How cells choose the way to die: caspase-8-dependent switch of apoptosis to necroptosis and pyroptosis

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Caspase-8 determines the selection of cell death pathway. It is well known that inactivation of caspase-8 suppresses apoptosis and prompts necroptosis. Recent studies further reveal that caspase-8 activity dictates the switch of cell death to pyroptosis when apoptosis and necroptosis are blocked, a critical step with unknown mechanism. In the first part of this talk, we will briefly describe how necroptosis is modulated by promyelocytic leukemia protein (PML). PML binds MAPK activated kinase 2 (MK2) and p38 MAPK, thereby inhibiting p38-MK2 interaction and MK2 activation, leading to reduced attenuated receptor-interacting protein kinase 1 (RIPK1) activation and enhanced necrosome complex formation, representing a novel tumor suppressive activity for PML. In the second part, we will discuss how caspase-8 inactivation, together with necroptosis blockade, initiates pyroptosis in myeloid cells. We show that caspase-8 inhibition via IETD treatment in Toll-like receptor (TLR)-primed *Fadd*$^{-/-}$ *Ripk3*$^{-/-}$ myeloid cells promoted inflammasome activation and pyroptosis induction. Caspase-8, caspase-1/11 and functional Gasdermin D (GSDMD), but not NLRP3 or RIPK1 activity, proved essential for caspase-8-inactivation-triggered inflammasome activation. Autophagy became prominent in these myeloid cells, followed by cathepsin-B activation, and inhibiting autophagy or cathepsin-B limited inflammasome activation and pyroptosis. Therefore, the switch to autophagy and cathepsin-B axis turns on atypical inflammasome activation in myeloid cells deficient in apoptosis and necroptosis, unveiling a new stage for pyroptosis generation during development and pathogen infection.