mutations, may be sensitive to tyrosine kinase inhibitors in vivo, or to agents inhibiting activated JAK-STAT signaling pathways, incorporating tyrosine kinase inhibitors into therapy may significantly improve clinical outcomes in these forms of ALL. Thus, these studies lay the foundation for new therapeutic approaches to the treatment of both B- and T-cell ALL cases with mutations in these pathways.

Another fascinating aspect of the study of Perez-Garcia et al is the observed co-association of autoimmune disorders and leukemia, underscoring the critical role of the pancreatic regulatory gene in the pathogenesis and therapy of ALL. Several highly interesting questions remain. Are homozygous mutations in SH2B3 alone sufficient to promote leukemogenesis? Although Perez-Garcia et al found that the affected sibling with a homozygous SH2B3 germline mutation and ALL also had deletions of CDKN2A, what other somatic or germline mutations were present in the leukemic cells? An unbiased sequencing study in this patient would be of great interest to identify additional potentially cooperating mutations. Indeed, in our own ongoing sequencing efforts in large cohorts of high-risk pediatric patients with B-precursor ALL, we have also found that SH2B3 mutations are rare, occurring in 12 of 784 patients, a frequency of only 1.5% (Roberts et al, unpublished data).

Yet despite their rarity, the discovery of SH2B3 mutations, both somatic and germline, provide new and important insights for the continued investigation of the role of this important regulatory gene in the pathogenesis and therapy of ALL. Further investigation of the critical relationship between these diseases and the central role that SH2B3 may play in the development and regulation of critical cytokine signaling pathways that may underpin both leukemia and autoimmunity. Further investigation of the critical role of SH2B3 regulation of JAK-STAT signaling, and other cytokine signaling pathways, will likely reveal important new insights into the pathogenesis and therapeutic approach to these diseases.

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Comment on Jerez et al, page 2453

STAT3 mutations and persistence of autoimmunity

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In this issue of Blood, Jerez et al show that signal transducer and activator of transcription 3 (STAT3) mutations resulting in persistent proliferation of cytotoxic autoimmune T-cell clones as seen in large granular lymphocytic (LGL) leukemia is present in the autoimmune disorders acquired aplastic anemia (AA) and myelodysplastic syndrome (MDS).1 They performed a study on a large number of adult-acquired AA and MDS patients, and a small number of these patients have identical STAT3 mutations as they have previously seen in LGL leukemia. In their studies, they found that there was oligoclonal transformation of LGL with STAT3 mutation in autoimmune Vβ11+ CD3+ CD8+ CD56- T-cell populations. They also supported their role in autoimmunity by showing a higher proportion of STAT3 mutation T-cell...
clones in HLA-DR15 previous associated with an increased incidence of acquired AA. An underlying immune-mediated pathophysiology in acquired AA is well supported by the observed expansion of cytotoxic T cells in acquired AA patients. Additional support to an immune-mediated mechanism is the fact that it is effectively treated by immunosuppressive therapy using cyclosporine and anti-thymocyte globulin in ~70% of patients. The immune basis of AA is further supported by the observation of an increased AA rate in patients with HLA-DRB15 and an increase incidence in different ethnic groups. Paroxysmal nocturnal hemoglobinuria (PNH) phenotype cells have been identified in patients with acquired AA. Studies in adults with AA have shown a superior immune suppressive therapy response in those with detectable PNH phenotype cells, suggesting a secondary escape from immune damage. Although the autoimmune basis of AA is relatively clear, autoimmunity as an underlying mechanism of MDS is much more complicated. MDS appears to come from a hematopoietic stem cell harboring irreversible DNA damage, with bone marrow hematopoietic exhaustion and dysplastic cellular morphology as common characteristics. An immune-mediated response against normal hematopoietic cells in MDS does appear to be a mechanism in at least some patients with MDS. An inflammatory environment with both Th22 and Th17 cells expanding differentially is also present. An “immune hypothesis” has been proposed for MDS whereby there is an immune-mediated myelosuppression in MDS leading to a preleukemia phenotype. Either way, both AA and MDS have a proportion of patients that have associated with clinical autoimmune phenomena in addition to T cell-mediated myelosuppression, and cytokine dysregulation in the bone marrow environment. Thus, the link of both disorders to an underlying autoimmune mechanism with an association with other autoimmune manifestations appears to be well established. The role of LGL expansion in chronic lymph proliferative disorders of natural killer (NK)- and T-cell LGL leukemia was described by the authors as the basis of their hypothesis. Others have described polyclonal expansion of CD4+CD56+ LGL in autoimmunity as mediated through the Fas/Fas ligand pathways. All of these observations, as well as those in the current study, point toward aberrant LGL expansion in autoimmunity as an important mechanism. Measurement of such a population may be clinically useful both as a diagnostic markers and as a measure of therapeutic response. Another characteristic of AA is short granulocyte telomeres. Adult AA studies have shown that short pan-leukocyte telomere length is not predictive of immunosuppressive therapy response but is associated with increased likelihood of relapse, clonal evolution, and death. In children, our group has observed that the telomeres of NK and fully differentiated T cells were short in a number of the patients, most who also had short granulocyte telomeres. Interestingly, many of these patients had normal telomere lengths in other leukocyte subsets, such as B cells and memory T cells. The shortened telomeres in granulocyte and NK cells in AA may be indicative of chronic autoimmune stimulation. Although no clear association currently exists, it is possible that shortened telomeres in NK, T cells, or LGL increase the possibility of STAT3 mutations in cytotoxic T lymphocyte clones, leading to persistent autoimmunity. The authors suggest that the STAT3 mutations are primarily required for the persistence of aberrant oligoclonal autoimmune T-cell clones, resulting in persistence of an autoimmune response. If this is true, then STAT3 mutations in LGL clone may be present in other autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosis, and scleroderma. Whether this is a mechanism only for hematopoietic-directed autoimmunity or autoimmunity that results into toxicity to other organs needs to be explored. A better understanding of this subgroup of AA and MDS in what appears to be a heterogeneous number of mechanisms is needed. Additional investigations are needed regarding whether similar or very different mechanisms play a role in other subtypes of AA and MDS. If STAT3 mutations can be clearly established as a major component of the pathogenesis of AA and MDS, targeted therapeutic approaches may be used in the future.

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