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INFLAMMATION

Cryopyrin — another guise of death

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A new report in *Cell Host & Microbe* identifies the protein cryopyrin (also known as NLRP3, NALP3 or CIAS1) as an important host mediator of a type of pathogen-induced necrotic-like cell death.

Cryopyrin is a member of a family of NLR (nucleotide-binding domain, leucine-rich-repeat-containing family) proteins, which are also known as nucleotide-binding oligomerization domain (NOD)-like receptors or CATERPILLER proteins. It is part of a cytosolic protein complex called the inflammasome, which also includes ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain (CARD); also known as PYCARD, TMS1 or CARD5) and which is responsible for processing caspase-1 to its active form; this, in turn, leads to the production of mature interleukin-1β (IL-1β), a potent pro-inflammatory cytokine, in response to bacterial, viral and other pro-inflammatory stimuli. But might cryopyrin have additional biological functions in the containment of pathogens? Macrophages deficient in cryopyrin are more resistant to cell death induced by certain Gram-positive bacteria, suggesting that cryopyrin can participate in the initiation of necrosis, but the nature of this involvement has not been defined.

Mutations in *CIAS1*, the gene that encodes cryopyrin, are associated with autoinflammatory periodic-fever syndromes, which are characterized by excessive production of IL-1β. The authors first confirmed that the presence of the disease-associated mutations in *CIAS1* results in necrosis-like cell death in a monocytic cell line, then examined the mechanism by which cell death is induced. Cells that expressed the mutant cryopyrin released substantially more IL-1β than cells that expressed wild-type cryopyrin, however, cell death was shown to occur independently of caspase-1 activity and IL-1β-mediated signalling (and thus independent of inflammasome formation). Cell death induced by the mutant cryopyrin was also shown to be ASC dependent, and resulted in the release of high-mobility group box 1 (HMGB1), a protein that acts as a potent pro-inflammatory factor when released from cells that are undergoing necrosis. Similarly, excessive cell death was shown in monocytes from patients with disease-associated *CIAS1* mutations, in response to lipopolysaccharide challenge, by a process that was dependent on ASC and cathepsin B, and which resulted in the production of HMGB1.

Because disease-associated cryopyrin mutants are considered to be gain-of-function mutants, wild-type cryopyrin should exhibit similar properties to mutant cryopyrin, but at a reduced level or following stimulation. The authors thus considered whether wild-type cryopyrin has a role in cell necrosis that is associated with bacterial pathogenesis — specifically, with the intracellular bacterium *Shigella flexneri*, which is thought to induce necrosis-like cell death. *S. flexneri*-induced necrosis of mouse macrophages was shown to require cryopyrin and ASC, but not caspase-1. It was also independent of IL-1β and was associated with the release of HMGB1. Therefore, *S. flexneri*-induced cell death exploits the same host cell signalling pathway as is induced by disease-associated cryopyrin.

So, *S. flexneri* infection of monocytes induces a caspase-1-independent and ASC- and cryopyrin-dependent form of necrotic cell death, which the authors called pyronecrosis, that is identical to that induced by disease-associated cryopyrin. This suggests that the inflammatory response that is normally stimulated by pathogenic bacteria is propagated in patients with gain-of-function *CIAS1* mutations.

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ORIGINAL RESEARCH PAPER Willingham, S. B. *et al.* Microbial pathogen-induced necrotic cell death mediated by inflammasome components CIAS1/cryopyrin/NLRP3 and ASC . *Cell Host Microbe* **2**, 147–159 (2007)