Nature Reviews Immunology | AOP, published online 9 March 2012; doi:10.1038/nri3195

INNATE IMMUNITY

Linking mitochondria and microbes to inflammasomes

Two recent studies published in *Immunity* further our understanding of the mechanisms of inflammasome activation. Khare *et al.* define the role of microbial lipopeptides in the activation of the NLRP7 (NOD-, LRR- and pyrin domain-containing 7) inflammasome in human macrophages. Shimada *et al.* implicate oxidized mitochondrial DNA as the link between apoptosis and NLRP3 inflammasome activation.

Inflammasomes are protein scaffolds that assemble in response to pathogens or stress signals and promote the release of the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18. IL-1β release has been shown to be induced by acylated lipopeptides, which are potent immune stimulatory pathogen-associated molecular patterns (PAMPs) and are the main *Mycoplasma* spp. PAMPs that cause macrophage activation. However, the mechanism of inflammasome activation was not known. Khare *et al.* showed that treatment of human macrophages with live or heat-killed *Mycoplasma* spp. caused a redistribution of the inflammasome component ASC from the nucleus to the cytosol and the secretion of mature IL-1β. Moreover, microbial acylated lipopeptides were sufficient to cause these effects.

Using small interfering RNAs to silence the expression of individual NLRPs, NLRP7 was found to be specifically involved in sensing microbial acylated lipopeptides and inducing IL-1β secretion through inflammasome formation. However, NLRP7-induced IL-1β secretion required an independent priming step that was mediated by Toll-like receptor 2, which also senses acylated lipopeptides and induces the transcription of *IL1B* in a nuclear factor-κB-dependent manner. Experiments using an inflammasome reconstitution system confirmed that NLRP7, ASC and caspase 1 are sufficient for the inflammasome response to *Mycoplasma* spp. and acylated lipopeptides. The leucine-rich repeats of NLRP7 seem to be necessary for this activity, although the authors were unable to observe a direct interaction between NLRP7 and lipopeptides. Importantly, the NLRP7 inflammasome response was shown to restrict the replication of intracellular bacteria, identifying a new role for NLRP7 in host defence.

For the NLRP3 inflammasome, three models of activation have been proposed: reactive oxygen species (ROS) generation, lysosomal damage and cytosolic potassium ion (K^+) efflux. Findings by Shimada *et al.* suggest that these events are all associated with mitochondrial dysfunction, which triggers apoptosis and NLRP3 inflammasome activation. In support of this, they show that activation of NLRP3 during *Chlamydia pneumoniae* infection was associated with the release of lactate dehydrogenase, decreased mitochondrial membrane potential and nuclear condensation (which are markers of apoptosis). In addition, treatment of bone marrow-derived macrophages (BMDMs) with the mitochondrial inhibitor cyclosporin A attenuated IL-1β secretion in response to lipopolysaccharide (LPS) and ATP. Exposure of BMDMs to high extracellular K^+ concentrations also blocked IL-1β secretion and protected from apoptosis. Pro-apoptotic stimuli activated caspase 1 and induced IL-1β secretion via the NLRP3 inflammasome, but only when given after priming with LPS. Finally, overexpression of the anti-apoptotic protein BCL-2 abrogated IL-1β maturation triggered by NLRP3-activating stimuli. Together, these findings suggest that, in the presence of a pro-inflammatory signal, NLRP3 inflammasome activation is triggered by mitochondrial apoptotic signalling.

Further investigation revealed that mitochondrial DNA that is released into the cytosol interacts with NLRP3 and activates the NLRP3 inflammasome. Moreover, the finding that oxidized mitochondrial DNA (which is probably generated by mitochondrial ROS during apoptosis) could outcompete normal mitochondrial DNA in the induction of IL-1β secretion suggested that cytosolic oxidized mitochondrial DNA is responsible for activating the NLRP3 inflammasome.

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ORIGINAL RESEARCH PAPERS Khare, S. *et al.* An NLRP7-containing inflammasome mediates recognition of microbial lipopeptides in human macrophages. *Immunity* 23 Feb 2012 (doi:10.1016/j.immuni.2012.02.001) | Shimada, K. *et al.* Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity* 16 Feb 2012 (doi:10.1016/j.immuni.2012.01.009)

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