Why do T cells cause so much trouble?

Kenneth L. McClain
Comment on Price et al, page 1989

Why do T cells cause so much trouble?

Kenneth L. McClain \textsuperscript{1}  SAVOR COLLEGE OF MEDICINE

In this issue of Blood, Price et al document a 20-year experience with autoimmune lymphoproliferative syndrome (ALPS) patients and healthy mutation-positive relatives, showing that defective lymphocyte apoptosis is associated with an increased incidence of lymphomas.\textsuperscript{1}

Nature provides physicians and scientists with opportunities to understand basic biologic mechanisms through the study of rare diseases, and ALPS is no exception. Supplemental Figure 1 of the Price et al article captures the fascinating core issue. Patients and some relatives have heterozygous mutations in the \textit{FAS} gene which lead to defective apoptosis. Although the relatives do not demonstrate the dramatic lymphadenopathy or splenomegaly found in the patients, relatives do have higher than normal numbers of immature T cells (CD4 neg/CD8 neg, “double negative T cell” [DNTs]), and several markers of ALPS: elevated vitamin B12, interleukin-10, and soluble FAS ligand, although these are lower in the healthy mutation-positive relatives. Clearly, there are other genetic or epigenetic modifiers of this syndrome to account for the differences. One explanation is that patients frequently have multiple mutations, often in the second allele.\textsuperscript{2} A key message of this work is that the observed over expected ratio of Hodgkin lymphoma in ALPS patients was 149 and for non-Hodgkin lymphoma, 61. It is apparent from this report that the incidence of lymphoma in ALPS patients is similar to that of patients with other congenital immune deficiencies such as severe combined immunodeficiency, X-linked agammaglobulinemia, X-linked lymphoproliferative syndrome, Wiskott-Aldrich syndrome, ataxia telangiectasia, and others.\textsuperscript{3} The common thread here is that a majority of the malignant lymphoproliferations are in B cells and many were associated with Epstein-Barr virus (EBV) as evidenced by detection of the viral EBV-encoded small RNA by in situ staining of the tumor tissue. Defective T-cell surveillance creates the environment for unregulated B-cell proliferation, often promoted by EBV infection, which leads to malignancy: think EBV and endemic Burkitt lymphoma in patients with high rates of malaria or other environmental causes of T-cell suppression or patients with post-transplant lymphoproliferative disease. In the case of ALPS patients, this connection is only partially defined and is obviously a question ripe for investigation. It is known that the DNTs stimulate B-cell proliferation in ALPS with excessive numbers accumulating because of the apoptosis defect, thus opening the door for malignant changes. Somatic mutations of the \textit{FAS} genes also occur frequently in lymphomas of nonimmune deficient patients.\textsuperscript{4} Mutations affecting the intracellular portion of FAS are more frequently in the death domain and allow the defective FAS protein to merge with a normal one, but the defective partner asserts a dominant-negative effect resulting in decreased apoptosis of lymphocytes. Strikingly, all lymphoma patients had the dominant-interfering type of mutation and not the missense mutations which lead to haploinsufficiency as a cause of ALPS.

Price et al have carefully cataloged the clinical features of these patients over the years, and in the current article drive home several fascinating and important points. The National Institutes of Health (NIH) group has treated ALPS patients with mycophenolate and finds that this helps improve the cytopenias that can be life-threatening. The theoretical reason for using mycophenolate (or sirolimus) is increased activity of the serine threonine kinase AKT which leads to stimulation of the mammalian target of rapamycin pathway and constitutive proliferation of the DNTs.\textsuperscript{5,6} Splenectomy has proven to be a futile and dangerous procedure as the cytopenias return, and overwhelming postsplenectomy is a major cause of mortality.

Conflict-of-interest disclosure: The author declares no competing financial interests.

\begin{thebibliography}{9}


© 2014 by The American Society of Hematology

\end{thebibliography}