In addition, other cytokines (ie, IL-15) and growth signals clearly play a role in T-cell proliferation and function. Finally, in its effort to answer a very specific question regarding the role of sIL-2Rα, the present article is not able to address the malignant lymphoma B-cell population itself and how it interacts with intratumoral T cells.

Nevertheless, this report by Yang and colleagues is the first to describe the adverse prognostic relevance of sIL-2Rα in patients with FL. The authors provide valuable insights into the intratumoral T-cell milieu and how CD4+ T cells are lulled into a tolerant Treg phenotype while the CD8+ cytotoxic T cells are made less effective by the sIL-2Rα/IL-2 complex. In contrast to blocking IL-2 activity, circulating sIL-2Rα binds to IL-2 and significantly enhances its signaling. Although it remains unknown as to why sIL-2Rα is increased, it is derived directly from activated T cells themselves, and is part of the toxic fertilizing mix permitting malignant B cells to grow.

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

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Comment on Sheng et al, page 2840

**Bcr-Abl adds another twist to cell fate**

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Bcr–Abl remains the prime target for CML therapy, but recent findings from Sheng and colleagues suggest that its inhibition may expose a new loophole in the cell death process. Their report defines a new role for the Bcr–Abl signaling complex in suppressing autophagy, a catabolic process that partially destroys a cell’s content.

The cell uses autophagy to reallocate its content to essential processes when no other source exists and to temporarily offset cell destruction during stressful or nutrient–lean times. Its activation can therefore relieve the cell of stress, such as the effects from inhibiting oncogene addiction via Bcr–Abl. Studies have shown that Bcr–Abl kinase inhibition with imatinib engages both apoptosis and autophagy; importantly, the latter diminishes the frequency of apoptosis in CML cells. Therefore, to improve the response to CML therapy, autophagy must be suppressed during the stress applied by Bcr–Abl kinase inhibition. To do this with precision rather than relying on generalized inhibitors of the autophagic pathway, we need a clear understanding of the signaling complexes engaged by Bcr–Abl to suppress autophagy. Keeping those pathways blocked while activating apoptotic pathways through inhibition of the Bcr–Abl kinase would likely increase the efficacy of imatinib against CML cells and possibly extend its benefit to Bcr–Abl–expressing cells with a highly responsive autophagic pathway (ie, stem cells).

The article by Sheng et al in this issue of Blood provides a clear description of the signaling cascade that connects Bcr–Abl to...
negative regulation of autophagy.1 This information may have significance and impact on the clinical management of CML.

Sheng and colleagues mapped out a clear path from Bcr-Abl to the master autophagy regulator, mTOR, as the major route by which Bcr-Abl represses autophagy. Bcr-Abl activates the PI3K/Akt pathway that phosphorylates many targets including the transcriptional repressor FOXO4. When phosphorylated, FOXO4 cannot repress transcription of ATF5, a gene previously shown to regulate apoptosis in cytokine-dependent cells. In Bcr-Abl–transformed cells, ATF5 takes on a new role as a regulator of autophagy, not apoptosis. Sheng et al demonstrate that ATF5 regulates mTOR expression by binding a previously unidentified ATF5 binding site in the mTOR promoter. Elevated expression of mTOR by ATF5, coupled with mTOR activation by other components of the PI3K/Akt cascade, suppresses autophagy. mTOR activation can be reversed on Bcr-Abl inhibition, resulting in the onset of autophagy, as illustrated in the figure. Unfortunately, imatinib-mediated reversal of this suppression blocks the full impact that Bcr-Abl kinase inhibition has on apoptosis. The observations of Sheng and coworkers provide a clear mechanism for correcting this unwanted effect of imatinib. Based on their model, activation of mTOR combined with Bcr-Abl inhibition should block the induction of autophagy to enhance the apoptotic response. This may translate into direct clinical benefit in terms of depth or kinetics of a molecular response.

However, the central question is how can we exploit this newly mapped Bcr-Abl path to autophagy to improve CML therapy? In addition, do the potential risks in modulating the autophagy pathway outweigh the potential benefits? As noted by many studies, engagement of autophagy can be both friend and foe to tumor cell survival.1 In CML, imatinib clearly engages autophagy, but the degree to which this diverts apoptosis may not significantly influence clinical imatinib responsiveness. On the other hand, the degree of apoptotic escape may be distinct in CML stem cells compared with progenitors, as suggested by earlier studies.1 Therefore, in the CML setting, preserving mTOR activity during imatinib therapy may be key to engaging a greater apoptotic impact, particularly against early CML progenitors or stem cells that are relatively resistant to tyrosine kinase inhibition.

As outlined in the figure, many pathways converge on mTOR. The Bcr-Abl/PI3K/Akt/ATF5/mTOR autophagic suppressor cascade is most relevant in CML, but other pathways may modify it and continue to suppress apoptosis during imatinib therapy. For example, Sheng et al demonstrate that a constitutively activated mutant of PI3K blocks induction of autophagy on imatinib treatment. This suggests that activating the PI3K pathway with other growth factors (insulin, IGF–1) or cytokines (IL–3, GM-CSF) might suppress autophagy during imatinib treatment. For example, Sheng et al demonstrate that a constitutively activated mutant of PI3K blocks induction of autophagy on imatinib treatment.

This model of the PI3K/Akt/ATF5/mTOR autophagic suppressor cascade and its potential for directing therapy may offer opportunities for future development. For example, multiple myeloma represents another disease with high levels of autophagy.2 Similarly, other cancers. CML treatment with Bcr-Abl kinase inhibitors may be an opportunity to examine the benefits and consequences of suppressing autophagy to improve therapy. The detailed map of the Bcr-Abl/autophagy cascade provided by Sheng et al provides a good starting point.

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

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PHAGOCYTES & GRANULOCYTES

Comment on Hsu et al, page 2653, and on Dickinson et al, page 2656

GATA2 finds its macrophage niche

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In this issue of Blood, Hsu et al1 and Dickinson et al2 independently report the presence of mutations in the region of GATA2 encoding the carboxy–terminal zinc-finger domain of the protein in a rare genetic disease associated with reduced production of marrow–derived immune cells susceptible to development of myelodysplastic syndrome and acute myeloid leukemia.

The central role of the GATA family of transcription factors in hematopoietic development has been well established in mice and in culture models of human hematopoiesis.3 The expansion of early cell compartments is under the control of GATA2. With maturation, this control switches to GATA1 for the erythroid/megakaryocytic lineage and to GATA3 for T cells. The GATA factor that controls the late phases of myelo-monocytic
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