IN BRIEF

INFLAMMATION

Inflammasome-mediated disease animal models reveal roles for innate but not adaptive immunity

Brydges, S. D. *et al. Immunity* 4 Jun 2009 (doi:10.1016/j.immuni.2009.05.005)

A mutation in the *Nlrp3* gene causing inflammasome hyperactivation potentiates Th17 cell-dominant immune responses

Meng, G. *et al. Immunity* 4 Jun 2009 (doi:10.1016/j.immuni.2009.04.012)

Missense mutations in the inflammasome component NLR family, pyrin domain-containing 3 (NLRP3; also known as NALP3) leading to excessive production of interleukin-1β (IL-1β) have been associated with several cryopyrin-associated periodic syndromes (CAPS). Through the generation of gene-targeted mice that express NLRP3 containing various mutations that are similar to those identified in patients with CAPS, these two studies provide insights into the pathogenesis of inflammasome-mediated diseases.

The three mutant mouse strains (two generated by Brydges ***et al.*** and one by Meng ***et al.***) showed varied phenotypes and mortality rates, but all mice developed severe autoinflammation. Both studies showed that activation of *Nlrp3*-mutant but not wild-type antigen-presenting cells (APCs) by low amounts of lipopolysaccharide in the absence of exogenous ATP resulted in high levels of IL-1β secretion, suggesting a lower inflammasome activation threshold. In addition, the autoinflammatory phenotypes were dependent on inflammasome hyperactivation specifically in APCs, and increased IL-1β production had a central, but not exclusive, role in the disease phenotype.

Meng ***et al.*** showed that APCs from mutant mice enhanced T helper 17 (T_H17) cell differentiation but inhibited the differentiation of other T_H cell subsets under polarizing conditions. Moreover, skin inflammation in the mutant mice could be reduced by blocking either IL-1 receptor signalling or IL-17A. By contrast, Brydges ***et al.*** showed that although APCs from their mutant mice could enhance T_H1 and T_H17 cell differentiation under polarizing conditions, a similar disease phenotype was observed if the mutant mice also lacked T cells, suggesting that T cells do not have a central role in CAPS-associated autoinflammation.

ANTIGEN PRESENTATION

IRAP identifies an endosomal compartment required for MHC class I cross-presentation

Saveanu, L. *et al. Science* 4 Jun 2009 (doi:10.1126/science.1172845)

This study identified insulin-regulated aminopeptidase (IRAP) as being involved in the trimming of exogenous peptides for cross-presentation on MHC class I molecules. IRAP was strongly enriched in early phagosomes that express RAB14 — a protein that prevents phagosome fusion with acidic lysosomes, which could be detrimental for cross-presentation — where it colocalized with MHC class I molecules. IRAP-deficient mice presented endogenous MHC class I-restricted antigens normally in a manner dependent on endoplasmic reticulum aminopeptidases (ERAPs), but the cross-presentation of exogenous antigens was inhibited by the absence of both ERAPs and the endosomal peptidase IRAP in an additive manner; ERAP and IRAP are functionally redundant but do not colocalize in the same intracellular compartment. This indicates that there are two parallel pathways for cross-presentation that involve loading of MHC class I molecules in the ER and endosomes.