## Neural control of immunity

**Complex yet largely ill-defined communication networks exist between the nervous and immune systems. In *Science*, Sun *et al.* identify a regulatory circuit in *Caenorhabditis elegans* whereby the nervous system negatively regulates innate immune responses. Mutant worms lacking expression of OCTR-1, a G protein–coupled catecholamine receptor expressed in sensory neurons, show enhanced resistance to bacterial pathogens. Surprisingly, these worms have higher expression of genes associated with the noncanonical arm of the unfolded protein response associated with cellular stress. This expression occurs in cells that line the intestine and pharynx and involves a pathway that includes the receptor CED-1 and the kinase p38. Wild-type cells likewise upregulate genes encoding molecules of the unfolded protein response in response to infection. How infection triggers OCTR-1 signaling and which neural products activate CED-1 must await future work.** ***LAD***

***Science* 332, 729–732 (2011)**

## TGF-β effects

Transforming growth factor-β (TGF-β) is required for $T_H17$ development in a mechanism independent of the Smad transcription factors. In *Immunity*, Yoshimura and colleagues identify the transcription factor Eomes as the target of such TGF-β signaling and a direct repressor of the genes encoding IL-17A and the transcription factor RORγt. TGF-β-activated signaling via the kinase Jnk and the transcription factor c-Jun directly suppresses Eomes expression. Eomes is induced by stimulation of the TCR, especially under T helper type 1 conditions, but is strongly and rapidly repressed under $T_H17$ conditions, such as stimulation with TGF-β and IL-6. Thus, multiple TGF-β-induced pathways are required for $T_H17$ development: the Smad pathway mediates the suppression of anti-$T_H17$ cytokines, such as IL-4 and interferon-γ, the RhoA-ROCK2-IRF4 pathway is required for RORγt induction, whereas Jnk–c-Jun represses Eomes and releases IL-17 production from the inhibitory effects of this transcription factor. *IV*

*Immunity* **34**, 741–754 (2011)

## B cells drive insulin resistance

**Pathological conditions such as insulin resistance and obesity are characterized by the infiltration of visceral adipose tissue (VAT) by M1 macrophages and activated T cells. In *Nature Medicine*, Engleman and colleagues demonstrate that B cells and their IgG production are directly involved in these conditions as well. Normal mice fed a high-fat diet have more class-switched B cells in VAT, especially B cells producing the proinflammatory IgG2c isotype. Mice depleted of B cells and knock-out mice that do not produce mature B cells still have greater body weight while on the high-fat diet but lack the proinflammatory 'signature' associated with pathological obesity. Adoptive transfer of B cells or purified IgG from mice fed a high-fat diet can initiate VAT inflammation and many other pathological aspects of obesity. Finally, insulin resistance in humans is associated with a distinct IgG profile targeted mainly at ubiquitously expressed intracellular proteins. B cells are therefore important in both the initiation and effector stages of insulin resistance.** ***ZF***

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## Sensing live bacteria

The ability of live vaccines to trigger more vigorous immune responses than their killed counterparts do has been attributed to the ability of live microorganisms to replicate and express specialized virulence factors. In *Nature*, Sander *et al.* show that the mammalian innate immune system can directly sense microbe viability through the detection of a special class of viability-associated pathogen-associated molecular patterns. Prokaryotic mRNA acts as such a pattern to elicit activation of the NLRP3 inflammasome and the production of class-switched immunoglobulin G (IgG) antibody responses. Viable avirulent bacteria are needed to induce cleavage of pro-IL-1β and pyroptosis in infected cells. Bacterial mRNA is able to gain access to cytosolic receptors via intrinsic phagosomal leakage. Several distinct features of prokaryotic RNA and the cellular context of recognition may have a role in determining the innate sensors involved in the recognition of bacterial mRNA. *IV*

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## Quelling microglial activity

**Hyperactivation of microglia contributes to the inflammation and pathology of central nervous system diseases such as multiple sclerosis and its mouse counterpart, experimental autoimmune encephalitis. In *Cell*, Glass and colleagues investigate the regulation of microglial activation. Estrogen receptor-β (ERβ) has known anti-inflammatory effects, and this study shows higher ERβ expression in microglia. Treatment with synthetic ligands or the endogenous ERβ ligand ADIOL ameliorates microglial inflammation, experimental autoimmune encephalitis and lessens the generation of pathogenic interleukin 17 (IL-17)-producing helper T cells ($T_H17$ cells). Impairment of the generation of ADIOL from its steroid precursor DHEA or lower expression of ERβ results in exaggerated proinflammatory responses. ADIOL seems to mediate its anti-inflammatory effects by facilitating the recruitment of a CtBP corepressor complex by ERβ to genes encoding proinflammatory molecules. Targeting this *trans*-repression pathway may prove to be a useful means of dampening inflammation in the central nervous system.** ***ZF***

***Cell* 145, 584–595 (2011)**

## T cell–maturation factors

Developing thymocytes undergo positive and negative selection, after which the 'chosen few' begin to functionally mature and exit the thymus. In the *Journal of Experimental Medicine*, Hsu *et al.* identify the transcriptional repressor NKAP as being necessary for thymocyte maturation. Conditional deletion of NKAP with a CD4-Cre model leads to a paucity of naive peripheral T cells. Those NKAP-deficient T cells present in the periphery are recent thymic emigrants but are functionally immature, as they do not robustly produce IL-2 after crosslinkage of the T cell antigen receptor (TCR) and coreceptor CD28. Phenotypically, these cells fail to upregulate Qa2 and downregulate CD24, both of which are associated with the maturation process. Neither enforced transgenic expression of a TCR nor expression of a transgene encoding the antiapoptotic molecule Bcl-2 'rescues' the cell-intrinsic effect. What remains is the identification of genes whose expression is altered by NKAP deletion and what other factors contribute to their regulation. *LAD*

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