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. 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. 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 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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REFERENCES

Heat shock proteins (HSPs) are evolutionarily 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. 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. 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...
escape caused by tumor immunoediting. The same group has previously reported that HLA-A*0201–restricted HSP96 specific CTLs generated from myeloma patients could recognize gp96–chaperoned peptides derived from primary myeloma cells and myeloma cell lines, substantiating the presence of a shared, HSP96-carried, antigenic repertoire in humans.6 The HSP96–specific CTLs were not autoreactive, and clinical trials with autologous HSP96 have not reported any significant autoimmune phenomena. Both the experience with idiotype and HSP96 vaccines suggest that mere vaccination of myeloma patients, even in combination with dendritic cells or adjuvants such as keyhole limpet hemagglutinin, GM-CSF, or IL12, is inadequate to induce meaningful clinical responses. MM cells and the MM microenvironment orchestrate a large array of immunosuppressive mechanisms that conspire to down-modulate vaccine-induced immune responses, including recruitment of regulatory T lymphocytes, excess production of immunomodulatory cytokines (eg, transforming growth factor B, IL10, and IL6), and co inhibition of T cells through the B7-H family of molecules. The result is suppression of CTL activity, skewing of the immune responses to a T2 type, and production of dysfunctional dendritic cells. In the paper by Qian et al, pooled allogeneic HSP96 vaccination in combination with the potent Toll-like receptor agonist, CpG, and antibody–mediated blockade of the B7-H1 pathway and IL10 could eradicate established tumors. These experiments may allow for the optimization of future clinical trials with pooled, allogeneic HSP96 vaccines as has been suggested by others.7 Lastly, despite these encouraging results, the hope for successful translation to clinic must be somewhat tampered by the knowledge that many antitumor vaccines are effective in mouse models against a variety of murine tumors. Myeloma is a highly heterogeneous disorder with at least 6 subtypes, and it is presently not clear if the tumor antigens contained in HSP96 from pooled myeloma cell lines sufficiently reflect the tumor protein repertoire present in the different types of myeloma.8 Further, we have as yet little insight into heterogeneity of the tumor environment in the various myelomas with potential differing mechanisms to suppress anti-MM effects induced by vaccines. Ultimately, any vaccine-based therapy will have to pass the acid test of human clinical trial.

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REFERENCES
Turning up the heat on myeloma

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