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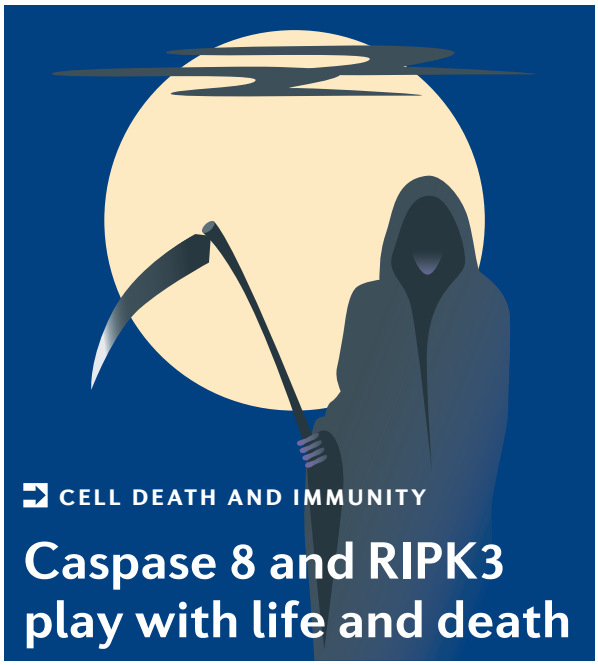

CELL DEATH AND IMMUNITY

Caspase 8 and RIPK3 play with life and death

> caspase 8 is an inhibitor of a necroptosis pathway in T cells that is mediated by RIPK3

Programmed cell death can be mediated by different mechanisms, including apoptosis, autophagy and programmed necrosis (also termed necroptosis). Although caspase 8 initiates T cell apoptosis following death receptor ligation, caspase 8-deficient T cells display decreased survival after stimulation compared with wild-type T cells. A recent study solved this paradox by demonstrating that caspase 8 is an inhibitor of a necroptosis pathway in T cells that is mediated by receptor-interacting serine/threonine protein kinase 3 (RIPK3).

Ch'en *et al.* investigated which mechanism of cell death is responsible for the decreased viability of activated caspase 8-deficient T cells. Cyclophilin D (also known as PPID) is an essential component of the mitochondrial permeability transition pore, which has been suggested to mediate necroptosis. However, T cells deficient for both caspase 8 and cyclophilin D still exhibited decreased survival *in vitro* and impaired population expansion in response to viral infection *in vivo*. This suggests that cell death induced in activated caspase 8-deficient T cells does not rely on cyclophilin D-mediated necroptosis.

So, is autophagy responsible for the decreased viability of activated caspase 8-deficient T cells? Inhibition of autophagy in activated T cells resulted in enhanced apoptosis, presumably owing to an increase in mitochondrial numbers. Moreover, the survival of activated T cells lacking both caspase 8 and autophagy-related protein 7 (ATG7) was even more impaired than the survival of caspase 8-deficient T cells. Although addition of the necroptosis inhibitor necrostatin 1 promoted expansion of caspase 8-deficient T cell populations following activation, it had only a partial effect on T cells deficient for both caspase 8 and ATG7. These results indicate that the decreased survival of caspase 8-deficient T cells is mediated by a necroptosis mechanism that is independent of autophagy-induced cell death.

Necroptosis was previously suggested to be initiated by a complex of RIPK1 and RIPK3. Indeed, deletion of *Ripk3* led to increased survival of activated caspase 8-deficient T cells. Moreover, following viral infection, T cells deficient for both caspase 8 and RIPK3 showed population expansion that was comparable to that of control T cells. These results demonstrate that caspase 8 inhibits RIPK3-mediated necroptosis. Interestingly, mice with T cells that lack both caspase 8 and RIPK3 develop a lymphoproliferative disorder over time, suggesting that both caspase 8-mediated apoptosis and RIPK3-mediated necroptosis are crucial for the control of T cell homeostasis.

These findings are in accordance with three recently published *Nature* papers, which demonstrated suppression of RIPK-mediated necroptosis by caspase 8, as well as by FAS-associated death domain protein (FADD) and the long splice variant of FLICE-like inhibitory protein ($FLIP_L$), during embryonic development and T cell proliferation.

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ORIGINAL RESEARCH PAPER Ch'en, I. L. *et al.* Mechanisms of necroptosis in T cells. *J. Exp. Med.* 14 March 2011 (doi:10.1084/jem.20110251)
FURTHER READING Kaiser, W. J. *et al.* RIP3 mediates the embryonic lethality of caspase-8-deficient mice. *Nature* **471**, 368–372 (2011) | Oberst, A *et al.* Catalytic activity of the caspase-8–$FLIP_L$ complex inhibits RIPK3-dependent necrosis. *Nature* **471**, 363–367 (2011) | Zhang, H *et al.* Functional complementation between FADD and RIP1 in embryos and lymphocytes. *Nature* **471**, 373–376 (2011)