Probing the Immune Dysregulation in Cutaneous T Cell Lymphomas

Peter Heald
Department of Dermatology, Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, Connecticut, USA

In their study of natural killer (NK) cell activity with tumor cell targets from cutaneous T cell lymphoma (CTCL) patients, our French colleagues have probed the immunologic underpinnings of several distinctive clinical features of these lymphomas (Bouaziz et al., 2005). The fascination of the French with this group of disorders is a notable legacy, with contributions from Alibert, Bazin, and Sezary. Sezary syndrome patients were the focus of this study and it is fitting that the authors pursue the demise of Sezary’s original patients—death by infection. The immune failure in Sezary syndrome and in CTCL is clinically relevant. Patients with this disorder develop second malignancies (Olsen et al., 1984; Kantor et al., 1989), succumb to bacterial infections and septicemia (Posner et al., 1981), and suffer from unchecked viral infections (Masessa et al., 1989) while their physicians frantically seek to reverse the immune failure. We can describe the components of the immune collapse. One unique feature is that as the malignant T cell clone expands, it does so at the expense of normal T cells, creating an immunodeficiency in numbers of cells that can be assessed by molecular (Kono et al., 1992) or flow cytometric (Heald et al., 1994) techniques.

The unique immunocompromise that plays such a pivotal role in the demise of patients with CTCL is a target for therapy. In this group of disorders a patient may benefit from extracorporeally damaging a small portion of the malignant cell pool followed by reinfusion of those cells (photopheresis). Other immunoenhancing modalities have included injections of interferon, injections of DNA vaccines, injections of bacterial DNA sequences, and the ultimate in immunotherapy—allogeneic stem cell transplantation. The paper in this issue of the Journal demonstrates that cultured or recently harvested CTCL cells are appropriate targets for NK cell-mediated lysis. If this mechanism plays a role in the tumor surveillance of CTCL, then the work would imply the escape from control is not on the basis of evading NK cell-mediated lysis. The finding that allogeneic NK cells could lyse patient-derived CTCL cells is significant in terms of the growing role of allotransplantation in the management of CTCL (Soligo et al., 2003). Previous attempts to utilize bone marrow transplantation were primarily designed to use the allograft as a way to survive the upper echelons of a chemotherapeutic’s dose–response curve. Those attempts were marked by failure and relapse. The novel approach of a mini-transplant is designed to utilize graft versus host disease as the major therapy instead of high dose chemotherapy. The results of this type of transplantation have been encouraging (Soligo et al., 2003), and probably these results reflect the ability of donor-derived NK cells to similarly lyse recipient-derived CTCL cells.

One of the more intriguing observations is that the autologous cytotoxicity assays demonstrated that patient-derived NK cells had the ability to specifically lyse patient-derived CTCL cells. Again, this fledgling anti-tumor response is probably the mechanism that so many immunomodulating measures (mentioned above) are trying to enhance and activate. But is the failure of this tumor surveillance the reason why patients have the disease? Is the root cause in the inability of these cells to do in vivo what they can in vitro? Or is the ineffectiveness of this mechanism a side effect of the progressive lymphoma, like smoke is to fire? These questions are raised by this provocative work.

Further studies spurred by this paper would lead in two directions. Specific modulation of the NK cell activity against the CTCL cells will open the door to more specific immunotherapies than those currently available. But the more intriguing answers will come from the dissection of the molecular targets that sit in the Class I MHC that underly the NK lysis function. Understanding the mechanisms of the specificity of cell lysis will lead to improved specificity of therapeutic maneuvers. Controlling this mechanism would benefit many patients other than the few who suffer progressive cutaneous lymphomas. These lessons would readily be applicable to other tumors, many of which already plague CTCL patients (Olsen et al., 1984; Kantor et al., 1989) because of the failure of NK-mediated tumor surveillance.

DOI: 10.1111/j.0022-202X.2005.23968.x

References