Comment on Biancotto et al, page 4272

# Looking at HIV-infected lymph nodes

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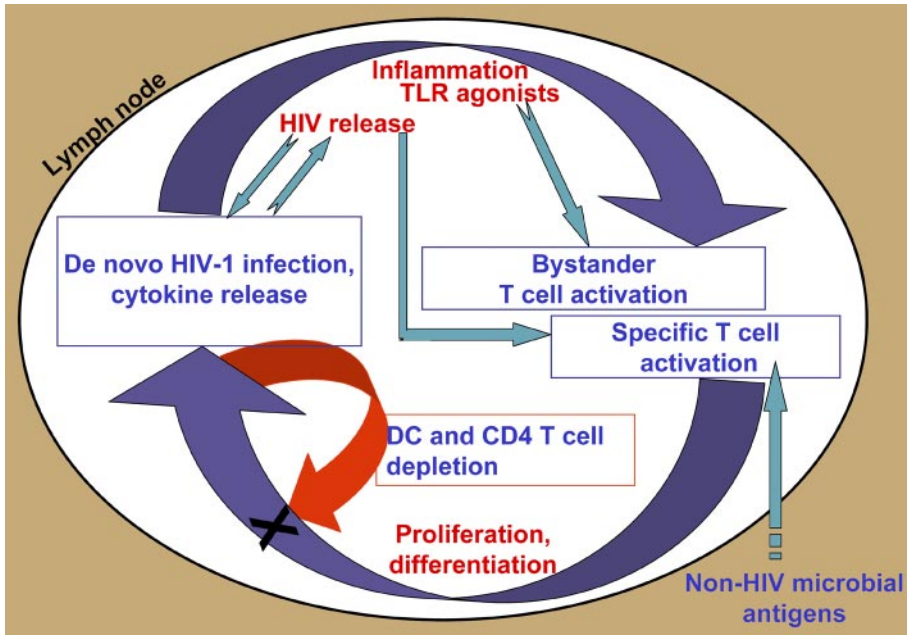
Chronic immune activation plays a major role in AIDS pathogenesis. Biancotto and colleagues compared freshly excised lymph nodes from chronically HIV-1–infected patients and uninfected individuals. The authors describe a vicious cycle of self-enhancing activation.

Although it has been documented that primary infection with human immunodeficiency virus 1 (HIV-1) rapidly destroys the bulk of the body's $CD4^+$ memory T cells, especially in extralymphoid tissues, naive and most central memory T cells are initially spared and the immune system retains its regenerative capacity. However, ongoing viral replication and persistent hyperactivation in lymph nodes are thought to slowly erode the functional organization of these organs, reducing the immune system's regenerative capacity, facilitating viral evolution, and ultimately resulting in acquired immunodeficiency syndrome (AIDS).[1,2] It is unclear what causes such hyperactivation and how it drives disease progression. To address these questions, it is necessary to quantify the cellular and cytokine profiles in secondary lymphoid organs and associate their dynamics with manifestations of structural and functional deterioration.

Applying a previously developed method of culturing lymphoid tissue that retains its complex structure,[3] Biancotto and colleagues measured a reduced fraction of $CD4^+$ T cells in cultured lymph nodes from chronically HIV-1–infected patients, as expected, but also a dramatic reduction in the representation of dendritic cells, which they suggest may interfere with the capacity to mount immune responses. Given that in the chronic phase, patients generally respond quite normally to common pathogens, the ability to specifically recruit antigen-presenting cells to lymph nodes of infected individuals on an ad hoc basis may remain largely intact, despite the chronic depletion. The authors also found that the frequency of memory and naive CD4 and CD8 T cells expressing the activation marker CD38 was elevated in lymph nodes from HIV-infected patients and suggest that such "activation" of naive cells might explain their impaired expansion response. Indeed, while naive (and memory) cells that are chronically stimulated below the threshold of full activation might become nonresponsive to subsequent stimulation by their cognate antigens, the authors' interpretation is confounded by the fact that a significant fraction of naive T cells normally expresses CD38. This reservation applies also to the argument that the clonal diversity of activated cells implied by the broad activation of naive cells proves that T-cell activation in the lymph nodes of HIV-1–infected persons is the result of exposure of bystander cells to cytokines (or other broad activating signals) rather than of T-cell receptor engagement. Yet, it is conceivable that bystander activation should be enhanced by proinflammatory factors and cytokines. Indeed, the authors demonstrated profound perturbations in the levels of cytokines. They describe a vicious cycle, whereby activated cells are the source of cytokines that in turn activate new cells. This cycle may be embedded in a somewhat more general scheme including positive and negative feedback effects, as well as amplification of effector memory T cells (and of apoptosis) due to the rapid, transient proliferation and differentiation of activated cells[2] (see figure). Thus, the higher proportion of lymph node T cells with effector-memory phenotype, reported here and elsewhere, may primarily be the result of increased turnover.

Are the changes in the cellular and cytokine profiles in secondary lymphoid organs truly "abnormal," or are they essentially reversible manifestations of immune activation and its physiological controls? To what extent do they reflect irreversible tissue destruction and loss of function? A better understanding of these




**Interacting positive and negative feedback loops promote and control chronic activation in HIV-1–infected lymph nodes. T cells are specifically activated by HIV and other microbial antigens, and nonspecifically, as bystanders, by cytokines and other factors associated with inflammation, including Toll-like receptor (TLR) agonists. Such activation leads to proliferation, differentiation, and cytokine secretion; the latter contribute to inflammation and bystander activation (positive feedback). Different effector cells secrete inhibitory cytokines and apoptosis-inducing factors that may affect T cells and dendritic cells (negative feedback). Also depicted are ongoing cycles of infection that connect to both feedback loops.**

issues may reveal, in the authors' words, "new targets for immune-based interventions to slow HIV-1 disease progression." The methodology used here provides opportunities for experimental manipulations in human lymphoid tissue aimed to normalize "abnormal" profiles and to identify irreversible damage.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■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TRANSPLANTATION

Comment on Hockenbery et al, page 4557

# At last, an "ointment" for gastrointestinal GVHD?

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Intestinal graft-versus-host disease (GVHD) has been notoriously difficult to treat. A simple measure such as topically active oral steroids can halt its progression, reduce systemic steroid use, and improve survival.

Too many studies have shown "promising" results in treatment of acute graft-versus-host disease (GVHD) during early phase 1/2 trials over the last decades; none has yet stood the test of a prospective randomized comparison. Trials did include drugs such as monoclonal and polyclonal antilymphocyte antibodies, anti–TNF alpha antibodies, proinflammatory cytokine-modifying agents, or more complex approaches such as extracorporeal photopheresis or infusion of mesenchymal stromal cells.[1-3]

Sometimes results were even worse with the new treatment than with steroids alone. The latter, steroids, still form the mainstay of GVHD treatment. They induce a response in about 50% of the patients with acute GVHD of grade II or higher.

Still, relapse of GVHD is frequent, steroids are associated with significant morbidity, and response is mainly seen in skin GVHD. Moreover, any reduction of GVHD is immediately linked with reduced graft-versus-leukemia (GvL) and increased relapse rate.[4]

Alternatives are urgently warranted. Hockenbery and colleagues from the OrBec GVHD Study Group have now identified a surprisingly simple but successful approach. In a prospective, randomized, placebo-controlled group, they tested efficacy and safety of oral beclomethasone diproprionate (BDP) in patients with steroid refractory gastrointestinal GVHD. The authors chose an elegant design, forcing rapid steroid tapering after 10 days of treatment.

Their postulate was that a topically active "ointment" should reduce symptoms, hence reduce the need for systemic drugs. Of eligible patients, risk of GVHD treatment failure was indeed significantly reduced in the BDP group. This approach did translate into a significantly improved survival in the BDP group, with a reduction in mortality by more than 50% at 1 year after transplantation.

Effects were even more pronounced in recipients of mismatched or unrelated transplants.

The results are clear and significant. There is no doubt. In addition, ease of application and relatively low costs make oral BDP an attractive treatment for gastrointestinal GVHD. It should be tested in any case of gastrointestinal GVHD, before more toxic or more expensive therapy is used. Still, questions remain, and it is premature to consider oral BDP as established from now on. Topical treatment is an accepted therapy for acute and chronic GVHD of the skin, oral mucosa, eyes, and vagina.[1-3] Why did it take so long from the first reports and from the first randomized study to the present results?

The answer lies probably in the outcome results. The authors present difficulties in interpretation. Reduction in mortality was primarily due to a reduction in deaths from infections and deaths from relapse, not in deaths from GVHD. The authors give their interpretation. Local treatment, by avoiding systemic immunosuppression, should more likely result in fewer serious infections. Vice versa, protracted exposure to systemic steroids, should result in an abrogation of T-cell response in the GVL direction in the placebo group. There is some logic in this view, but questions remain. No data on absorption, or "nonabsorption" of the drug are provided. Furthermore, it would be the first time that any reduction in GVHD would not be associated with a reduction in GVL.

Above all, numbers in the trial were small and the statistical analysis was skewed. Survival difference was mainly based on an exceedingly low mortality in the mismatched or unrelated transplants (1 of 23, 4%) in the BDP group compared to 10 (42%) of 24 in the placebo group. This cannot reflect reality. As it stands, BDP has become an attractive alternative for severe gastrointestinal GVHD. Still a confirmatory trial needs to be done before BDP can be declared as the new standard of care in gastrointestinal GVHD.

*Conflict-of-interest disclosure: The author declares no competing financial interests.* ■


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