Controlling migration

Cell migration is integral to the inflammatory response, but leukocyte trafficking must be properly regulated to avoid infiltration of cells into healthy tissues. Barriers such as the maintenance of vascular endothelium integrity help prevent aberrant cell migration. In the *Proceedings of the National Academy of Science USA*, Kinane and colleagues show that active negative guidance cues also prevent inappropriate cell trafficking. Netrin-1, a guidance molecule that both attracts and repulses neuronal cells, is expressed by vascular endothelium, whereas the netrin-1 receptor UNC5b is expressed by leukocytes. *Staphylococcus aureus* infection, which causes acute inflammation, induces rapid downregulation of netrin-1 expression. *S. aureus* infection also promotes the production of interferon-γ and tumor necrosis factor, two proinflammatory cytokines that can mediate netrin-1 downregulation. Pretreatment of leukocytes with nectrin-1 *in vitro* and administration of nectrin-1 *in vivo* block cell migration. These data therefore suggest nectrin-1 functions as a regulator of cell migration during inflammation. ***JDKW***

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Induced selective suppressors

Induced (or adaptive) T regulatory (T_R1) cells arise in the periphery and respond to either self or foreign antigens. T_R1 cells, one type of induced T regulatory cell, are $CD4^+$ T cells that express CD46 and produce interleukin 10 (IL-10) after stimulation with endogenous ligands of CD46 and antigen via the T cell receptor. In *Blood*, Kemper and colleagues find that T_R1 cells also produce the cytokine GM-CSF and soluble CD40 ligand, which can stimulate dendritic cell (DC) maturation. Thus, T_R1 cells both suppress bystander T cell proliferation (via IL-10) and stimulate DC maturation (via GM-CSF and CD40 ligand). This dual activity may be particularly important in the gut, where antigen-induced T cell proliferation and suppression of bystander T cell proliferation are critical. *DCB*

Blood (20 October 2005) doi:10.1182/blood-2005-07-2951

Unwinding antiviral responses

The RNA helicases RIG-I and MDA-5 can mediate type I interferon production in response to virus infection. In the *Journal of Immunology*, the Kitzgerald and Fugita groups characterize another RIG-I-like RNA helicase called Lgp2. Although Lgp2, like RIG-I and Mda5, contains a helicase domain that is known to sense viral RNA, it lacks N-terminal caspase recruitment domains that mediate signaling. Lgp2 overexpression impairs the Toll-like receptor–independent RIG-I-mediated antiviral response to infection with Sendai virus or Newcastle virus. There is less expression of Lgp2 mRNA than RIG-I mRNA in resting cells but equivalent expression after virus infection. Because Lgp2 also binds double-stranded RNA, these data suggest Lgp2 functions as a negative regulator of antiviral signaling by sequestering double-stranded RNA from RIG-I and Mda5. ***JDKW***

***J. Immunol.* 175**, 2851–2858 & 5260–5268 (2005)

Research notes written by Douglas C. Braaten, Laurie A. Dempsey and Jamie D.K. Wilson.

Linking selenoprotein S

Selenoprotein S senses and protects the endoplasmic reticulum against various forms of metabolic stress, which when detected can lead to the expression of proinflammatory cytokines. In *Nature Genetics*, Blangero and colleagues link polymorphisms in the human *SEPS1* gene to variations in the circulating concentrations of IL-1β, IL-6 and tumor necrosis factor (TNF). *SEPS1* is located on chromosome 15 in a region previously associated with increased susceptibility to diabetes, Alzheimer disease and celiac disease. One *SEPS1* promoter variant identified in this study correlates with increased expression of all three proinflammatory cytokines examined. This promoter polymorphism involves a G→A change at position –105, which is centered in a putative endoplasmic reticulum stress-response element (ERSE). Reporter constructs fused to the –105G→A *SEPS1* promoter sequence are expressed less abundantly than are other *SEPS1* variant constructs. Knockdown of *SEPS1* expression by small interfering RNA in macrophage cell lines also leads to increased expression of IL-6 and TNF. Thus, selenoprotein S seems to be a negative regulator of inflammatory cytokine expression. *LAD*

Nat. Genet. **37**, 1234–1241 (2005)

Anti-inflammatory fat

The gut environment, by its constant exposure to both microbes and dietary proteins, poses a challenge for the immune system to avoid inflammatory responses that can lead to loss of intestinal integrity. In the *Journal of Experimental Medicine*, Luyer *et al.* report that ingestion of fats triggers release of the neuroendocrine chemical messenger cholecystokinin (CCK), which dampens inflammatory responses to dietary antigens. Rats fed a high-fat diet elicit less release of TNF and IL-6 after systemic challenge. CCK acts indirectly by stimulating the efferent vagal nerve. Blockade of the CCK receptors expressed on vagal afferent nerves, vagotomy to sever the nerve, or inhibition of peripheral nicotinic receptors (which are activated by efferent vagal nerve release of acetylcholine) leads to loss of the gut barrier function and increases TNF and IL-6 blood concentrations in challenged rats. Thus, dietary fats can modulate immune responses via neuroendocrine circuits. ***LAD***

***J. Exp. Med.* 202**, 1023–1029 (2005)

Regulating proinflammatory TLRs

Innate signaling via Toll-like receptors (TLRs) is normally tightly regulated. Two reports in the *Proceedings of the National Academy of Science USA* demonstrate that interferon regulatory factor 4 (IRF-4) negatively regulates signaling by TLRs that require the adapator protein MyD88. Honda *et al.* also determine that IRF-4 and IRF-5 (a positive regulator of TLRs) interact with the same domain of MyD88, indicating direct competition between IRF-4 and IRF-5. Both groups show that production of proinflammatory cytokines by IRF4-deficient macrophages is enhanced, whereas ectopic expression of IRF-4 blocks cytokine induction. Yui *et al.* confirm the inhibitory activity of IRF-4 in wild-type macrophages by 'knockdown' of IRF-4 mRNA with small interfering RNA. These reports link the function of IRF-4 and regulation of TLR-dependent inflammation. *DCB*

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