

Pyroptosis, inflammation and antitumor immunity

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Pyroptosis is a highly proinflammatory form of cell death executed by a newly identified family of pore-forming proteins known as gasdermins, including gasdermin A to E. Among the family, gasdermin D (GSDMD) is cleaved by inflammasome-activated caspase-1 and LPS-activated caspase-11/4/5. The cleavage unmasks the pore-forming domain from GSDMD-C terminal domain. We found that site-specific caspase-4/11 autoprocessing, generating a p10 product, is required and sufficient for cleaving GSDMD and inducing pyroptosis. The p10-form autoprocessed caspase-4/11 bind the GSDMD-C domain with a high affinity. Structural comparison of autoprocessed and unprocessed caspase-11 identifies a β -sheet induced by the autoprocessing. In caspase-4/11-GSDMD-C complex crystal structures, the β -sheet organizes a hydrophobic GSDMD-binding interface that is only possible for p10-form caspase-4/11. The binding promotes dimerization-mediated caspase activation, rendering a cleavage independently of the cleavage-site tetrapeptide sequence. Crystal structure of caspase-1-GSDMD-C complex shows a similar GSDMD-recognition mode, further highlighting this unprecedented substrate-targeting mechanism for caspases. To probe the effect of pyroptosis on antitumour immunity, we used a bioorthogonal system—a cell-enterable cancer-imaging probe phenylalanine trifluoroborate (Phe-BF₃) desilylates and “cleaves” a silyl ether-containing linker, which allowed controlled release of an active gasdermin from nanoparticulate conjugates (NPs) specifically into tumors in mice. We found that pyroptosis of < 15% tumour cells was sufficient to clear the entire 4T1 mammary tumourgraft. The tumour regression was absent in immune-deficient mice or upon T-cell depletion. A reduced ineffective dosage of NP-gasdermin+Phe-BF₃ injection sensitized 4T1 tumours to anti-PD1 therapy. Thus, pyroptosis-induced inflammation triggers robust antitumour immunity and can synergize with the checkpoint blockade.