Myeloid quiescence

The transcription factor HIF-1α is a central integrator of the hypoxic and innate immune stimulation in myeloid cells. In *Immunity*, Jain and colleagues demonstrate that the transcription factor KLF2 inhibits HIF-1α-dependent activation of myeloid cells. Myeloid-specific deficiency in KLF2 leads to spontaneous activation of myeloid cells, manifested as higher concentrations of several inflammatory cytokines in the serum of KLF2-deficient mice. These mice have higher expression of genes encoding antimicrobial and metabolic molecules and enhanced bactericidal activity after bacterial infection, as well as greater sensitivity to endotoxin challenge. This phenotype is rescued by ablation of HIF-1α. Mechanistically, KLF2 negatively regulates the recruitment of critical coactivators of NF-κB to the promoter of the gene encoding HIF-1α. Lower expression of KLF2 mRNA and higher expression of HIF-1α mRNA is seen in circulating human myeloid cells from patients with sepsis. ***IV***

***Immunity* 34, 715–728 (2011)**

Darkness, depression & NF-κB

Circadian rhythms influence emotional states, and disturbances in circadian clock activity are associated with depression and mood disorders. In the *Journal of Neuroscience*, Monje *et al.* show that mice continuously deprived of light develop depression-like behavior. This induced condition is associated with more NF-κB signaling in hippocampus cells, accompanied by higher expression of IL-6 and the IL-1 receptor. Hippocampal NF-κB activity likewise alters expression of the clock genes *Per2* and *Npas2* and diminishes the proliferation of hippocampal progenitor cells known as dentate gyrus cells. Inhibition of NF-κB activation or blockade of IL-6 reverses the effects of constant darkness on the clock genes and hippocampal cell proliferation. These studies indicate involvement of NF-κB in the control of circadian clock patterns and influencing mood-related behavior. *LAD*

J. Neurosci. **31**, 9075–9083 (2011)

An inflammatory turn-off

The NF-κB inhibitor ABIN has a Lys63 (K63)-polyubiquitin binding domain similar to that present in the kinase IKKγ (NEMO), an important regulator of the NF-κB pathway. In the *Journal of Experimental Medicine*, Cohen *et al.* report the generation of mice that express mutant ABIN molecules which are defective in the ability to bind K63-polyubiquitin chains (ABIN[D485N]). These mice spontaneously develop aggressive systemic lupus erythematosus–like autoimmunity. B cells in particular are defective in that they hyperproliferate and secrete more autoantibody. ABIN[D485N] mice show enhanced activity of the canonical NF-κB pathway, but this activation can be prevented by knockout of the upstream adapter MyD88. Interestingly, the knock-in phenotype is distinct from ABIN deficiency, which is embryonically lethal. K63-polyubiquitin binding by ABIN therefore seems to have an important role in modulating NF-κB activity and autoimmunity. ***ZF***

***J. Exp. Med.* 208, 1215–1228 (2011)**

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

Networking with NEMO

Sharpin is a component of a complex that enzymatically adds linear ubiquitin chains to client proteins. In the *Proceedings of the National Academy of Science*, Zak *et al.* show that Sharpin complexes modify IKKγ (NEMO), the regulatory subunit of the IKK complex. Mutant mice of the cpdm strain have a null mutation in *Sharpin* and impaired responses to Toll-like receptor ligands. Transcriptome analysis shows selective defects in NF-κB- and AP-1-regulated gene expression in cpdm macrophages, including much lower *Il12* expression. Similar alterations in gene expression are seen in panr2 mice, which have hypomorphic mutations in the gene encoding NEMO. Sharpin and NEMO physically interact, but this association is lost in panr2 macrophages. Deficiency in either Sharpin or NEMO leads to less phosphorylation of the NF-κB subunit p105 and the kinase Erk but does not alter activation of the NF-κB subunit RelA (p65) or the kinases p38 and Jnk. Thus, the Sharpin-NEMO interaction contributes to the specificity of the ensuing immune response. *LAD*

Proc. Natl. Acad. Sci. USA (27 June 2011) doi:10.1073/pnas.1107577108

Antiviral effects

Expression of the transmembrane protein CD4 in cells of the myeloid lineage is 5–10% that in T cells; however, it can have important physiological effects. In the *Journal of Immunology*, James and colleagues report that downregulation of CD4 expression on macrophages after treatment with supernatants of activated T cells lowers the susceptibility of the treated cells to infection with human immunodeficiency virus type 1. The lower CD4 expression is independent of transcriptional regulation but involves proteasomal degradation after NF-κB–dependent upregulation of LMP2, a catalytic active subunit of the proteasome. CD4 downregulation is independent of conventional cytokines, such as interferon-γ, RANTES and interleukin 16 (IL-16), known to downregulate CD4 expression, or MIF. Instead, the T cell supernatant fraction containing the antiviral activity is enriched in proteins that modulate macrophage adherence and spreading, such as attractin, fibronectin and galectin-3-binding protein. ***IV***

***J. Immunol.* (10 June 2011) doi:10.4049/jimmunol.1003678**

Regulating IL-6

IL-6 is a pleiotropic cytokine involved in inflammation and autoimmune disease, and its tight regulation is therefore critical. IL-6 can be regulated at several levels. In the *Journal of Biological Chemistry*, Fang and colleagues focus on potential microRNAs that might regulate IL-6. Using *in silico* prediction, they show that the microRNA miR-365 targets IL-6 mRNA. Treatment with miR-365 results in much less IL-6 translation but has no effect on the stability of IL-6 mRNA. Moreover, miR-365 itself is substantially induced by both triggering of the Toll-like receptor and infection with virus. This induction of miR-365 is dependent on the transcription factors NF-κB and Sp1, which seem to act in a synergistic way. The induction of miR-365 by a proinflammatory transcription factor such as NF-κB therefore suggests that a potential autoregulatory loop controls IL-6 expression. *ZF*

J. Biol. Chem. **286**, 21401–21412 (2011)