Instigating hyperactivity

Natural killer–T (NKT) cells are versatile immune cells that seem to be involved in both tumor immunity and protection against autoimmune diseases. However, the importance of NKT cells in asthma and allergy is unclear. In addition, many of the conclusions drawn from previous studies were based on stimulation of NKT cells with the artificial agonist α-galactosylceramide. In *Nature Medicine*, Akbari *et al.* show that NKT cell–deficient mice do not develop allergen-induced airway hyperreactivity (AHR), a cardinal feature of asthma. AHR was restored when these mice received wild-type NKT cells but not NKT cells that lacked interleukin-4 (IL-4) and IL-13. Thus, upon exposure to antigens, lung NKT cells may activate and license other type 2 cells to drive the development of an asthmatic response.

Nat. Med. **9**, 582–588 (2003)

Population control

Stem cells are defined by their ability to self-renew, thus enabling the continual generation and propagation of differentiated daughter cells. Tumor cells also aim to proliferate, albeit in a less stringently controlled manner. In *Nature*, Park *et al*. and Lessard and Sauvageau identified a factor common to both cell types that maintains their ability to divide. By using Bmi-1–deficient mice or cells derived from these mice, *Bmi-1* was shown to modulate the expression of several hematopoietic stem cell (HSC)–associated genes, including two specific downstream targets: $p16^{Ink4a}$, which allows proliferation of HSC, and $p19^{Arf}$, which inhibits apoptosis *via* p53. Through a similar mechanism, *Bmi-1* is required by leukemic 'stem cells' to maintain their proliferative capacity. Thus, Bmi-1 appears to be a master controller of stem cell proliferation.

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Memorable liaison

The generation of $CD8^+$ T cell responses under inflammatory conditions, such as acute viral infection, is thought to be independent of $CD4^+$ T cell help. However, the requirements and nature of the ensuing recall memory response of these $CD8^+$ T cells are less clear. Two pairs of authors writing in *Science*, Sun and Bevan and Shedlock and Shen, both came to the conclusion that memory $CD8^+$ T cells generated in the absence of $CD4^+$ T cell help are quantitatively and qualitatively inferior. Recall responses of $CD8^+$ T cells do not require $CD4^+$ T cell help. However, $CD8^+$ T cells primed in the absence of $CD4^+$T cell help have lower proliferative capacity and secrete less IFN-γ. Thus, the signals provided by $CD4^+$ T cells, which have yet to be fully elucidated, are integral to the developmental program of $CD8^+$ T cell responses.

Science **300**, 337–339 & 339–342 (2003)

Who regulates whom?

LPS triggers proinflammatory responses by activating IκB and MAP kinase signaling pathways. A report in *Molecular Cell* describes how activation of the kinase Erk by LPS is regulated by components of the NF-κB pathway. Erk activation by LPS requires the kinase Tpl2. Waterfield *et al.* show that Tpl2 forms a stable, inactive complex with the cytosolic precursor of NF-κB1. Curiously, only p105, not other Rel isoforms or the activated form of NF-κB1 (p50), binds Tpl2. Upon LPS stimulation, Tpl2 is activated and dissociates from p105 to phosphorylate downstream targets, ultimately resulting in CREB activation. Tpl2 is highly labile and rapidly degraded upon release from p105. Thus, p105 functions to stabilize inactive Tpl2, but such regulation might be mutual, as one target of activated Tpl2 could turn out to be p105, liberating active p50.

Mol. Cell **11**, 685–694 (2003)

SLAT skews TCR signals

How differences in T cell receptor (TCR) signal strength can polarize naive helper T cells to either T_H1 or T_H2 effectors has been unclear. In *Immunity*, Altman and colleagues identify a new adaptor, SLAT (Swap-70-like adapter of T cells), that is enriched in T_H2 cells and reinforces T_H2 development, even in the absence of polarizing cytokines. SLAT over-expression represses IFN-γ expression but enhances that of IL-4. TCR ligation with strong agonist peptides, but not with weaker altered peptide ligands, induces SLAT recruitment to the immune synapse, where it selectively interacts with and inhibits ZAP-70 signaling. Similar T_H2 skewing occurs when ZAP-70 is inhibited by pharmacologic agents. Thus, SLAT appears to be a physiologic regulator of TCR signals to enforce T_H2 development.

Immunity **18**, 403–414 (2003)

Gfi1 regulates thymopoiesis

Gfi1 is a zinc-finger DNA binding factor expressed during early T cell development and upon TCR engagement of mature cells. In the *Journal of Experimental Medicine*, Yucel *et al*. describe Gfi1-deficient mice, which have defective thymopoiesis. Total thymic cellularity was reduced by 90% as a result of defects in early thymocyte survival and DN1→DN2 progression. Surviving thymocytes were overwhelmingly $CD8^+$ SP cells, suggesting that Gfil acts to regulate CD4-CD8 lineage commitment. Loss of Gfi1 led to the aberrant expression of genes encoding c-Maf, TRAF5, Id1, Id2 and lung Kruppel-type factor (LKLF). These results suggest Gfi1 is a negative regulator of gene expression that is required for T lineage specification and survival.

J. Exp. Med. **197**, 831–844 (2003)

Casp8$^{-/-}$ T cells

Many lymphoproliferative and autoimmune diseases are thought to result from loss of death-receptor signaling in lymphocytes. Caspase-8 is a major effector of the death receptor pathways; however, defining its normal physiological role has been difficult because caspase-8 deficiency results in embryonic lethality. In *Genes & Development*, Salmena *et al*. report targeted mutation of *Casp8* in murine T lineage cells. Surprisingly, thymocyte development was normal in the absence of caspase-8. However, peripheral CD4 and especially CD8 T cell survival was decreased in the caspase-8–deficient animals, in contrast to the lymphadenopathy observed in animals lacking death receptors or their ligands. Mice without caspase-8 were unable to combat viral infection, owing to altered CD8 homeostasis. Thus, caspase-8 is required for peripheral T cell maintenance.

Genes Dev. **17**, 883–895 (2003)