

Restricting Cell Death Through Generation of Extracellular Vesicles

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Activation of the pseudokinase Mixed Lineage Kinase Domain-Like (MLKL) by proinflammatory ligands such as TNF triggers necroptosis, a form of programmed cell death in which rupture of cellular membranes yields release of components that are potentially pro-inflammatory. Such activation occurs upon phosphorylation of MLKL by the protein kinase RIPK3. We found that MLKL also controls transport of endocytosed proteins, thereby enhancing degradation of receptors and ligands, modulating their induced signaling, and facilitating generation of extracellular vesicles. This role is exerted on two quantitative levels: a constitutive one independent of RIPK3, and an enhancement triggered by RIPK3. RIPK3 activation induces, prior to any sign of death, association of MLKL with ESCRT proteins and the flotillins, and exclusion of phospho-MLKL from cells within vesicles in association with these proteins. We suggest that release of phosphorylated MLKL within extracellular vesicles serves as a mechanism for self-restricting the necroptotic activity of this protein. It seems to further serve to convert the signaling for necroptosis, a form of death believed to initiate inflammation through release of damage-associated molecular-patterns through the ruptured membranes of the dying cells, to a non-deadly form of intercellular delivery of inflammatory mediators.