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CELL DEATH

ESCRTing dying cells back to life

Necroptosis is a form of programmed cell death that is induced by various stresses, whereby receptor-interacting Ser/Thr protein kinase 3 (RIPK3) phosphorylates mixed lineage kinase-like protein (MLKL). Phosphorylated MLKL then translocates to the plasma membrane and induces its permeabilization, leading to cell rupture. Gong *et al.* now show that MLKL phosphorylation does not signify an absolute commitment to cell death and that the components of a membrane scission complex — endosomal sorting complex required for transport III (ESCRT-III) — act to maintain membrane integrity on initiation of necroptosis, thereby counteracting cell rupture and death.

> “ESCRT-III counteracts the loss of membrane integrity”

The authors observed that cultured mammalian cells in which necroptosis had been induced by the enforced dimerization of either RIPK3 or MLKL released vesicle-like particles from their plasma membrane. These structures most likely represent broken membranes that are shed from the cell surface, as they were not intact and were devoid of cytoplasmic content. The release of these ‘vesicles’ was dependent on the presence of the ESCRT-III components charged multivesicular body protein 4B (CHMP4B) and CHMP2A.

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Silencing of *CHMP4B* expression sensitized cells to necroptosis and induced cell death even in conditions that normally do not considerably impair cell fitness. In addition, deficiency of ESCRT-III components was found to reduce the amount of time between the activation of MLKL and membrane permeabilization. This indicated that ESCRT-III counteracts the loss of membrane integrity, most likely by its previously demonstrated ability to seal and repair membrane damage.

In their experimental setup, the authors were able to prevent further progression of necroptosis by washout of the dimerizing agent. Interestingly, they observed that, after washout, a substantial percentage of cells (reaching 75%) recovered from necroptosis — they showed normal morphology and the ability to proliferate both *in vitro* and *in vivo* in tumour formation assays in mice. Importantly, *CHMP2A* or *CHMP4B* silencing impaired this ‘cell resuscitation’, indicating that ESCRT-III can counteract necroptotic cell rupture and preserve cell viability.

Cells that recovered from necroptosis showed increased expression of ESCRT-III components. Furthermore, analysis of human and murine kidney samples revealed that, upon stress such as human tissue transplantation or murine ischaemia–reperfusion injury, expression of ESCRT-III components was elevated in these cells, suggesting that ESCRT-III confers resistance to necroptotic cell death, allowing cell survival under stress conditions.

The presence of ESCRT-III was also important for the release of cytokines by cells undergoing necroptotic cell death and for the proper activation of the immune system by dying cells. This suggests that, by delaying cell rupture, ESCRT-III augments the expression and processing of immunomodulators in cells that are destined to die, in order to support cell–cell communication. In sum, the study identified ESCRT-III as an important regulator of necroptosis, which modulates the outcome of this mode of programmed cell death.

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ORIGINAL ARTICLE Gong, Y.-N. *et al.* ESCRT-III acts downstream of MLKL to regulate necroptotic cell death and its consequences. *Cell* **169**, 286–300 (2017)

FURTHER READING Weinlich R. *et al.* Necroptosis in development, inflammation and disease. *Nat. Rev. Mol. Cell Biol.* **18**, 127–136 (2017)