The metabolic link

In patients with metabolic syndrome, nonalcoholic fatty liver disease can lead to cirrhosis and other hepatic disorders. In *Nature*, Flavell and colleagues show that the NLRP3 and NLRP6 inflammasomes and the effector cytokine IL-18 regulate the progression of nonalcoholic fatty liver disease. Various mouse models show that inflammasome deficiency induces changes in the gut microbiota that are associated with more influx of bacterial products into the portal circulation, activation of the Toll-like receptors TLR5 and TLR9 and enhanced expression of tumor necrosis factor in the liver. The changes in microbiota composition involve over-representation of bacteria of the family Porphyromonadaceae, combined with alterations in organisms of other taxa. Some metabolic aberrations associated with the altered gut microbiota, such as obesity, can be horizontally transferred to other mice. These results demonstrate a complex and cooperative effect of two families of sensors, the NLRs and TLRs, in shaping metabolic events. ***IV***
***Nature* 482, 179–185 (2012)**

Inflammasome caspase

Human caspase-4 and caspase-5 are potential functional orthologs of mouse caspase-11, which is required for activation of caspase-1 in macrophages in response to certain stimuli. In the *Journal of Immunology*, Beer and colleagues show that caspase-4 is required for the activation of caspase-1 by the NLRP3 inflammasome and, in turn, for the maturation of pro-IL-1β. Human epidermis has high expression of caspase-4, and ultraviolet irradiation induces the release of caspase-4. Expression and the enzymatic activity of caspase-4 are required for efficient IL-1β secretion, whereas knockdown of caspase-5 has no effect on the secretion of IL-1β from keratinocytes. Caspase-4 interacts with caspase-1 in these cells but not with pro-IL-1β or with the critical inflammasome adaptor ASC. Caspase-4 is also required for activation of the NLRP3 inflammasome in THP-1 mouse macrophages, which suggests that other cells types might also require caspase-4 for the secretion of IL-1β. *IV*
J. Immunol. **188**, 1992–2000 (2012)

Lipopeptides activate NLRP7

TLR2 can recognize acylated bacterial lipopeptides and trigger the secretion of mature IL-1β. In *Immunity*, Stehlik and colleagues identify NLRP7 as an intracellular sensor of bacterial lipopeptides. Infection with mycoplasma or exposure to acylated lipopeptides triggers the aggregation of ASC, NLRP7 and pro-caspase-1 in inflammasome complexes in human macrophages. Knockdown of either TLR2 or NLRP7 results in less inflammasome activation and secretion of IL-1β and IL-18 in response to acylated lipopeptides, but knockdown of other NLR proteins does not. Neither scavengers of reactive oxygen species (ROS) nor a high potassium concentration, which blunt mitochondrial stress-mediated inflammasome activation, result(s) in less NLRP7 inflammasome activity. These findings suggest that activation of the NLRP7 inflammasome in response to acylated lipopeptides differs from the activation of those containing NLRP3. ***LAD***
***Immunity* (16 February 2012) doi:10.1016/j.immuni.2012.01.009**

Written by Laurie A. Dempsey, Zoltan Fehervari & Ioana Visan

Inflammasome clue to bacterial Rhs

The *rhs* genes are a family of composite genes widespread throughout Gram-negative bacteria, but the functions of the molecules they encode remain largely unknown. In the *Proceedings of the National Academy of Sciences*, Hauser and colleagues attribute an inflammasome-activation role to RhsT from *Pseudomonas aeruginosa*. RhsT is expressed at the bacterial cell surface and is translocated into macrophages during coculture. That translocation results in the death (pyroptosis) of macrophages and is accompanied by more release of IL-1β and IL-18. Transfection of RhsT alone is sufficient to induce pyroptosis. Inhibition of caspase-1 or knockout of ASC demonstrates that pyroptosis and the release of inflammatory cytokines in response to RhsT requires assembly and/or activation of the inflammasome. Finally, in a mouse model of acute pneumonia, the authors observe that an isogenic mutant of RhsT induces less inflammation and is much less toxic to hosts. RhsT is thus an important virulence factor for *P. aeruginosa* that acts via inflammasome activation. *ZF*
Proc. Natl. Acad. Sci. USA **109**, 1275–1280 (2012)

Inflammatory regulation by NLRP12

In many ways, cancer can be seen as the end stage of chronic inflammation, but the steps in this transition are still being delineated. Kanneganti and colleagues, in *Cancer Cell*, provide evidence that NLRP12, a member of the Nod-like receptor family of proteins, has a pivotal role in regulating inflammation and tumorigenesis in the gut. Published studies have suggested that NLRP12 may have an anti-inflammatory function, but the data on this have been conflicting. To address this, the authors generate *Nlrp12*$^{-/-}$ mice and find that they are hypersusceptible to both chemically induced colitis and tumorigenesis in the colon. In these conditions, *Nlrp12*$^{-/-}$ mice are also characterized by more inflammation and infiltration of the colon by granulocytes and T cells. Colon samples from *Nlrp12*$^{-/-}$ mice and *Nlrp12*$^{-/-}$ macrophages *in vitro* also show dysregulated signaling via the transcription factor NF-κB, mitogen-activated kinases and cytokines. Studies of bone marrow chimeras indicate that NLRP12 is important mainly in the hematopoietic compartment. NLRP12 therefore has a critical role in restraining inflammation and tumorigenesis. ***ZF***
***Cancer Cell* 20, 649–660 (2011)**

Apoptosis and NLRP3 activation

Apoptotic stimuli induce mitochondrial dysfunction, including more generation of ROS and release of mitochondrial DNA. In *Immunity*, Shimada *et al.* link apoptosis with more NLRP3-dependent activation of caspase-1 and release of IL-1β. Infection with viable *Salmonella* or *Chlamydia* can induce apoptosis-linked activation of NLRP3. Notably, cells must first incur signal 1 to upregulate the synthesis of NLRP3 and pro-IL-1β before receiving an apoptotic signal. Enforced expression of the antiapoptotic protein Bcl-2 attenuates the response by NLRP3. NLRP3 recognizes oxidized mitochondrial DNA released into the cytoplasm after mitochondrial stress. When 8-hydroxy-guanosine is added, it blunts apoptosis-induced secretion of IL-1β by competitively binding to NLRP3. Thus, in sensitized cells, mitochondrial ROS oxidize guanosine residues, and release of this modified mitochondrial DNA triggers NLRP3-dependent inflammasome activation. *LAD*
Immunity (23 February 2012) doi:10.1016/j.immuni.2012.02.001