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Mini Review | *Open Access*

RIPK1-Mediated Pathways and Neurotoxic Reactive Astrocytes in Neurodegeneration: A Mini Review

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Abstract

Receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and neurotoxic reactive astrocytes are gaining recognition for their pivotal roles in the progression of neurodegenerative diseases. RIPK1, a key regulator of necroptosis and inflammation, interacts with astrocytes to exacerbate neuroinflammation and neuronal damage. Neurotoxic reactive astrocytes, often induced by inflammatory microglia, contribute to synaptic dysfunction and neuronal death, further advancing disease pathology. This review highlights the mechanisms underlying RIPK1-mediated signaling and the generation of reactive astrocytes, emphasizing their interplay in neurodegenerative conditions such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Understanding these pathways offers new opportunities for targeted therapeutic strategies to mitigate neurodegeneration.

1. Introduction

Neurodegenerative diseases, characterized by the progressive loss of neuronal function, are driven by complex interactions between neuronal and non-neuronal cells. Among the non-neuronal contributors, RIPK1-mediated necroptosis and reactive astrocytes have emerged as significant players in the pathology of these disorders. RIPK1's role in programmed necrosis and its regulation of inflammatory pathways are particularly critical in the context of chronic neuroinflammation. Similarly, reactive astrocytes, specifically the neurotoxic "A1" phenotype, exacerbate neuronal damage. This review explores the relationship between RIPK1 signaling and the induction of neurotoxic astrocytes, with implications for understanding and treating neurodegenerative diseases.

2. RIPK1-Mediated Pathways in Neurodegeneration

RIPK1 is a multifunctional kinase involved in regulating apoptosis, necroptosis, and inflammation. In the central nervous system (CNS), RIPK1 is activated in response to pro-inflammatory cytokines such as tumor necrosis

factor-α (TNF-α) and cellular stress signals. Its role in neurodegeneration includes:

- **Necroptosis Induction**: RIPK1 forms a necrosome complex with RIPK3 and mixed lineage kinase domain-like protein (MLKL), leading to necroptotic cell death. This process releases damage-associated molecular patterns (DAMPs), amplifying inflammation and neuronal damage [1,2].
- **Inflammatory Signaling**: RIPK1's interaction with nuclear factor-κB (NF-κB) and other inflammatory pathways perpetuates a pro-inflammatory environment in the CNS [3].

Aberrant activation of RIPK1 has been implicated in various neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Alzheimer's disease (AD). In mouse models, inhibition of RIPK1 using pharmacological agents such as necrostatins has shown promise in reducing neuroinflammation and neuronal loss [4].

3. Reactive Astrocytes: From Protectors to Pathogens

Astrocytes, the most abundant glial cells in the CNS, perform vital roles in maintaining neuronal health, including synaptic regulation, neurotransmitter recycling, and blood-brain barrier maintenance. However, in response to injury or inflammation, astrocytes can adopt reactive phenotypes, including the neurotoxic A1 phenotype.

Neurotoxic reactive astrocytes:

- Are induced by activated microglia secreting interleukin-1α (IL-1α), TNF-α, and complement component 1q (C1q) [5].
- Exhibit downregulated neuroprotective genes and upregulated pro-inflammatory and neurotoxic factors [6].
- Release harmful substances such as reactive oxygen species (ROS) and glutamate, contributing to excitotoxicity and neuronal death [7].

Reactive astrocytes have been linked to disease progression in AD, Parkinson's disease (PD), and Huntington's disease (HD). Their activation correlates with the loss of synaptic integrity and the propagation of neurodegenerative pathology [8].

4. Interplay Between RIPK1 and Neurotoxic Astrocytes

RIPK1-mediated signaling plays a crucial role in the activation of neurotoxic reactive astrocytes. Mechanisms include:

- **Microglia-Astrocyte Crosstalk**: RIPK1 activation in microglia drives the release of pro-inflammatory cytokines, which in turn induce neurotoxic astrocytes [5].
- **Direct Astrocytic Pathways**: RIPK1 signaling within astrocytes contributes to their reactive transformation by regulating NF-κB-mediated transcription of pro-inflammatory genes [6].
- **Amplification of Neuroinflammation**: Both RIPK1 and neurotoxic astrocytes propagate a feedback loop of inflammation, exacerbating neuronal damage and synaptic dysfunction [7,8].

5. Therapeutic Implications

Targeting RIPK1 and reactive astrocytes holds potential for mitigating neurodegeneration:

- **RIPK1 Inhibitors**: Small molecules like necrostatins and newer RIPK1-specific inhibitors can block necroptosis and reduce inflammation [4,9].
- **Astrocyte Modulation**: Therapies aimed at preventing the transition of astrocytes to the A1 phenotype or restoring their neuroprotective functions may halt disease progression [10].
- **Combination Approaches**: Strategies targeting both RIPK1-mediated pathways and astrocyte reactivity could provide synergistic benefits in treating neurodegenerative diseases [11].

6. Conclusion

The interplay between RIPK1-mediated pathways and neurotoxic reactive astrocytes represents a critical axis in the pathophysiology of neurodegenerative diseases. Advances in understanding these mechanisms can inform the development of targeted therapies, offering hope for alleviating the burden of these debilitating disorders. Continued research into these pathways is essential to unravel their complexities and translate findings into clinical applications.

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