NF-κB resolves inflammation

The inflammatory response is self-limiting. Much attention has focused on the pathways that initiate inflammation but little is known about how the response is resolved. NF-κB plays a pivotal role in the induction of the inflammatory immune response. In *Nature Medicine*, Lawrence *et al.* show that NF-κB also plays a role in the resolution of this response. In two rodent models of carrageenin-induced inflammation, rat pleurisy and mouse dorsal air pouches, NF-κB activation was coincident with the expression of endogenous anti-inflammatory pathways and inflammatory cell apoptosis during the resolution phase. *In vivo*, inhibition of NF-κB DNA-binding activity prolonged the inflammatory response and induction of apoptosis. Thus, these data suggest that the NF-κB pathway is involved in regulating the anti-inflammatory response.

Nature Med. **7**, 1291–1297 (2001)

Functionless memory cells?

Vaccination with heat-killed *Listeria monocytogenes* (HKLM) is ineffective at generating protective immunity. However, immunization with live *L. monocytogenes* induces a protective antigen-specific $CD8^+$ T cell response. In *Science*, Lauvau *et al.* show that HKLM immunization and live infection both support expansion of memory $CD8^+$ T cells. However, HKLM immunization primed T lymphocytes that remain $CD62L^{hi}$ and lack effector function. The difference between the protective immunity induced after live immunization, and the lack of protective immunity in HKLM-immunized mice, could not be accounted for by the $CD4^+$ T cell response. Thus, protective immunity mediated by T cells can be dissociated from memory T cell expansion. This suggests that long-term protective immunity is depends upon the generation of effector T cells.

Science **294**, 1735–1739 (2001)

Host-virus *détente*

Members of the TNF family of cytokines are crucial for antiviral immune responses through regulation of cell death and survival pathways. These cytokines could provide strong selective pressures, under which viruses evolve counter strategies that allow them to persist in the host. In *Immunity*, Ware and colleagues show signaling by lymphotoxin β receptor (LTβR) or TNFR1, but not Fas or TRAIL, initiates IFN-β production and inhibits the cytopathicity and replication of human cytomegalovirus (CMV), without inducing apoptosis. IFN-β production is dependent on both viral infection and LT signaling; thus, both host and viral factors are required to prevent viral replication without cellular elimination. The importance of LT in host defense against murine CMV was showed in LTα-deficient mice and LTβR-Fc–transgenic mice that were highly susceptible to murine CMV infection. Thus, LT and CMV cooperatively induce IFN-β to establish a state of coexistence in immunocompetent hosts.

Immunity **15**, 617–626 (2001)

Control of NKT cells

NKT cells play a crucial role in anti-tumor immunity and other immune surveillance activities by rapidly secreting cytokines upon T cell receptor engagement or ligation of CD1d by α-galactosylceramide. But where NKT cells recognize natural ligands, yet undefined, and how they are triggered to produce either T_H1 or T_H2 cytokines has remained unknown. In *J. Exp. Med.*, Ikarashi *et al.* show that stressed DCs can override inhibitory signals provided to the NKT cells by major histocompatibility antigens. Expression of DC B7 costimulatory molecules was key to directing NKT production of IFN-γ. Thus, DCs may be the physiologic regulators of NKT activation and the source of endogenous CD1d-restricted antigens.

J. Exp. Med. **194**, 1179–1186 (2001)

What does RAG-2 really do?

Despite the known deficiencies of lymphocytes in RAG-$2^{-/-}$ mice, the molecular role that RAG-2 plays in catalyzing V(D)J recombination has remained elusive. In *Molecular Cell*, Fugmann and Schatz individually mutated conserved basic or hydroxy group–containing amino acids within RAG-2. Mutant RAG-2 proteins that maintained the ability to interact with RAG-1 showed specific defects in either DNA recognition, RAG-1–mediated nicking and hairpin formation or a more stringent test of *in vivo* recombination. Thus, RAG-2 does not merely form a structural platform for RAG-1; specific RAG-2 basic, but not hydoxy, residues are critical for cognate DNA interactions.

Mol. Cell **8**, 899–910 (2001)

GADD45β blocks Jnk apoptosis

How the signals generated by NF-κB antagonize programmed cell death is poorly understood. In *Nature*, Tang *et al.* and De Smaele *et al.* show sustained Jnk activation in cells defective for NF-κB activation leads to apoptosis, whereas transient Jnk signaling in NF-κB–proficient cells precludes activation of capases and other apoptosis effectors. NF-κB up-regulates expression of GADD45β, which, in turn, blocks the pro-apoptotic signals generated by the death receptor–induced Jnk pathway. GADD45β was identified in "death-trap" screens done in NF-κB–null cells treated with TNF-α. Ectopic expression of GADD45β in $RelA^{-/-}$ T cells blocked both sustained Jnk signaling and induction of apoptosis. Thus, GADD45β abrogates TNF-α–induced death signals, linking NF-κB to Jnk inhibition.

Nature **414**, 308–313 and 313–317 (2001)

PGE_2 receptors function

Prostaglandin E_2 (PGE_2) potently alters immune responses by inhibiting T cell activation, polarizing cytokine production and dampening antigen presentation. PGE_2 has the potential for treating autoimmune diseases and aiding transplantation, but its complex regulatory effects are generated by multiple G protein–coupled receptors that differ in their signaling pathways. In the *J. Clin. Invest.*, Coffman and colleagues systematically deleted the four PGE_2 receptors (EP1–EP4) in mice and showed their nonredundant functions in dampening immune responses. T cells lacking either EP1 or EP3 remained sensitive to PGE_2, whereas EP2-deficient T cells were resistant to PGE_2 inhibition. Only EP4-deficient macrophages showed defects in antigen presentation and cytokine production. Thus, the nonredundant functions of PGE_2 receptors may allow fine-tuning of these lipid mediators to control immune reactions.

J. Clin. Invest. **106**, 1239–1249 (2001)