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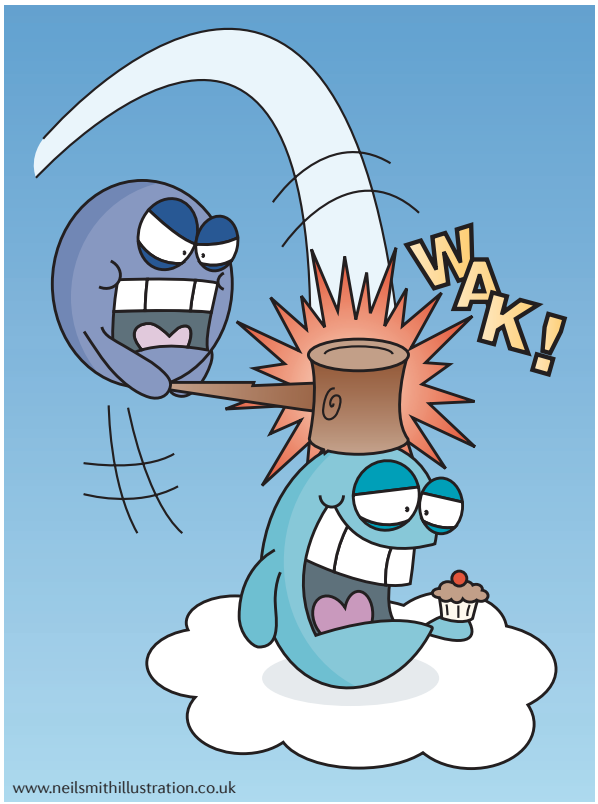
CELL DEATH

A killer puts a stop on necroptosis

> caspase 8 and FADD promote survival by suppressing the function of RIPK3 and RIPK1, and therefore necroptosis, during development.

During the extrinsic apoptotic pathway, activated death receptors recruit the adaptor protein FAS-associated death domain protein (FADD), which recruits and activates caspase 8 to initiate apoptosis. This pathway can be blocked by FLICE-like inhibitory protein long ($FLIP_L$). Despite their role in cell death, FADD, caspase 8 and $FLIP_L$ are all essential for embryonic development, suggesting that they also have a pro-survival role, but the mechanism behind this has been unclear. Three studies in *Nature* now show that these proteins inhibit an alternative programmed cell death pathway, necroptosis, during development.

In some cases, necroptosis can be initiated by receptor-interacting Ser/Thr protein kinase 1 (RIPK1) and RIPK3 in response to the activation of death receptors. The authors of these studies sought to determine whether interplay between apoptosis and necroptosis results in the embryonic lethality caused by loss of caspase 8 or FADD. Oberst *et al.* and Kaiser *et al.* generated mice lacking caspase 8 and RIPK3. Unlike caspase 8-deficient mice, these double-knockout mice were viable. Zhang *et al.* generated mice lacking FADD and RIPK1, which were also viable; double-knockout embryos were comparable to control embryos. These data indicate that FADD and caspase 8 promote survival by suppressing the function of RIPK1 and RIPK3, and therefore necroptosis, during development.



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Lethality in caspase 8-null embryos coincides with haematopoietic defects, and the conditional knockout of FADD impairs lymphocyte proliferation. Oberst *et al.* and Kaiser *et al.* found that the proliferation of T cells was normal in young mice lacking caspase 8 and RIPK3. However, older double-knockout mice accumulated abnormal T cells, perhaps owing to the fact that cell types isolated from these mice were resistant to death receptor-induced apoptosis and/or RIPK3-dependent necroptosis. This suggests that, although caspase 8 is not needed for embryonic development in the absence of RIPK3, it contributes to homeostasis in the adult immune system. Zhang *et al.* found that RIPK1 deficiency restored the proliferation of FADD-null T cells, but not FADD-null B cells, suggesting that FADD might inhibit RIPK1-mediated necroptosis in a cell-type-specific manner.

Oberst *et al.* also investigated how caspase 8 might inhibit RIPK3-mediated necroptosis. They found that caspase 8 and $FLIP_L$ are both required to block RIPK3-dependent cell death, and that $FLIP_L$ also prevents caspase 8 from triggering apoptosis in this setting. Furthermore, caspase 8 inhibits the association of FADD, RIPK1 and RIPK3, and thus prevents necroptosis, only when it forms a heterodimer with $FLIP_L$.

Together, these studies show that FADD–caspase 8-mediated apoptosis inhibits RIPK1- and RIPK3-dependent necroptosis during development, and in particular in the development of the immune system.

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ORIGINAL RESEARCH PAPERS Oberst, A. *et al.* Catalytic activity of the caspase-8–$FLIP_L$ complex inhibits RIPK3-dependent necrosis. *Nature* **471**, 363–367 (2011) | Kaiser, W. J. *et al.* RIP3 mediates the embryonic lethality of caspase-8-deficient mice. *Nature* **471**, 368–372 (2011) | Zhang, H. *et al.* Functional complementation between FADD and RIP1 in embryos and lymphocytes. *Nature* **471**, 373–376 (2011)

FURTHER READING Vandenabeele, P. *et al.* Molecular mechanisms of necroptosis: an ordered cellular explosion. *Nature Rev. Mol. Cell Biol.* **11**, 700–714 (2010)

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