Role of necroptosis in neurodevelopmental disorders.

Hazzle Scarlet*

Department of Neurosciences, Central south university, China

Introduction

Neurodevelopmental disorders encompass a wide range of conditions that affect brain development and function, resulting in long-term cognitive, social, and behavioral impairments. While significant progress has been made in understanding the genetic and environmental factors contributing to these disorders, the underlying cellular mechanisms remain elusive. Recently, emerging research has shed light on the involvement of necroptosis, a regulated form of cell death, in the pathogenesis of neurodevelopmental disorders. This article aims to explore the role of necroptosis in neurodevelopmental disorders and its potential implications for therapeutic interventions. Necroptosis, once considered an accidental and unregulated form of cell death, has emerged as a significant player in neurodevelopmental disorders. In recent years, studies have provided compelling evidence for the involvement of necroptotic signaling pathways in the pathogenesis of these disorders. Necroptosis has been implicated in critical processes such as neural progenitor cell proliferation, neuronal migration, synapse formation, and synaptic pruning, all of which are fundamental for normal brain development [1].

One of the neurodevelopmental disorders in which necroptosis has been extensively investigated is autism spectrum disorder (ASD). ASD is characterized by impaired social interactions, communication difficulties, and repetitive behaviors. Postmortem studies on ASD brains have revealed increased expression levels of necroptotic markers, including RIPK3 and MLKL, in the cerebral cortex and hippocampus. This dysregulation of necroptosis can lead to abnormal neural connectivity and impaired synaptic pruning, which are believed to contribute to the cognitive and behavioral deficits observed in ASD. Schizophrenia is another neurodevelopmental disorder with a complex etiology involving both genetic and environmental factors. Altered necroptotic signaling has been implicated in the pathogenesis of schizophrenia. Studies have reported aberrant expression of necroptotic proteins in the prefrontal cortex and hippocampus of individuals with schizophrenia. Disrupted synaptic pruning and impaired synaptic plasticity, associated with dysregulated necroptosis, may contribute to the cognitive and perceptual abnormalities observed in this disorder. Intellectual disability (ID) encompasses a range of cognitive impairments and is often characterized by deficits in intellectual functioning and adaptive behavior. Dysregulated necroptosis has also been associated with ID. Increased expression of RIPK1 and enhanced necroptotic signaling has been observed in the brains of individuals with ID. Excessive necroptosis-induced neuronal death and impaired synaptic plasticity are potential mechanisms underlying the cognitive deficits seen in this disorder [2].

Necroptosis is a programmed form of necrosis, traditionally considered an unregulated and accidental type of cell death. Unlike apoptosis, which is characterized by controlled cell death, necroptosis involves a tightly regulated series of molecular events, primarily orchestrated by the activation of receptor-interacting protein kinases (RIPKs) and mixed lineage kinase domain-like protein (MLKL). Necroptosis has gained attention in recent years due to its emerging significance in various pathological conditions, including neurodegenerative disorders and now neurodevelopmental disorders [3].

Several lines of evidence suggest that dysregulation of necroptotic signaling pathways can contribute to the development of neurodevelopmental disorders. Studies have highlighted the involvement of necroptosis in various key processes during brain development, such as neural progenitor cell proliferation, neuronal migration, synaptogenesis, and synaptic pruning. Dysregulation of necroptosis during these critical stages can lead to abnormal neuronal connectivity, disrupted circuitry, and impaired brain development. Autism Spectrum Disorders (ASD): ASD is a complex neurodevelopmental disorder characterized by social and communication deficits. Recent studies have identified dysregulated necroptotic signaling in ASD patients, with increased levels of RIPK3 and MLKL observed in the brains of affected individuals. Excessive necroptosis in neural progenitor cells and disrupted neuronal migration may contribute to the aberrant brain connectivity observed in ASD [4].

Schizophrenia is a chronic mental disorder involving disturbances in perception, cognition, and social functioning. Abnormal necroptotic signaling has been implicated in the pathogenesis of schizophrenia. Altered expression of necroptotic proteins in the prefrontal cortex and hippocampus may disrupt synaptic pruning and contribute to the synaptic abnormalities observed in schizophrenia. Intellectual disability encompasses a range of cognitive impairments. Dysregulated necroptosis has been associated with ID, with studies indicating increased RIPK1 expression and enhanced necroptotic signaling in the brains of affected individuals.

***Correspondence to:** Hazzle Scarlet, Department of Neurosciences, Central south university, China, E-mail: scarleth@csu.edu.cn

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Necroptosis-induced neuronal death and impaired synaptic plasticity may underlie the cognitive deficits observed in ID .

The growing recognition of necroptosis involvement in neurodevelopmental disorders opens up new avenues for therapeutic interventions. Targeting necroptotic signaling pathways may provide potential treatment options to modulate disease progression. Several experimental approaches have shown promise in preclinical studies, including the use of RIPK inhibitors and MLKL-targeting agents. By inhibiting necroptosis, it may be possible to prevent neuronal death, preserve neuronal connectivity, and potentially ameliorate the cognitive and behavioral deficits associated with neurodevelopmental disorders [5].

Conclusion

The role of necroptosis in neurodevelopmental disorders represents an exciting frontier in the field of neuroscience. Understanding the intricate mechanisms underlying necroptotic signaling during brain development will provide crucial insights into the pathogenesis of these disorders. Furthermore, the identification of novel therapeutic targets within the necroptotic pathway may pave the way for the development of innovative treatments, offering hope for individuals affected by neurodevelopmental disorders and their families. Continued research and collaboration across disciplines are vital in unraveling the complex interplay between necroptosis and neurodevelopment, ultimately leading to improved diagnostic tools and effective therapeutic strategies.

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