needed to address what downstream pathways lead from a decrease in UBA1b to systemic inflammation and to assess both the direct cellular effects and cell-type specificity of a loss of UBA1b function. These findings have important clinical implications for risk stratification and, potentially, therapy selection in VEXAS. Should patients with the p.Met41Val variant be selected for allogeneic hematopoietic stem cell transplantation? Are there differences in therapeutic responses (eg, azacytidine, ruxolitinib) between VEXAS genotypes? These remain important questions to be further assessed in future studies. Significantly, the identification of the centrality of the loss of UBA1b translation in VEXAS opens the possibility of future therapeutic approaches that could restore UBA1b function within cells.

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LYMPHOID NEOPLASIA

Comment on Li et al, page 1507

Do you need the immune system to cure ALL?

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How much does a patient's immune system contribute to achieving cure for acute lymphoblastic leukemia (ALL)? This question is at the heart of the study by Li et al[1] in this issue of *Blood*.

This is a longstanding controversy. Initially, the failures of robust graft-versus-leukemia effects with donor leukocyte infusions after allogeneic bone marrow transplantation[2,3] suggested that immune mechanisms are much less effective and less critical to curing ALL than to curing myeloid diseases. However, since the remarkable success of chimeric antigen receptor (CAR) T-cell therapies in B-cell ALL (B-ALL), it has become clear that ALL is indeed very amenable to long-term, potentially curative, immunologic control.[4] Between these 2 extremes, a host of studies support immune mechanisms that contribute to long-term cures, but the precise mechanisms and the interplay between chemotherapy and/or molecular targeted therapies remains elusive.

In their study, Li et al used an immunocompetent murine model of *BCR-ABL* ALL to carefully investigate cytotoxic effects of endogenous T cells against B-ALL blasts and the contribution of standard ALL chemotherapeutic agents and tyrosine kinase inhibitors (TKIs) to the antileukemic effect. Li et al addressed 3 main questions:

1. Do immune mechanisms contribute to achieving cure with standard ALL chemotherapy or TKIs in a measurable way? At least in the Li et al model, this does seem to be the case. Doses of mercaptopurine (6MP), dexamethasone, and dasatinib that cured immunocompetent mice failed to cure mice of the same strain (B6) that lacked both T and B cells (*Tcra*-KO). Both CD4 and CD8 T cells were required for this effect. This has long been suspected, but the results presented by Li et al provide both mechanistic proof and a system that can be used to study molecular mechanisms and therapies.
2. Is there an interplay between immune mechanisms and the emergence of kinase mutations during TKI therapy? Intriguingly, immunocompetent mice that relapsed had unmutated BCR-ABL and were no longer receiving dasatinib (after completing a 35-day course), whereas the majority of immunodeficient mice that relapsed had developed a resistance-inducing mutation and were still receiving dasatinib when the relapse occured. These provocative data suggest a role for the immune system in preventing the emergence of TKI-resistant clones, a fascinating possibility that deserves further investigation.
3. What are the key pathways involved in this response? And can they be enhanced for therapeutic purposes? Transcriptomic analysis of leukocytes and serum cytokines during treatment suggested that interferon-γ (IFN-γ) and interleukin-12 (IL-12) are critical mediators of antileukemic immunologic control. Indeed, exogenous IL-12 improved cure rates achieved with dasatinib in the immunocompetent model. IL-12

was previously studied in several malignancies (albeit not ALL) and was found to be quite toxic, with minimal efficacy. The data reported by Li et al suggest that IL-12 deserves another look.

The identification of IFN-γ and IL-12 as potential mediators or enhancers of immunologic control of leukemia is particularly tantalizing. However, more work will be needed to precisely define the molecular role of IFN-γ and IL-12, the dosing and sequencing of their combinations with cytotoxic agents, and other immunotherapy approaches. The effect of IFN-γ on T-cell function in ALL seems particularly complex. High acute levels of IFN-γ have been shown to contribute to cytokine release syndrome after CAR T-cell therapy, and IFN-γ blockade was not detrimental to CAR T-cell function. In fact, IFN-γ has been reported to decrease T-cell proliferation and result in upregulation of inhibitory checkpoint proteins in this context.[5] Precisely how IL-12 acts in this system is not clear. The model described by Li et al will be useful for working out mechanisms, dosing, and sequencing that optimizes the efficacy of IL-12 while reducing toxicity.

Dexamethasone, 6MP, and dasatinib all impair T-cell function. Yet, clearly the antigen and inflammatory stimuli resulting from their cytotoxic activity toward leukemia cells were able to awaken an immune system that was previously dormant to the transplanted leukemia cells. It is remarkable that this is powerful enough to improve the survival of animals despite the direct immunosuppressive effect of the agents used. Would an agent that induces apoptosis without negatively affecting immune function, such as venetoclax,[6] be even better suited to combine with immune stimulants?

Despite intriguing findings, a few drawbacks remain; chief among them is the relatively artificial model. The human BCR-ABL protein may be substantially more immunogenic in a murine host than it would be in an actual human patient in whom the fusion is composed of the BCR and ABL sequences that the patient is fully tolerant to. It is encouraging that fusion-reactive T cells have been isolated from patients with *ETV6-RUNX1* ALL, *BCR-ABL* ALL, and chronic myeloid leukemia,[7-10] suggesting that the model described here indeed recapitulates key aspects of human disease. Nevertheless, it is critical that future studies determine the degree to which immune mechanisms contribute to overall treatment success in patients treated with chemotherapy. Does it vary by molecular subtype? Are there age-dependent differences that could potentially contribute to the much inferior outcomes in infants and older adults (on top of the obvious culprits of more high-risk molecular subtypes and comorbidities)?

With several large clinical trials currently investigating the incorporation of blinatumomab into first-line therapy, it is clear that ALL immunotherapy is moving into the mainstream. At the same time, hematopoietic stem cell transplantation and CAR T-cell therapy (or a combination of both) are powerful immune-based modalities in the relapsed setting that can be effective where chemotherapy has failed, but long-term response rates remain suboptimal. Understanding the molecular wiring of anti-ALL immune responses and devising ways to enhance them is likely to have a critical impact on ALL cure rates in the next decade.

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