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A new platform for death

Recent studies have highlighted the intricate relationship between apoptotic and necroptotic cell death, although the molecular details of this were incomplete. Two groups now identify a ~2 MDa signalling platform, which they term the 'Ripoptosome', that activates both cell death pathways.

The extrinsic apoptosis pathway is mediated by death receptors, such as tumour necrosis factor receptor 1 (TNFR1). Although activated TNFR1 initially forms complex I, which activates nuclear factor-κB (NF-κB) signalling, TNFR1 internalization leads to the formation of complex II, which triggers apoptosis or necroptosis. Complex II includes caspase 8, the kinases receptor-interacting protein 1 (RIP1) and RIP3 and the adaptor proteins FAS-associated DEATH domain (FADD) and TNFR1-associated DEATH domain (TRADD). Caspase 8 activity is negatively regulated by FLICE-inhibitory protein long ($FLIP_L$), FLIP short ($FLIP_S$), cellular inhibitor of apoptosis 1 (cIAP1) and cIAP2.

Feoktistova *et al*. asked whether IAPs influence Toll-like receptor 3 (TLR3)-mediated cell death. Depletion of IAPs promoted TLR3-induced cell death in response to the artificial ligand poly(I:C) in certain cell lines, suggesting that IAPs normally inhibit this process. But, which proteins are responsible for this cell death? The authors immunoprecipitated caspase 8 from cells following TLR3 stimulation and IAP depletion and identified a complex containing RIP1, FADD, FLIP isoforms and caspase 10, which they termed the Ripoptosome. Upon TLR3 ligation, the Ripoptosome is recruited to the TLR3 adaptor TRIF.

Tenev *et al*. were interested in how genotoxic stress kills cancer cells and sought to determine whether the depletion of cIAP1, cIAP2 and X chromosome-linked IAP (XIAP) by the chemotherapeutic agent etoposide contributes to cell death. Etoposide triggered caspase 8 activation and stimulated caspase 8–RIP1 binding. Importantly, as formation of the caspase 8–RIP1 complex was independent of TNFR1 (an observation also made by Feoktistova *et al*.), Tenev *et al*. proposed that this complex, the Ripoptosome, was different from complex II. Tenev *et al*. found that the Ripoptosome also contained FADD, and that cIAPs inhibit the Ripoptosome by targeting components of this complex, including RIP1, for ubiquitylation-mediated inactivation.

Looking at the Ripoptosome in more detail, both groups found that cell death could be only blocked by co-treating cells with inhibitors against caspases and RIP1 kinase, indicating that the Ripoptosome can trigger apoptosis and necroptosis. They also found that RIP1 kinase activity is necessary for the formation and activation of the Ripoptosome, which also contains, and is negatively regulated by, $FLIP_L$. In addition, Feoktistova *et al*. found that, in contrast to $FLIP_L$, $FLIP_S$ promoted Ripoptosome formation and seemed to push the Ripoptosome towards RIP3-dependent necroptosis.

In conclusion, these important studies have identified a new signalling platform for apoptosis and necroptosis, which forms in the absence of IAPs and is subject to opposing regulation by different FLIP isoforms.

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