of Gaucher disease and as-yet unknown genetic risk factors for the development of gammopathies in some patients. The difficulties in determining the genetic and mechanistic bases for this association highlight the complexities of this "simple" Mendelian disorder. ■

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NEOPLASIA

Comment on De Keersmaecker et al, page 4849

A remarkABL new fusion oncogene in T-cell ALL

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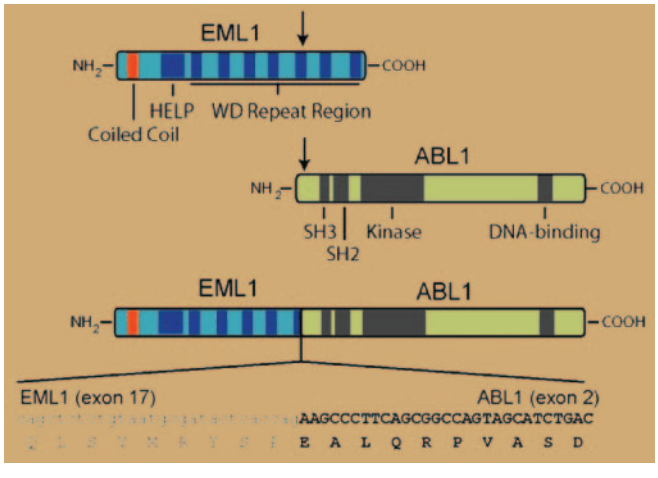
A novel fusion of *ABL1* to *EML1* adds to a growing list of chimeric ABL proteins in patients with acute T-cell lymphoblastic leukemia.

Until recently, our recognition of the involvement of the *ABL1* gene (which encodes the nonreceptor protein tyrosine kinase c-ABL1) in the pathogenesis of T-cell acute lymphoblastic leukemia (T-ALL) was limited to rare cases of Philadelphia chromosome–positive T-ALL, some of which likely represented lymphoid blast crisis of chronic myeloid leukemia. The first hint that *ABL1* might be involved more frequently in this disease came from a United Kingdom Medical Research Council study that used fluorescent in situ hybridization (FISH) with probes from the *ABL1* locus to analyze interphase nuclei from lymphoid leukemia blasts. The study was intended to detect cryptic *BCR-ABL1* fusion but instead found extrachromosomal amplification of the *ABL1* locus independent of *BCR* in 8 of 280 T-ALL samples.[1] The nature of the amplification was soon revealed when researchers from the University of Leuven in Belgium demonstrated that *ABL1* was fused to *NUP214* via episomal amplification in 5 of 90 patients with T-ALL.[2] This resulted in fusion of N-terminal sequences of the NUP214 protein, a ubiquitously expressed component of the nuclear pore complex, with the same 1104 C-terminal amino acids of c-ABL1 found in the BCR-ABL1 fusion protein. Like BCR-ABL1, the NUP214-ABL fusion is a constitutively active tyrosine kinase with transforming activity in vitro. Collectively, these results suggested that *ABL1* might be involved in the pathogenesis of 5% to 6% of T-ALLs.

In the current issue of *Blood*, the Leuven group extends these results to identify a new *ABL1* fusion gene in T-ALL. A patient with T-ALL whose blasts lacked *ABL1* amplification but demonstrated a split in the hybridization signal between 5′ and 3′ *ABL1* probes was found to have cryptic t(9;14), leading to fusion of *ABL1* with *EML1* on chromosome 14. *EML1* encodes a protein with similarity to an echinoderm microtubule-associated protein (EML1), and the resulting 190-kDa echinoderm microtubule-associated protein–like 1–Abelson 1 (EML1-ABL1) fusion is a dysregulated tyrosine kinase that alleviates interleukin-3 dependence in Ba/F3 hematopoietic cells and constitutively activates extracellular signal-related kinase (ERK), signal transducers and activators of transcription 5 (Stat5), and Src signaling pathways. As with BCR-ABL1, EML1-ABL kinase activity was dependent on a coiled-coil domain in the N-terminus, suggesting that oligomerization and autophosphorylation are necessary to overcome the autoinhibition of the ABL kinase domain.[3] The leukemic cells from this patient exhibited ectopic expression of the homeobox transcription factor TLX1 and hemizygous deletion of the *CDKN2A* tumor suppressor gene. These alterations were also seen frequently in patients with *NUP214-ABL1* fusion[2] and provide more evidence that T-ALL can be divided into subgroups with distinct molecular pathogenesis.[4] Interestingly, expression of *EML1* was not observed in other T-ALL blasts or cell lines, suggesting that the *EML1* promoter may be activated as a consequence of the translocation.

These findings have therapeutic implications, of course. The EML1-ABL1 fusion protein was inhibited by imatinib mesylate, the small molecule inhibitor of ABL kinase activity, with approximately the same sensitivity as BCR-ABL1, raising the possibility that patients with T-ALL with NUP214-ABL1 and EML1-ABL1 might respond clinically to imatinib treatment. In the previous study, imatinib was found to inhibit the growth of a T-ALL cell line with the NUP214-ABL1 fusion,[2] but the clinical utility of imatinib in these patients might be limited by rapid selection for resistance, as is observed in Philadelphia chromosome–positive patients with



In T-ALL with cryptic t(9;14), N-terminal sequences from the EML1 polypeptide, including a coiled-coil domain, are joined to the same C-terminal ABL sequences present in the more common BCR-ABL1 fusion protein. The resulting 190-kDa EML1-ABL1 fusion protein is a dysregulated tyrosine kinase that transforms Ba/F3 cells. For details, see the article beginning on page 4849.

B-ALL with amplification of *BCR-ABL1*.[5] Patients with *ABL1* fusions from balanced translocations might fare better. Finally, the search for activated *ABL1* genes in T-ALL is not over. Although the FISH studies[1,2] suggest that there are no other frequent *ABL1* amplifications in acute lymphoid leukemias, additional cryptic *ABL1* translocations will no doubt continue to pop up. In addition, point mutations in *ABL1* can also dysregulate c-ABL1 kinase activity and cause lymphoid leukemia in mouse models,[6] but finding these cases will require direct exon sequencing of genomic DNA. ■

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TRANSPLANTATION

Comment on Tivol et al, page 4885

Chronic graft-versus-host disease: a breakdown of self-tolerance?

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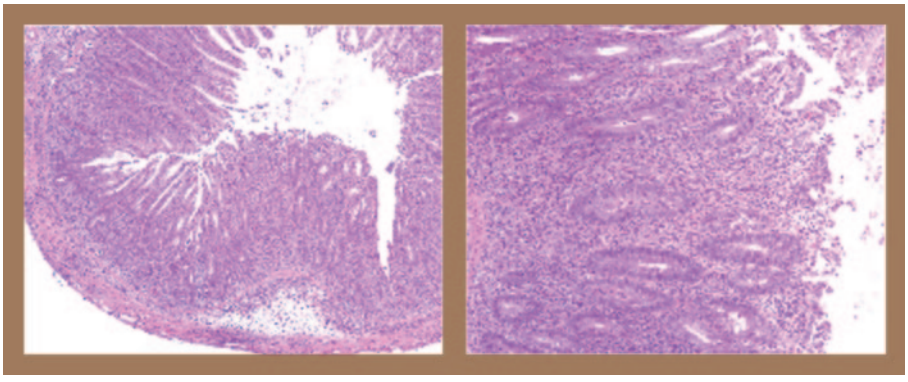
The immunologic response to foreign alloantigens in graft-versus-host disease can lead to the breakdown of self-tolerance precipitating autoimmunity.

Graft-versus-host disease (GVHD) is a major life-threatening complication of allogeneic bone marrow transplantation (BMT). Initially presenting as an acute inflammatory response, GVHD can evolve into a chronic disease that shares many characteristics with several autoimmune disorders. In this issue of *Blood*, innovative research by Tivol and colleagues reveals that immune tolerance to self-antigens is broken during GVHD with the emergence of autoreactive T cells capable of mediating disease.

During the past decade, considerable progress has been made in elucidating the pathophysiology of acute GVHD. Following allogeneic BMT, a graft-versus-host reaction is initiated when donor T cells transferred along with the bone marrow graft directly recognize alloantigens presented by the antigen-presenting cells (APCs) of the host. The activated donor antihost-specific T cells expand in the developing "cytokine storm," resulting in tissue destruction that is normally limited to the skin, liver, and intestinal tract as the target organs.[1] Host APCs are also destroyed during the initial phases of acute GVHD.

The underlying immune mechanisms responsible for chronic GVHD, however, have remained controversial. Chronic GVHD usually develops after an episode of acute GVHD but may also occur de novo.[2] Comparatively, chronic GVHD has discrete clinical features resembling a variety of collagen vascular disorders, including Sjogren syndrome and scleroderma. These clinical manifestations led to the hypothesis that chronic GVHD is an autoimmune disorder. The detection of autoreactive T cells of donor origin (donor-antidonor reactivity) following allogeneic BMT in human and in murine systems further supported this premise.

In an elegant series of studies, Tivol et al confirm this hypothesis, providing direct evidence that $CD4^+$ autoreactive T cells of donor origin emerge during GVHD. These cells, which recognize self (donor) major histocompatibility complex (MHC) class II antigens, target the colon when adoptively transferred into naive donor strain recipients. The pathologic damage is consistent with autoimmune colitis. Cells of the innate immune system (granulocytes) appear to play a significant role in this autoimmune process. Moreover, the studies by Tivol et al also reveal that there is a disparate requirement for host and donor APCs in acute and chronic GVHD. Although host APCs are required for the initiation of acute GVHD, donor APCs play a central role in both the progression of acute GVHD and the development of chronic GVHD. These APCs present both donor and host antigens to the engrafted donor T cells, allowing for the activation of alloreactive and autoreactive T cells. However, it remains unclear whether the autoreactive T cells arise due to thymic damage during acute GVHD (compromising negative selection) or due to the cross-presentation of self-antigens. Nevertheless, the research from Tivol et al provides not only important insights into some of the underlying immune mechanisms involved in acute and chronic GVHD, but also emphasizes the importance of establishing tolerance to both host and donor antigens after allogeneic BMT. ■



Colitis is characterized by extensive infiltration of T cells and granulocytes. See the complete figure in the article beginning on page 4885.