Commensals and autoimmunity

Gut-resident bacteria influence the maturation and function of the immune system. In *Immunity*, Wu *et al.* show that a single member of the commensal gut microbiota, the segmented filamentous bacteria (SFB), can trigger an extra-gut autoimmune response by promoting the expansion of interleukin 17 (IL-17)-producing helper T (T_H17) cells. K/BxN mice, which express a transgenic T cell antigen receptor specific for the self peptide glucose-6-phosphate isomerase, develop arthritis in specific pathogen–free conditions but are largely protected in germ-free conditions. Monocolonization with SFB is sufficient to trigger arthritis in germ-free mice. SFB are linked with the emergence of T_H17 cells in the small intestine lamina propria. These 'gut-imprinted', integrin $\alpha_4\beta_7$–positive T cells can migrate to the spleen and provide IL-17–dependent help for the formation of germinal centers and the production of antibodies specific to glucose-6-phosphate isomerase. Thus, not only infectious microorganisms but also commensals can potentially influence the onset of autoimmune disease. ***IV***

***Immunity* 32, 815–827 (2010)**

Targeting polycomb repressors

The polycomb protein PRC2 is known to catalyze trimethylation of lysine 27 of histone H3 (H3K27me3), leading to gene repression, yet target genes of PRC2 are thought to be poised, as these genes are commonly associated with H3K4me3, an activating chromatin mark. In *Molecular Cell*, Jenner and colleagues show that target genes repressed by PRC2 are transcribed into short truncated RNAs 50–200 nucleotides in length in human $CD4^+$ T cells. RNA polymerase II initiation complexes are associated with these short RNAs, but elongation complexes and full-length mRNAs are not. These short RNAs produced from genes repressed by PRC2 correlate with H3K27me3 but not with binding of H3K79me2, a mark of productive transcription. However, the generation of short RNAs does not depend on polycomb activity or H3K27me3. Instead, these short RNAs show a propensity to form stem-loop structures that can target PRC2 to the locus. The production of short RNAs is lost after differentiation or activation; thus, these short RNAs confer gene repression *in cis* via PRC2 recruitment. *LAD*

Mol. Cell **38**, 675–688 (2010)

Probing immunity with PET

Positron emission tomography (PET) is a widely used imaging technique that can ascertain the location and metabolic demands of various physiological processes. Although PET has the potential to offer new insights, it has remained relatively unexplored by immunologists. In the *Journal of Clinical Investigation*, Witte and colleagues use two different PET probes to monitor the immune response to a retrovirally induced tumor. They find that the probes have characteristic patterns of accumulation in cells of the innate and adaptive immune responses, which indicates that these cell types have different metabolic requirements. The different specificities of these PET probes suggest that they may be useful for assessing immune function *in vivo* and for monitoring the effects of targeted therapies. ***ZF***

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

SphK1-S1P in NF-κB activation

Sphingosine 1-phosphate (S1P) is better known for triggering G protein–coupled receptors in immune cell trafficking, yet accumulating evidence suggests a second intracellular signaling role for S1P. In *Science*, Puneet *et al.* show that the cytosolic kinase SphK1, which generates intracellular S1P, acts downstream of many receptors to activate the production of proinflammatory cytokines dependent on the transcription factor NF-κB. Knockdown or inhibition of SphK1, but not of the related kinase SphK2, results in less NF-κB activation and release of inflammatory mediators. Interference with SphK1 results in greater survival in sepsis models. In *Nature*, Alvarez *et al.* show that SphK1 associates with the E3 ligase TRAF2 after signaling by tumor necrosis factor. The generation of S1P via SphK1 activates K63-linked ubiquitination of the signaling scaffold RIP1, which is critical for activation of the kinase IKK complex necessary for phosphorylation of the NF-κB inhibitor IκB. The effect of intracellular S1P is specific, as the related intracellular dihydro-S1P or signaling by extracellular S1P through its receptors does not activate TRAF2 ligase activity. Both reports identify a necessary role for SphK1-S1P in the NF-κB-activation pathway that leads to the production of proinflammatory cytokines. *LAD*

Science **328**, 1290–1294 (2010) & *Nature* **265**, 1084–1088 (2010)

It's not all TLR

A common immune-evasion strategy of pathogens is to downregulate their Toll-like receptor (TLR) ligands. The loss of bacterial flagella after infection has therefore generally been interpreted as pathogen avoidance of detection by TLR5, the host receptor. In *Infection and Immunity*, Berwin and colleagues offer a very different interpretation. This study examines mutant *Pseudomonas aeruginosa* expressing a nonfunctional but otherwise normal flagellum. These usually motile bacteria demonstrate a complete lack of swimming ability but are highly resistant to phagocytosis by macrophages and dendritic cells both *in vitro* and *in vivo*. This impaired phagocytosis does not seem to be an obvious failure of TLR signaling, as dendritic cells deficient in the adaptor MyD88 do not recapitulate the effect of motility loss. Bacterial resistance to phagocytosis thus seems to be independent of the expression of both flagella and TLRs, and motility itself somehow triggers phagocytosis and clearance. ***ZF***

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New LRR proteins

Innate pattern-recognition receptors commonly contain any number of leucine-rich repeat (LRR) motifs that can confer unique substrate recognition. In the *Proceedings of the National Academy of Science*, Ng *et al.* present a systematic analysis of 375 human LRR-containing proteins that include those of unknown function. Clustering analysis as well as expression-based classification identify many LRR proteins expressed in immune cells that are associated with ubiquitin ligase complexes. Various microbial pathogens trigger distinct clusters of LRR proteins, a result confirmed by RT-PCR analysis of infected primary human macrophages. Knockdown of the LRR protein MFHAS1, whose function was previously unknown, leads to enhanced IL-6 production after TLR stimulation, which suggests a negative regulatory role. Another LRR protein, LRSAM1, has a role in executing autophagy in response to intracellular bacterial infection. Thus, bioinformatics approaches can provide hints about the biological functions of unassigned LRR-containing proteins. *LAD*

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