Comment on Taylor et al, page 3480

FTY720 prevents GVHD: the host perspective

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In this issue of Blood, Taylor and colleagues report that FTY720 hinders the initiation of GVHD by reducing the number of host DCs in the spleen, rather than by trapping T cells in secondary lymphoid tissues.

Sphingosine 1-phosphate (SIP) is a biologically active lysophospholipid that controls cellular differentiation, survival, and migration of several cell types. SIP is produced by mast cells, platelets, and macrophages, and is secreted in the extracellular fluid. SIP binds a family of G protein–coupled receptors with a diverse pattern of expression on immune cells, thus mediating the emigration of thymocytes from the thymus and the trafficking of lymphocytes and dendritic cells (DCs) to secondary lymphoid organs. SIP, is the most abundant SIP receptor on T cells and is also expressed on DCs. T cells from SIP-deficient mice or mice treated with SIP downregulating drug FTY720 (FTY) rapidly leave the blood, are sequestered in the lymph nodes, and mount a diminished response to immune challenges in tissues. FTY also inhibits DC function, thereby preventing IgE secretion and asthma in experimental animals. In patients with multiple sclerosis, oral FTY reduces the number of lesions and the amount of clinical disease activity. In de novo renal transplantation, FTY is as effective as mycophenolate mofetil in preventing graft rejection when used in combination with cyclosporine. Therefore, FTY appears to be a very promising immune-modulating agent.

Graft-versus-host disease (GVHD) is mediated by donor T cells that recognize host alloantigens, and is associated with beneficial graft-versus-tumor (GVT) effects in recipients of allogeneic hematopoietic cell transplantation. In murine bone marrow transplantation (BMT) models, administration of FTY inhibits GVHD without abrogating GVT. It has been accepted that FTY prevents GVHD by trapping T cells in secondary lymphoid organs.

In this issue of Blood, Taylor and colleagues present an elegant approach to visualize donor GFP-expressing T cells migrating to various recipient organs after transplantation. In the early phase of GVHD development, greater numbers of donor effector T cells accumulated in Peyer patches and mesenteric lymph nodes in FTY-treated recipients, but such an accumulation quickly diminished. Consistent with these data is the concept that FTY facilitates activation-induced T-cell death in the lymph nodes. Taylor and colleagues found fewer donor effector T cells in spleen, inguinal, and axillary lymph nodes, and in the gut-associated lymphoid tissues in FTY-treated recipients. In contrast, FTY did not reduce donor effector T cells in the liver or lung, implying that FTY does not prevent effector T cells from reaching epithelial organs targeted by GVHD.

The other novel finding presented in the article is that FTY reduced host DCs in recipient spleen before transplantation, and that pretreatment of the host alone was sufficient to inhibit GVHD. After transplantation, expansion of donor CD4+ and CD8+ effector cells was blunted by the same magnitude as host DCs were depleted by FTY before transplantation. Because host DCs are also required for optimal GVT, it was no surprise that FTY therapy impaired GVT. FTY alone appeared modestly immune suppressive, and combination therapy was required to prevent GVHD. FTY was additive with adoptively transferred donor T regulatory cells (Tregs), providing the rationale for testing the combination for GVHD prevention in humans.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Comment on Sellick et al, page 3326

Advances in genome-wide CLL linkage

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In this issue of Blood, Sellick and colleagues update a previous report1 with a combined genome-wide linkage study in 206 families with chronic lymphocytic leukemia (CLL), making their study the largest effort so far to localize CLL predisposition genes. The findings of this study are important because they provide information to pursue familial predisposition to the most frequent type of adult leukemia, CLL.

Single nucleotide polymorphism (SNP)–based genotyping has matured quickly, and it is now possible to analyze hundreds of thousands of markers per genome in a single assay. “Chipping away” at the genome has become fashionable in the scientific community, and several studies are being published every month. However, without some clear concept of how to scrutinize the resulting candidate loci, many studies seem not to fulfill their promises completely. The major questions are not whether a locus is dominant or
recessive, penetrant or merely modifying disease risk. It boils down to whether there is a gene or gene-controlling element (promoter, enhancer, or suppressor) that would make functional sense to be broken or dysfunctional in a given disease. Thus, when a genome-wide linkage analysis results in a map of candidate loci, the hard work follows in formulating testable hypotheses to guide the mappers to the right gene loci.

Sellick and colleagues have undertaken the first major step by analyzing which families contribute to which candidate loci. Unfortunately for all of us, that is where the story ends, without clear coordinates for which genes to implicate in the pathogenesis of familial CLL. The authors have speculated about a gene in 2q21, CXCR4, and SMAD7 in 18q21, but there are no significant results about these 2 genes or any other in these regions. This represents the challenge of studying such genes, in which correct identification of germ line mutations can take teams many years to fully validate. Responsible genetic factors were once more confirmed to be heterogeneous, which complicates hunting for familial CLL predisposition genes.\(^1\)\(^2\) Publication of valuable, but not conclusive, work such as that of Sellick and colleagues is important because it provides all those working in the field of CLL familial predisposition with information to pursue further.

Despite the effort, why were no definitive loci identified for future study? The problem may, in part, be due to the study cohort; 122 families (approximately 60%) had only 2 affected individuals, and a further 54 (approximately 26%) contained only 3 affected individuals. These pedigrees provide only limited linkage power. On the other hand, there were 2 large families with 10 and 12 individuals with CLL, respectively. Such families should provide substantial linkage. The main drawback appears to be the lack of unaffected relatives in the study, as only 54 were included to reconstruct genotypes. For decades, geneticists have successfully studied single-gene disorders in relatively few large sibships and collected all obtainable samples. In cancer research, the notion of collecting samples from healthy relatives is still stigmatized because they may not (yet) present with a phenotype, and there is great potential to raise the anxiety of the uninvolved person. Nevertheless, such samples provide powerful means to exclude large chromosomal regions. People are understandably afraid to know what their genome holds in store for them in the future, and extensive counseling is required to provide patients with confidence in the value of contributing such samples. Additionally, collaborative efforts such as the one described by Sellick and colleagues are required so that a large number of extensively characterized families with CLL predisposition can be studied. The separate academic groups included in this work are to be commended for their selfless collaboration.

**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

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