Catching fire: inflammatory responses mediated by inflammasomes, caspases, and gasdermins

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The inflammasome signaling pathways are activated by infections and sterile stimulation, which lead to the maturation of inflammatory caspases that promote the secretion of inflammatory cytokines such as IL-1β and IL-18. The recognition and cleavage of the gasdermin family members by caspases trigger the activation of their pore-forming activities that lead to pyroptotic cell death. A prominent example is the targeting of gasdermin D (GSDMD) by inflammatory caspases-1/4/5/11 as an essential step in initiating pyroptosis following inflammasome activation. Previous work has identified cleavage site signatures in caspase substrates such as GSDMD and inflammatory cytokines, but it is unclear if these are the sole determinants for caspase engagement. Here we describe structural studies of a complex between caspase-1 (CASP1) and the full-length GSDMD, which reveals that the cleavage site-containing linker in GSDMD adopts a long loop structure that engages the CASP1 active site. In addition, an exosite is observed between the caspase-1 L2 and L2' loops and a hydrophobic pocket within the GSDMD C-terminal domain distal to its N-terminal domain. The exosites endows a novel function for the GSDMD C-terminal domain as a caspase-recruitment module, in addition to its role in autoinhibition. The dual site recognition may allow stringent substrate selectivity while facilitating efficient cleavage and pyroptosis upon inflammasome activation. Such mode of tertiary structure recognition may be applicable to other physiological substrates of caspases.

Keywords: inflammasome; caspase; gasdermin

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