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🌐 Protocols for "Mitochondrial Anchored Protein Ligase MAPL is an inflammatory rheostat that regulates immune signalling and cell death"

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Abstract

Cell death is inhibited in cancers but increased in neurodegeneration, highlighting that its regulation is essential for human health. MAPL is an outer mitochondrial membrane SUMO ligase with roles in cancer and neurodegeneration *in vivo*, yet how MAPL controls cell death remains unclear. Combining genome-wide screening and cell biological approaches, we found that MAPL induces pyroptosis through an inflammatory pathway involving mitochondria and lysosomes. MAPL overexpression promotes mitochondrial DNA (mtDNA) trafficking in mitochondrial-derived vesicles (MDVs) to lysosomes, which are permeabilised in a process requiring gasdermin pores. This triggers release of mtDNA into cytosol, activating the DNA sensor cGAS, which is required for cell death. Additionally, multiple Parkinson's disease-related genes, including VPS35 and LRRK2, also regulate MAPL-induced pyroptosis. Consistent with our findings, genetic deletion of MAPL, LRRK2 or VPS35 inhibited inflammatory cell death in primary macrophages, placing MAPL and the mitochondria to lysosome pathway at the nexus of immune signalling and cell death.

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Protocol

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