokines, such as IFN-γ, activate JAK kinase after binding to receptor, phosphorylate STAT protein and form dimer into nucleus, which regulates the expression of immune-related genes. There is a cross-talk between this pathway and NF-κB, and they jointly maintain the chronic inflammatory state.

(3) Negative feedback regulation of autophagy-lysosomal system

Autophagy alleviates inflammation by removing misfolded proteins tau and α-synuclein, but excessive autophagy may activate NLRP3 [13]. As a key node, mTOR signal integrates energy metabolism and inflammatory response.

(4) Epigenetic regulation

DNA methylation, histone modification and non-coding RNA regulate the expression of TLR4 or NF-κB, and realize the long-term memory regulation of inflammation. Multi-channel interaction forms an "inflammatory signal hub", for example, NF-κB and NLRP3 promote each other to form a

positive feedback loop [14]; P38 MAPK enhances IL-6 secretion by phosphorylating STAT3; Complement C3a and TLR4 synergistically activate microglia polarization (M1 type).

3. The regulatory role in NDDs

3.1 Disease-specific pathway activation pattern

As unique "danger signals", pathological protein aggregates Aβ, tau and α-syn of different neurodegenerative diseases preferentially activate specific microglia surface receptors, thus starting the core inflammatory signaling pathway with disease characteristics [15]. Table 1 below summarizes the specific pathway activation patterns in three main NDDs.

Table 1. Activation patterns of core neuroinflammatory signaling pathways in major NDDs

Disease name	Main pathological proteins/characteristics	Core activation receptor	Downstream critical signal path	Main inflammatory effect
AD	**Aβ plaque, neurofibrillary tangles**	TLR2, TLR4, TLR6, TREM2, CD14	**NF-κB pathway, NLRP3 inflammasome pathway**	Microglia aggregate to Aβ plaque, releasing IL-1β, IL-18 and TNF-α, which aggravates the pathology of tau.
PD	**α -synuclein aggregation**	TLR2, TLR4	**NF-κB pathway, MAPK pathway**	Produces proinflammatory factors and damages dopaminergic neurons; Inflammatory environment promotes abnormal aggregation of α-syn
Amyotrophic Lateral Sclerosis (ALS)	**Protein aggregation such as TDP-43, astrocytosis**	Multiple pattern recognition receptors	**NF-κB pathway (in neurons and microglia) and cGAS-STING pathway (for cytoplasmic DNA/RNA)**	Strong activation of astrocytes and microglia releases toxic factors and accelerates the death of motor neurons.

Aβ fiber aggregates can be recognized by Toll-like receptors and TREM2 on microglia. TREM2 function deletion mutation is an important risk factor for AD, which should transmit the signal of "inhibiting inflammation and promoting phagocytosis", and its loss of function leads to the disorder of Aβ clearance and uncontrolled inflammation. The activated TLR further activates the NF-κB pathway and promotes the transcription of a large number of proinflammatory factors [16]. More importantly, Aβ, especially oligomer, can be swallowed by microglia and activate NLRP3 inflammasome, which leads to the activation of caspase-1, and then cuts and releases strong pro-inflammatory factors IL-1β and IL-18, forming a positive feedback loop, which continues to aggravate inflammation.

Pathological α -synuclein fibers act as endogenous risk-related molecular patterns, and also activate NF-κB and p38 MAPK pathways in microglia through TLR (especially TLR2). This leads to a persistent inflammatory environment in the substantia nigra region, which is selectively

susceptible to dopaminergic neurons [17]. At the same time, inflammatory factors themselves can promote the wrong folding and aggregation of α-syn and form a vicious circle.

In addition to the classic NF-κB pathway, cGAS-STING pathway plays an increasingly prominent role in ALS. DNA damage or mitochondrial dysfunction in motor neurons may lead to the appearance of self-DNA/RNA in cytoplasm. These molecules can activate cGAS, produce cGAMP, and then activate STING protein [18]. STING activation will strongly induce the production of type I interferon and other inflammatory factors, and amplify the neuroinflammatory response.

3.2 Multi-channel cooperative regulation network

The regulation of neuroinflammation is not a linear function of a single pathway, but a highly interconnected and cross-talk network system. This synergistic regulation amplifies the inflammatory signal and determines the final outcome of the inflammatory reaction.

(1) Positive feedback loop amplifies inflammatory signal.

Activation of NF-κB can up-regulate the transcription of NLRP3 and pro-IL-1β, providing "initial signal" and substrate for the assembly of NLRP3 inflammasome. The mature IL-1β produced after activation of NLRP3 can further activate NF-κB pathway, forming a self-reinforcing inflammatory cycle, which makes the inflammatory reaction rapidly escalate and difficult to stop [19]. TNF-α released by microglia can bind to its own TNFR1 receptor in autocrine or paracrine way, further activating NF-κB pathway and maintaining its own activation state.

(2) Cross-channel dialogue and integration

Synergy between MAPK and NF-κB pathway: After TLR4 is activated, downstream NF-κB and JNK/p38 MAPK pathways can be started simultaneously [20]. These two pathways synergistically regulate the production of proinflammatory cytokines at transcription level and post-transcription level.

The metabolic state of cells profoundly affects the inflammatory response. For example, the increase of glycolysis is the metabolic basis of microglia polarization to pro-inflammatory phenotype (M1) [21]. Important metabolic receptors, such as AMPK and mTOR pathways, can directly interact with inflammatory pathways such as NF-κB: AMPK activation can inhibit NF-κB and play an anti-inflammatory role; While mTOR activation usually promotes inflammation [22].

(3) Neural-immune-glial cell network

Neurons are not passive victims, they can actively release "don't eat me" signals or neurotransmitters, and inhibit the overactivation of microglia through their receptors. In the disease state, this steady-state regulation is destroyed [23]. At the same time, activated astrocytes also secrete a large number of inflammatory factors, which stimulate each other with microglia to form a complex inflammatory microenvironment.

4. Prospect

Neuroinflammatory signaling pathway plays a core driving role in NDDs. Its regulatory function shows the characteristics of "specific initiation and network amplification": specific pathological proteins initiate disease-specific initial inflammatory response by activating core receptors; Subsequently, the main pathways, such as NF-κB, NLRP3, MAPK and cGAS-STING, formed a powerful synergistic regulatory network through positive feedback loop and cross-dialogue, which led to uncontrolled and chronic inflammatory reaction.

Understanding this complex regulatory network provides a key target for developing new therapeutic strategies. The future research direction is no longer limited to inhibiting a single pathway, but focuses on developing regulators for key nodes. To explore how to reprogram harmful pro-inflammatory microglia/astrocytes into anti-inflammatory/repair phenotype with neuroprotective function. The dynamic changes of the whole regulatory network are analyzed by system biology method in order to realize more accurate and effective immune intervention, thus delaying or preventing the progress of NDDs.

5. Conclusion

Neuroinflammation is not a simple secondary reaction, but directly drives neuronal damage through the chronic inflammatory microenvironment, forming a vicious circle of "inflammation-degeneration". Different NDDs present specific pathway activation patterns: Aβ in AD activates NF-κB and NLRP3 inflammatory body pathways through TLR/TREM2 receptors; α -synuclein in PD triggers MAPK cascade reaction through TLR2; Amyotrophic lateral sclerosis highlights the key role of cGAS-STING pathway in sensing cytoplasmic DNA. These pathways construct a highly interconnected cross-talk network through the positive feedback loop of NF-κB and NLRP3, the coordinated regulation of MAPK and NF-κB, and the polarization of M1 microglia driven by metabolic reprogramming, which leads to the cascade amplification and chronicity of inflammatory signals. The integration of single cell sequencing and spatial transcriptomics technology confirmed that the regulatory network has the dual characteristics of "specific startup-network amplification", and its out-of-control is the core driving force of disease progress.

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