Axonal degeneration induced by glutamate excitotoxicity is mediated by necroptosis

Hernández, D. E., Salvadores, N. A., Moya-Alvarado, G., Catalán, R. J., & Bronfman, F. C. (2018). Axonal degeneration induced by glutamate excitotoxicity is mediated by necroptosis. Journal of cell science, 131(22). <10.1242/jcs.214684> Accessed 24 Feb 2021.

Abstract

Neuronal excitotoxicity induced by glutamate leads to cell death and functional impairment in a variety of central nervous system pathologies. Glutamate-mediated excitotoxicity triggers neuronal apoptosis in the cell soma as well as degeneration of axons and dendrites by a process associated with Ca2+ increase and mitochondrial dysfunction. Importantly, degeneration of axons initiated by diverse stimuli, including excitotoxicity, has been proposed as an important pathological event leading to functional impairment in neurodegenerative conditions. Here, we demonstrate that excitotoxicity-induced axonal degeneration proceeds by a mechanism dependent on the necroptotic kinases RIPK1 and RIPK3, and the necroptotic mediator MLKL. Inhibition of RIPK1, RIPK3 or MLKL prevents key steps in the axonal degeneration cascade, including mitochondrial depolarization, the opening of the permeability transition pore and Ca2+ dysregulation in the axon. Interestingly, the same excitotoxic stimuli lead to apoptosis in the cell soma, demonstrating the co-activation of two independent degenerative mechanisms in different compartments of the same cell. The identification of necroptosis as a key mechanism of axonal degeneration after excitotoxicity is an important initial step in the development of novel therapeutic strategies for nervous system disorders..

Keywords

Neurodegeneration, Axonal degeneration, Excitotoxicity, Necroptosis.