IL-7: success without a formal education

Decimation of the T-cell pool following intensive chemotherapy, bone marrow transplantation, or infection with HIV renders the patient highly susceptible to a variety of life-threatening infectious pathogens and/or fatal malignancies. Restoration of normal T-cell immunity can occur by 2 distinct paths: The first is an educational process whereby now-naïve T-cell precursors in the bone marrow traffic through the thymus to acquire the diverse receptor repertoire necessary to face the multitude of pathogens. The second pathway relies on the few surviving T-cell soldiers in the blood, wounded and fragile but with the potential to regroup and expand into a competent lymphocyte pool in the absence of a thymus. How these few peripheral T cells can avoid remedial education in the thymus, survive, and grow to contribute to host immune restoration has remained a mystery. Fry and colleagues (page 1525) examine restoration of T-cell immunity in the absence of thymic education. They demonstrate that, in thymectomized mice receiving exogenous IL-7, low numbers of peripheral T cells can attack target antigens via at least 3 mechanisms: better T-cell expansion, enhanced T-cell survival, and improvement in target antigen–presenting cells. The absence of exogenous IL-7 renders the thymectomized host unable to recognize the target antigen.

This has potentially exciting clinical application in adults with T-cell deficiencies and a restricted amount of thymic function. Should the study results in the mouse model of HY-disparate skin grafts prove comparable in models of high-dose chemotherapy, one could soon envision clinical trials of high-dose chemotherapy followed by low-dose IL-7 therapy to assess the cytokine’s effect on quantitative and qualitative aspects of peripheral T-cell reconstitution. More effective T-cell recovery in states of minimal residual malignant disease that often follow high-dose chemotherapy might impact on disease-free and overall survival. Comparable studies in the setting of allogeneic transplantation would need to balance the possible advantages of improved T-cell function in combating life-threatening infections and in mediating graft-versus-tumor effects with the potential adverse consequences of intensifying graft-versus-host disease or graft rejection. But in patients with HIV infection on effective antiretroviral therapy, low-dose IL-7 therapy might contribute to a more sustained and diverse T-cell recovery by enhancing both the proliferative response and the threshold for apoptosis.

—Michael A. Caligiuri
Ohio State University

Foiling IL-6 to treat B-lymphoproliferative disorder

Approximately 21 000 solid organ transplantations are performed annually in the United States. These transplantations offer hope to those about to die of a failing heart, a hepatitis C–ravaged liver, or severe chronic obstructive pulmonary disease, or they improve the quality of life for those on chronic dialysis. But the dark side of solid organ transplantation is the need for long-term immunosuppression to prevent organ rejection. This results in a substantial risk of Epstein-Barr virus–driven B-lymphoproliferative disorder (BLPD), ranging from approximately 1% in kidney-transplant recipients to 5% in heart-transplant recipients, and possibly higher in lung-transplant recipients. Treatment of BLPD has been challenging. Unlike patients with other types of aggressive non-Hodgkin lymphoma, patients with BLPD can be cured by resection of localized disease (often pulmonary nodules). Interferon alpha, multiagent systemic chemotherapy, or rituximab can also be curative. Haddad and colleagues (page 1590) used the observation that IL-6 is a growth factor for EBV-infected B lymphocytes to design a novel treatment approach for these patients. They treated 12 solid organ–transplant recipients who developed BLPD, with an anti–IL-6 monoclonal antibody. After daily injections of the anti–IL-6 monoclonal antibody for 15 days, 5 patients achieved a complete response and 3 patients achieved a partial response. No major toxicity was observed, and the remissions were durable in most patients. How will anti–IL-6 therapy fit into the panoply of treatments for B-lymphoproliferative disorder? This will require further study and larger numbers of patients.

—Virginia C. Broudy
University of Washington

Boosting a natural anticoagulant

The protein C pathway performs a critical anticoagulant function by subverting the procoagulant effects of thrombin, and a paper by Taylor and colleagues (page 1685) suggests that an endothelial membrane cofactor besides thrombomodulin modulates this function in vivo. The protein C pathway begins with the binding of thrombin to thrombomodulin on endothelial cells, and the thrombin-thrombomodulin complex then activates protein C, a serine protease zymogen. In a reaction that is facilitated by plasma protein S, activated protein C (APC) degrades clotting factors Va and VIIIa, shutting down blood clotting. Defects in the protein C pathway are common causes of thrombosis, underlining the importance of this regulatory mechanism. Even a modest acquired or inherited decrease in the level of protein C or protein S confers a substantially increased risk of venous thrombosis, and total deficiency of protein C causes purpura fulminans, a neonatal thromboembolic disorder that is fatal if untreated.

The endothelial protein C receptor (EPCR) is a plasma membrane protein that binds protein C and accelerates its activation by thrombin-thrombomodulin at least
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