showed a decrease in reticulin staining with discontinuation of the study drug.

The prospective study involved 10 patients who received doses of romiplostim that were between the recommended 2 to 10 μg/kg. Six patients had both pretreatment and posttreatment bone marrow studies that could be evaluated for reticulin fiber formation. Only one patient had clear increase in reticulin fiber formation upon treatment, which then remained stable for the remaining months. This patient remained on romiplostim and had no change in response to therapy or in other blood counts.

These preliminary studies suggest that bone marrow reticulin fiber formation after TPO-mimetics is real and can occur in some patients receiving the recommended dosage. This fibrosis is reversible after short-term treatment and may be dose related. This is consistent with a previous study in patients with acute myeloid leukemia treated with TPO.[9] Preliminary evidence is also presented that perhaps long-term treatment may not cause continuously worsening fibrosis if the dose is within the presently recommended range. Certainly these studies are encouraging, but further studies will not only need to systematically and prospectively evaluate the consequences of short-term administration of these medications, but also address the long-term consequences of treatment with any TPO-mimetic drugs. For this reason, caution is still required when considering long-term management of patients with chronic ITP with TPO-mimetics, and patients should be made aware of this potential complication.

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IMMUNOBIOLOGY

Comment on Stary et al, page 3854

HIV infection: TRAILing the killers

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Progressive loss of CD4$^+$ T cells is a hallmark of HIV infection, but its mechanism remains poorly understood. In this issue of *Blood*, Stary and colleagues show that CD4$^+$ T cells from viremic patients undergo apoptosis in response to death-inducing signals generated by TRAIL expressed on the surface of plasmacytoid dendritic cells.

HIV infection is characterized by progressive depletion of both infected and uninfected CD4$^+$ T cells, which leads to the development of AIDS. Increased apoptosis is regarded as the primary cause of HIV-induced CD4$^+$ T-cell loss, and multiple mechanisms have been brought forward to explain the immunopathogenesis of this apoptotic process.[1] Whereas direct cytopathic effects affect the survival of infected CD4$^+$ T cells, indirect mechanisms, such as activation-induced cell death, are likely to play a major role in the elimination of uninfected CD4$^+$ T cells.[2,3] Activation-induced cell death may involve an augmented responsiveness of CD4$^+$ T cells to various inhibitory and death-inducing ligands such as PD-1L, CTLA-4, and FasL.[4,5] Recent evidence points to an additional contribution of TNF-related apoptosis-inducing ligand (TRAIL).[6]

Soluble TRAIL is elevated in the plasma of HIV-infected patients and CD4$^+$ T cells from these patients are more sensitive to TRAIL-induced death signals. A possible source of TRAIL is plasmacytoid dendritic cells (pDCs), a professional interferon (IFN)–producing dendritic cell subset that usually plays a key role in antiviral immunity.[6] In infected patients, pDCs release massive amounts of IFN-α in response to HIV, but cannot achieve the control of the infection. Rather, in vitro studies indicate that pDCs up-regulate TRAIL expression in response to HIV-induced IFN-α and thereafter acquire cytotoxic activity on bystander CD4$^+$ T cells.[6] Of note, the up-regulation of TRAIL expression by HIV-exposed pDCs is highly dependent on sensing viral single-stranded RNA through the intracellular sensor Toll-like receptor 7 (TLR7).[6]

In this issue, Stary and colleagues sought to extend these in vitro findings to an in vivo setting and explored the presence of TRAIL-expressing killer pDCs in HIV-infected persons.[7] They found that pDCs and CD4$^+$ T cells from infected patients expressed TRAIL and its cognate receptor TRAIL-R1, respectively. TRAIL expression directly correlated with viremia, whereas there was an inverse correlation between TRAIL-expressing pDCs and CD4$^+$ T cells. Remarkably, TRAIL-expressing pDCs were proximal to apoptotic CD4$^+$ T cells in tissue sections from systemic lymph nodes. In vitro, pDCs from viremic patients, but not pDCs from aviremic or noninfected persons, triggered death of activated CD4$^+$ T cells through a mechanism that required TRAIL and to a lesser extent IFN-α. This study clearly shows that TRAIL-expressing killer pDCs are present in vivo and likely play an important role in the loss of CD4$^+$ T cells.

Stary and colleagues' findings also raise intriguing questions. For instance, it is remarkable that, although expressing comparable or higher surface levels of TRAIL, monocytes and myeloid dendritic cells (mDCs) from viremic patients do not have cytotoxic activity on activated CD4$^+$ T cells. One possible interpretation is that monocytes

and mDCs lack surface molecules with immunoregulatory activity required for TRAIL to deliver optimal cytotoxic signals to targeted $CD4^+$ T cells. Another interesting aspect is the up-regulation of surface TRAIL-R1 but not TRAIL-R2, TRAIL-R3, and TRAIL-R4 by $CD4^+$ T cells from viremic patients.[7] What is the mechanism by which HIV selectively augments TRAIL-R1 expression? And why does TRAIL-R1 up-regulation occur on $CD4^+$ T cells but not on other cell types such as monocytes? One possibility is that monocytes express constitutively high levels of TRAIL and are not susceptible to further up-regulation.

At any rate, the present work clearly suggests that HIV alters the responsiveness of $CD4^+$ T cells to TRAIL-induced signals by perturbing the normal balance between death-inducing (R1 and R2) and regulatory (R3 and R4) TRAIL receptors on the surface of $CD4^+$ T cells.[7] Yet, the mechanism behind the establishment of this receptor imbalance remains puzzling. Furthermore, the expression of TRAIL and TRAIL-R1 by intestinal pDCs and $CD4^+$ T cells, respectively, remains unknown. In both HIV-infected humans and SIV-infected macaques, $CD4^+$ T cells undergo early and massive death in the intestinal mucosa.[1,8,9] This mucosal catastrophe causes systemic leakage of intestinal antigens, which in turn promotes dysregulated systemic immune activation.[1,2] Thus, a top future priority will be to address the presence, phenotype, and function of TRAIL-expressing killer pDCs and TRAIL-R1 $CD4^+$ T cells in the intestinal mucosa of acutely and chronically infected HIV patients.

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● ● ● LYMPHOID NEOPLASIA

Comment on Qian et al, page 3880

Turning up the heat on myeloma

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In this issue of *Blood*, Qian and colleagues report that vaccination with heat shock protein 96 (HSP96) derived from pooled allogeneic, MM cell lines are as effective as autologous HSP96 in preventing MM growth and treating MM in a mouse model.[1] Further, administration of anti-B7H1 or anti-IL10 monoclonal antibodies counteracted myeloma-mediated immune-subversion of the vaccine-induced anti-tumor effect and allowed for treatment of mice with larger tumor burdens. This study raises the prospect of using allogeneic MM cell line–derived HSP96 as an universal tumor vaccine in MM.

Idiotype protein in myeloma is unique to the patient and has been explored as a therapeutic patient-specific protein vaccine for more than 3 decades. However, in general, the results of clinical trials have been disappointing. This is likely due to the abundance of immunoregulatory mechanisms mediated both by the myeloma cells and the multiple myeloma (MM) microenvironment, which prevent the induction of a comprehensive and potent anti-myeloma response.[2] However, it also has been reported that idiotype-specific T cells can be deleted or tolerized and that idiotype antigenic immunodominant epitopes may not exist in all MM patients.

Heat shock proteins (HSPs) are evolutionary highly conserved proteins that function as chaperones during protein synthesis, assist in protein folding and unfolding in cells, and mediate protection to mechanical and thermal stress. HSP96 is found in the endoplasmic reticulum, where it is involved in the assembly of MHC class II complexes. HSP96 also relays peptides from the transporter associated with antigen processing (TAP) to MHC class I. HSP96 associates with a large number of tumor proteins and effectively carries a unique antigenic fingerprint of a tumor, thus obviating the need for the identification of proteins specific for individual cancers.[3] HSP96 can access immature dendritic cells via receptor-mediated endocytosis and cross-present chaperoned peptides on MHC class I molecules necessary for the priming of $CD8^+$ cytotoxic T cells. HSP peptides are also presented by MHC class II and activate $CD4^+$ T helper responses required for the longevity of antigen-specific cytotoxic T lymphocytes (CTLs). Importantly, HSP96 induces dendritic cell maturation and promotes their migration to draining lymph nodes.

HSP96 preparations were first described to have antitumor properties in rat hepatosarcoma and murine fibrosarcoma models.[4] Clinical trials with autologous HSP96 vaccines in a variety of malignancies, including metastatic melanoma, colon cancer and renal cell cancer, and non-Hodgkin lymphoma have shown disappointing response rates of less than 10%. Similar to idiotype, autologous HSP96 requires a custom-made vaccine for each patient, which is both arduous and expensive to manufacture. It is also not feasible to isolate sufficient HSP96 from each patient. In one recent study, the success rate for production of tumor-derived HSP96 sufficient for administration of 4 vaccines was only 49%.[5]

The study by Qian et al suggests that it might be feasible to produce an "off-the-shelf" universal HSP96 vaccine, which would allow for the therapy of all MM patients. In contrast to idiotype, HSP96 vaccines will provide a multitude of tumor epitopes, which will likely minimize tumor