

Necroptosis: a regulated cell death pathway and potential therapeutic target in neurodegenerative disorders

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This article may be cited as: Qadir H, Ikram M, Jahan S. Necroptosis: a regulated cell death pathway and potential therapeutic target in neurodegenerative disorders. *Int J Pathol*; 24(3):250-2: DOI: <https://doi.org/10.59736/IJP.24.03.1146>

Necroptosis is a form of regulated cell death characterized by specific morphological and biochemical features, including plasma membrane rupture, organelle swelling, nuclear and cytoplasmic disintegration, leakage of intracellular contents, and the release of damage-associated molecular patterns (DAMPs) that promote inflammatory responses. Increasing evidence indicates that necroptosis contributes to the pathogenesis and progression of a wide range of pathological conditions, including organ injuries and inflammatory disorders (1).

Unlike conventional forms of cell death, necroptosis represents a distinct programmed cell death pathway that shares characteristics with both apoptosis and necrosis (2). Apoptosis is a regulated form of programmed cell death in which activated caspase proteases cleave specific cellular substrates, leading to the orderly elimination of damaged or unwanted cells. These events produce a highly organized and controlled process of cellular degradation. Necrosis has been regarded as a passive and non-regulated form of cell death resulting from direct cellular injury and pathological trauma; this type of cellular death is typically associated with disruption of the plasma membrane, leakage of intracellular

components, and activation of inflammatory responses (3).

Necroptosis combines several properties usually associated with both apoptosis and necrosis. Similar to apoptosis, necroptosis is genetically regulated and requires the participation of specific signaling proteins, with the affected cell actively engaging in a programmed process leading to its own demise. However, similar to necrosis, necroptosis is characterized by increased plasma membrane permeability, cellular rupture, leakage of intracellular contents, and activation of the immune system. Necroptosis is strongly associated with induction of inflammatory responses and may produce physiological and pathological consequences (4, 5).

As necroptosis has both physiological and pathological functions, it could be considered a “double-edged sword”; on one hand, excessive or dysregulated necroptosis can initiate uncontrolled inflammatory cascades, leading to severe tissue injury, persistent disease, and in some pathological states, tumor progression. On the other hand, necroptosis serves important protective functions, particularly in host defense by contributing to antimicrobial and antitumor responses through its potent pro-inflammatory activity. In addition,

necroptosis has been implicated in physiological processes such as development and tissue regeneration. A comprehensive understanding of these multifaceted functions is therefore essential for the development of therapeutic strategies aimed at modulating necroptotic signaling (6, 7).

At the molecular level, necroptosis is primarily mediated through the formation and activation of the necrosome, which is a signaling complex involving receptor-interacting serine/threonine-protein kinase 1 (RIPK1) and receptor-interacting serine/threonine-protein kinase 3 (RIPK3), followed by phosphorylation and activation of mixed lineage kinase domain-like protein (MLKL). Activation of death and pattern recognition receptors, including tumor necrosis factor receptor 1 (TNFR1), Fas, and Toll-like receptor 4 (TLR4), by their respective ligands can facilitate the activation of necroptotic signaling. Inflammatory stimuli are major inducers of the canonical necroptosis pathway, particularly under conditions in which apoptotic signaling is impaired (8, 9).

Through the promotion of acute and chronic inflammatory responses, necroptosis has been implicated in many human diseases. The phosphorylation of RIPK3 and MLKL has been detected in the airways of patients with chronic obstructive pulmonary disease (COPD). Similarly, increased expression of activated RIPK3 and MLKL, together with enhanced hepatocyte cell death, has been observed in patients with non-alcoholic fatty liver disease (NAFLD). A potential role for RIPK3 in atherosclerosis has also been reported (10).

The pathological relevance of necroptotic signaling has been investigated across several major neurodegenerative disorders, including Alzheimer's disease (AD),

Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS). Experimental studies have reported alterations in necroptosis-associated signaling in these disorders, while pharmacological modulation of RIPK1 and its downstream effectors, particularly RIPK3 and MLKL, has demonstrated beneficial effects on several disease-associated pathological manifestations in experimental models (11, 12).

Targeting the necroptotic signaling pathway may therefore represent a potential therapeutic approach for diseases associated with excessive or dysregulated necroptosis. Further investigation of the molecular mechanisms governing necroptotic cell death may provide important insights into disease pathogenesis and identify novel opportunities for therapeutic intervention. Because RIPK1, RIPK3, and MLKL are critical steps in the necroptotic signaling cascade, modulation of these molecular components represents a potential strategy for controlling pathologies. Inhibitors targeting components of the necroptotic pathway may have the potential to attenuate disease-associated tissue injury and improve pathological outcomes in selected disease conditions (3).

A comprehensive understanding of regulation of RIPK1, RIPK3 and MLKL signaling, together with development of pharmacological inhibitors, may facilitate the identification of novel therapeutic opportunities for attenuation of neurological disorders. Further investigation of this pathway is therefore needed to determine whether modulation of necroptosis can effectively attenuate neuronal injury and associated inflammatory responses and to establish its potential as a therapeutic target in currently difficult-to-treat neurological disorders.

References

1. Zhu T, Wu BW. Recognition of necroptosis: from molecular mechanisms to detection methods. *Biomed Pharmacother.* 2024;178:117196.
2. Tang J, Zhuang Y, Zhang Y, Hu H, Wang H, Xu H, et al. Necroptosis in cancer: insight from epigenetic, post-transcriptional and post-translational modifications. *J Hematol Oncol.* 2025;18(1):77.
3. Chaouhan HS, Vinod C, Mahapatra N, Yu SH, Wang IK, Chen KB, et al. Necroptosis: a pathogenic negotiator in human diseases. *Int J Mol Sci.* 2022;23(21):12714.
4. Morgan MJ, Kim YS. Roles of RIPK3 in necroptosis, cell signaling, and disease. *Exp Mol Med.* 2022;54(10):1695-704.
5. Mahnoor, Jahan S, Elahi L, Zakria M, Rabia, Ikram M, Ullah N. Alpha-linolenic acid for mitigating neuroinflammation and dopaminergic neuronal loss in Parkinson's disease: insights from in vivo and in silico studies. *Clin Exp Pharmacol Physiol.* 2025;52. doi.org/10.1111/1440-1681.70043
6. Jahan S, Ikram M, Khan Z. Beyond the brain: the peripheral revolution in neurodegenerative diseases. *Int J Pathol.* 2024;24(2):80-2. doi:10.59736/IJP.24.02.1100.
7. Ye K, Chen Z, Xu Y. The double-edged functions of necroptosis. *Cell Death Dis.* 2023;14(2):163.
8. Balusu S, De Strooper B. The necroptosis cell death pathway drives neurodegeneration in Alzheimer's disease. *Acta Neuropathol.* 2024;147(1):96.
9. Yang M, Chen W, He L, Liu D, Zhao L, Wang X. A glimpse of necroptosis and diseases. *Biomed Pharmacother.* 2022;156:113925.
10. Kang K, Park C, Chan FK-M. Necroptosis at a glance. *J Cell Sci.* 2022;135(17). doi:10.1242/jcs.260091.
11. Kang A, Qiao Y, Pan S, Yan F, Chen H, Bai Y. From RIPK1 to necroptosis: pathogenic mechanisms in neurodegenerative diseases. *Neurochem Res.* 2025;50(3):194.
12. Jahan S, Ikram M, Siraj S, Ullah S, Zakria M, Ahmad N. Emodin, a potent anthraquinone mitigates MPTP-induced Parkinson's disease pathology by regulating Nrf2 and its downstream targets: in silico and in vivo approach. *Mol Neurobiol.* 2025; 62:8103-20. doi.org/10.1007/s12035-025-04762-3.