The emerging picture is that HTLV-1 infection, which was previously thought to be latent, is in fact a persistent active infection, and that the HTLV-1–specific CTL response plays a critical role in limiting the replication of HTLV-1, the proviral load, and the risk of the inflammatory disease HAM/TSP. But in this dynamic equilibrium between host and virus, the frequency and the differentiation state of virus–specific T cells are both the cause and the effect of the level of the proviral load. This dynamic complexity makes it difficult to distinguish cause and effect: for example, in patients with HAM/TSP, is the perforin content of the CTLs low because they are subject to frequent stimulation (and consequent degranulation) by the high antigen load, or conversely does the high viral load in such patients result from the low perforin content in inefficient CTLs? Or both? The role of host genetics is perhaps the key to avoid this potential circularity. The association of a single class I HLA allele such as HLA–A2 with protection against HAM/TSP and with a lower proviral load strongly suggests that the CTL response to HTLV-1 is a dominant determinant of the outcome of HTLV-1 infection, not a passive follower of the proviral load: HTLV-1 infection cannot, of course, determine the host genotype.

Sabouri and colleagues then compared the lytic capacity of HTLV-1–specific CTLs between patients with HAM/TSP and healthy carriers by staining T cells for CD107. CD107 is expressed on the CTL surface when the lytic granules are discharged during target-cell ly- sis; CD107 staining can be used to quantify the recent killing history of CTLs. Sabouri et al found that stimulation of CD8+ T cells from HLA–A2+ subjects with the immunodominant Tax11–19 peptide elicited lower CD107 staining in HTLV-1 antigen-specific CD8+ T cells from patients with HAM/TSP than in those from healthy carriers (see figure). The lower CD107 staining in CD8+ T cells from HAM/TSP patients observed by Sabouri et al appears at first sight to conflict with a report in this issue of Blood from Enose-Akahata et al in which CD8+ T cells from HAM/TSP patients gave greater staining for CD107 than those from healthy carriers. However, there was a crucial difference between the 2 studies: Enose-Akahata et al quantified CD107 expression as the fraction of CD107+ PBMCs, whereas Sabouri et al quantified CD107 expression as the fraction of CD107+ antigen-specific CD8+ T cells (those that bound the HLA–A2/Tax11–19 tetramer). Putting these 2 results together, the message of Sabouri and coauthors seems clear: patients with HAM/TSP have a high frequency of HTLV-1–specific CD8+ T cells with poor lytic capacity, whereas healthy carriers have a lower frequency of cells with high lytic capacity.

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**Comment on Oerlemans, page 2489**

**Many facets of bortezomib resistance/susceptibility**

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In this issue of Blood, Oerlemans and colleagues present a fascinating report, detailing a mechanism by which cells acquire resistance to therapy with the proteasome inhibitor, bortezomib.

Proteasome inhibition represents one of the most successful anticancer strategies of this decade, improving the outcomes of many patients. The ubiquitin proteasome pathway is critical to normal cellular functioning and is involved in signal transduction, transcriptional regulation, and response to stress, among other pathways. The 26S proteasome consists of a core 20S catalytic complex and a 19S regulatory complex, forming 2 outer and 2 inner rings that are stacked to form a cylindrical structure. The 19S complex is responsible for selecting the ubiquitinated proteins for catalytic degradation by the 20S complex, which possesses chymotryptic, tryptic, and peptidylglutamyl-like activities. This critical cellular function has been successfully targeted for cancer therapy, as highlighted by the efficacy of proteasome inhibitor bortezomib in a wide spectrum...
of hematological and solid tumors. In fact, the introduction of bortezomib resulted in a paradigm shift in the treatment of multiple myeloma, and has undoubtedly contributed to the improved survival seen among patients with this incurable malignancy. The mechanism of antmyeloma activity of bortezomib is the subject of intense study. Bortezomib is currently believed to exert its effects through multiple pathways that target both the tumor cell and its microenvironment. For example, inhibition of the NFκB pathway leading to decreased cell proliferation and induction of apoptosis is one of the major effects of bortezomib therapy. Treatment with bortezomib prolongs survival in relapsed myeloma as well as newly diagnosed disease, leading to its regulatory approval for clinical use in both situations. However, resistance to therapy develops inevitably. Furthermore, nearly a third of the patients with multiple myeloma never respond to treatment with bortezomib, depending on the clinical situation. While some resistance mechanisms may be reversible in a small proportion of patients following withdrawal of the drug, as demonstrated by the efficacy of retreatment, the majority need to switch therapy. Understanding the mechanisms of resistance to proteasome inhibition will not only allow better use of proteasome inhibitors such as bortezomib, but should also allow the rational design of synergistic drug combinations.

Malignant cells may develop several mechanisms to escape the effects of proteasome inhibition, including alterations in the proteasome complex itself leading to decreased function, increasing the efficiency of alternate mechanisms of protein degradation (the aggresome pathway), or modulation of cell signaling pathways that are affected by proteasome inhibition. Oerlemans et al, in this issue of Blood, report on a mutation involving the β unit of the proteasome catalytic unit (PSMB5) that leads to impaired binding of bortezomib and thus decreased proteasome inhibition. These investigators also noted a significant upregulation of the PSMB5 subunit following exposure to bortezomib and other proteasome inhibitors, an effect that wanes with time off-therapy, but reappears rapidly after re-exposure to the inhibitors. These studies were carried out using human monocytic/macrophage THP1 cells, and whether these findings are applicable to malignant cells in diseases like myeloma is unclear. However, these findings do highlight the susceptibility of proteasome units to genetic modifications under constant selection pressure, as can occur with continued treatment in patients. Mutation and overexpression of PSMB5 can lead to bortezomib resistance in lymphoma cells lines. While mutations such as this may explain development of resistance, baseline differences in susceptibility may be due to polymorphisms involving the PSMB5 locus.

An alternate mechanism used by the cell for ubiquitinated protein degradation and disposal is the aggresome pathway, which can potentially compensate for proteasome pathway inhibition and contribute to drug resistance. This physiological compensatory mechanism has been targeted for enhancing the efficacy of proteasome inhibitors. Use of HDAC6 specific inhibitors, such as tubacin, can shut down the aggresome pathway and can synergize with and enhance the effect of proteasome inhibition on the tumor cell. Upregulation of the heat shock protein Hsp27 is yet another mechanism of proteasome inhibitor resistance and has been targeted as an avenue for enhancing proteasome inhibition as well as reversing resistance to this class of drugs.

Finally, identification of mechanisms that confer sensitivity to proteasome inhibition is as important as understanding mechanisms of resistance. Recent studies have identified mutations involving genes associated with regulation of NFκB pathways that result in constitutive activation of the NFκB pathway. Cells that carry these mutations appear to be particularly sensitive to the effects of proteasome inhibition, a finding that could allow us to tailor the use of this class of drugs in the future.

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