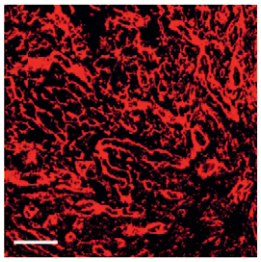
in the periphery. This analysis of multiple gut sites from a relatively large number of individuals therefore provides data that link HIV-induced damage to the GI tract with peripheral T cell activation and will be important for future approaches to vaccine and therapy development.

Lymph Node Profiling



Much is known about host genes involved in HIV-1 replication in vitro, but much less is understood about the factors involved in viral replication in lymphoid tissue in vivo. To address this gap in our knowledge, Smith et al. (p. 5417) examined gene expression associated with HIV-1 replication in the inguinal lymph nodes of HIV-1–infected individuals through microarray analysis. Approximately 95% of the 592 genes whose expression was significantly associated with viral load were downregulated with increasing HIV-1 replication. These genes encoded proteins involved in collagen deposition, inhibition of transcription and translation, chromatin modification, and inhibition of cell activation and proliferation, as well as several potential anti–HIV-1 host restriction factors. Interestingly, the ~5% of genes whose expression was positively associated with viral load generally coded for proteins involved in innate and adaptive immunity, including many involved in the IFN response, which would be expected to inhibit viral replication. However, chronic immune activation was significantly associated with increasing viral load and may instead have caused enhanced viral replication. This profile of the host response to HIV-1 in lymphoid tissue provides insights into HIV-1 replication that will act as useful starting points for future research.

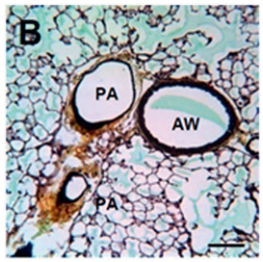
Checkpoint Control

B cell differentiation involves transient DNA breakage during V(D)J recombination, somatic hypermutation, and class switch recombination. Cell cycle progression is tightly regulated in DNA-damaged cells by mitotic checkpoint proteins, such as MAD2. To clarify how mitotic checkpoints are regulated in B cells, Nakaya et al. (p. 5180) examined the role of the ribonucleoprotein complex protein Pcid2 in B cell differentiation. *Pcid2* mRNA was expressed at high levels in pre-B, immature B, spleen transitional (T)1 B, and follicular B cells, but not in pro-B, spleen T2 B, or marginal zone B cells. Small interfering RNA-mediated knockdown of *Pcid2* led to apoptosis and polyploidy, suggesting a defect in mitosis. Supporting the involvement of Pcid2 in the mitotic spindle assembly checkpoint, *Pcid2* knockdown led to a specific reduction in *MAD2* mRNA in the cytoplasm but did not affect the expression of other checkpoint proteins or of the cell-cycle–associated proteins cyclin A, cyclin B1, or CDK1. Conditional knockout of *Pcid2* in B cells indicated that it was required for the survival of mature splenic B cells. Taken together, these data advance our understanding of the involvement of mitotic checkpoints in the regulation of *Ig* gene diversification and suggest differential checkpoint regulation at different stages of B cell differentiation.

Foreseeing Viral Escape

Although $CD8^+$ T cells are known to be involved in controlling the progression of HIV, SIV, and simian HIV (SHIV) infections, it is not clear whether this control is dominated by cytolytic mechanisms. To address this question, Balamurali et al. (p. 5093) studied acute SHIV infection in pigtail macaques and compared the dynamics of wild-type (WT) and escape mutant (EM) viruses differing at one immunodominant epitope. The authors predicted that if $CD8^+$ T cell-mediated viral control was dominated by cytolysis, WT viral decay should occur more quickly than EM viral decay, as WT-infected cells would be selectively killed by CTLs. However, there were no significant differences in WT versus EM viral decay. A mathematical modeling approach predicted that, in the case of cytolytic control of SHIV infection, maximal viral escape would occur during times of rapid viral decay, whereas noncytolytic mechanisms would drive escape during viral expansion. In agreement with a predominance of noncytolytic $CD8^+$ T cell activity, maximal viral escape most often occurred during rapid viral growth and correlated with $CD4^+$ T cell numbers. These data challenge the common assumption that the antiviral activity of $CD8^+$ T cells is mainly cytolytic and suggest that it will be important to address the noncytolytic activities of these cells in future studies of HIV pathogenesis and in vaccine development.

Hypoxic Hypertension



Hypoxia-induced mitogenic factor (HIMF; also known as FIZZ1 and RELMα) is upregulated in inflammatory lung diseases, including pulmonary hypertension (PH), pulmonary fibrosis, and allergic lung inflammation, and has mitogenic, chemotactic, and fibrinogenic activities. Yamaji-Kegan et al. (p. 5539) investigated the role of IL-4 in HIMF expression and activity in a model of hypoxia-induced PH to clarify the mechanism of HIMF action in this disease. Surprisingly, unlike in other models of lung inflammation, HIMF expression was not dependent on IL-4 or STAT6. However, IL-4 was involved in many HIMF-mediated functions in the lung, including proliferation in pulmonary arteries, extracellular matrix deposition and collagen synthesis, macrophage infiltration, and production of vascular endothelial growth factor and chemokines. IL-4Rα blockade suppressed HIMF-induced proliferation of primary pulmonary microvascular endothelial cells, but did not inhibit their migration. Together, these data indicate cooperation between the Th2 and hypoxia pathways in hypoxia-induced PH through IL-4's control of HIMF activity in lung inflammation and vascular remodeling.

Summaries written by Jennifer Hartt Meyers, Ph.D.