Comment on Larrue et al, page 882

Not only TKI! Targeting FLT3-ITD by autophagy

Guido Marcucci and Ling Li

In this issue of Blood, Larrue et al identify the downstream posttranslational regulation of the Fms-related tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) protein. This study adds further to the understanding of beneficial impact of using “dirty” proteasome inhibitor in acute myeloid leukemia (AML). This study also provides a novel antileukemia role of autophagy, since it is a well-known physiological process that controls normal cell homeostasis through protein degradation and turnover of cell organelles.

The extensive cytogenetic and molecular characterization of AML has led to a better understanding of basic mechanisms of leukemiaogenesis, has defined prognostic subgroups of AML patients, and has provided much-needed treatment guidance for selecting the most appropriate therapies based on genetic lesions present. Although these lesions have been informative, an understanding of how these genetic lesions act in concert to deregulate fundamental mechanisms of normal cell homeostasis and contribute to leukemic transformation is necessary for a rational design of more active therapies.

Nevertheless, the discovery of recurrent mutated genes encoding proteins with proleukemic activity has created opportunities for designing “smart” targeting therapeutics and led to the concept of personalized medicine for AML. The ITD is a gain-of-function mutation of the FLT3 gene encoding 1 of the receptor tyrosine kinases, and is one of the most common genetic abnormalities in AML. The ITD mutation results in constitutive ligand-independent FLT3 activation, which aberrantly activates a signaling cascade of downstream effectors (ie, mitogen-activated protein kinase, STAT5, PI3K), thereby supporting leukemia cell proliferation and survival. Although patients harboring FLT3-ITD are initially sensitive to chemotherapy, they frequently relapse even after allogeneic stem cell transplantation, consistent with the failure of these approaches to eradicate the so-called leukemia stem cell subpopulation. Tyrosine kinase inhibitors (TKIs) have been designed to target the aberrantly activated FLT3 receptor and to “shut off” constitutive tyrosine phosphorylation in AML blasts. Although these compounds have shown initial preclinical and early clinical results, a survival benefit from their use in combination with chemotherapy has only recently been reported in FLT3-ITD AML patients. However, this class of compounds may still have limitations related to an inherent deficiency of substrate specificity (potentially less problematic with newer generation TKIs), early onset of mutagenesis in the FLT3 kinase domain, and inevitable toxicity.

In addition, complex regulatory feedback mechanisms that govern the expression of the mutated and/or wild-type alleles and the stability of the corresponding encoded proteins may contribute to early occurrence of TKI resistance in FLT3-ITD AML blasts. Finally, the concurrent presence of other gene mutations (eg, NPM1, DNMT3A, IDH1, and IDH2) not only impacts the prognostic significance of FLT3-ITD, but may also contribute to reduced clinical response of this subset of patients. Thus, understanding the multifaceted biological role of FLT3-ITD in AML is a necessary step to discover how to deactivate completely tyrosine kinase-mediated proleukemogenic signals.

The complexity of upstream transcription regulation of genes encoding receptor tyrosine kinases has been dissected, and strategies for inhibiting the expression of FLT3 mutated alleles have been already suggested and tested in early clinical trials.

In this issue, Larrue et al take a different approach and focus on the downstream posttranslational regulation of the FLT3-ITD protein (see figure). The authors demonstrate an antileukemia role of autophagy, a well-known physiological process that controls normal cell homeostasis through protein degradation and turnover of cell organelles. The fine-tuned mechanisms regulating autophagy are complicated and not fully understood, especially in the context of cancers in which contrasting roles of autophagy-dependent cell survival and death have been reported previously. Upon observing proteasome inhibitor-initiated autophagy induced by the conversion of LC3-I to LC3-II, Larrue et al show that FLT3-ITD molecules become detectable within the autophagosomes and eventually are degraded. Using both genetic and pharmacological tools, they validate the involvement of key autophagy steps in the degradation of the FLT3-ITD protein, which

REFERENCES

resulted in effective regression of leukemia in vivo. TKI resistance can emerge during treatment as the result of selection of FLT3-ITD point mutations (eg, D835Y) that interfere with drug binding. Larrue et al show that bortezomib induced a similar degradation of both D835Y and parental FLT3 mutants and suggest combinations of TKIs with proteasome inhibitors (eg, bortezomib) to aim not only at protein enzymatic inhibition, but also at induction of autophagy-dependent degradation for a complete deactivation of FLT3-ITD in AML.

Whereas TKIs have shown antileukemia activity as single agents, bortezomib, the first Food and Drug Administration–approved proteasome inhibitor, has no antileukemia effect when used alone in AML patients, but the beneficial impact of this agent could be observed when incorporated into chemotherapy-based regimens. A concern for the use of TKIs and bortezomib together may derive from a relatively high frequency of toxicities with each agent alone (eg, peripheral neuropathy, diarrhea, lung toxicity), which could be significantly reduced or perhaps eliminated by switching to a newer generation of these compounds. The proteasome inhibitors have several off-target activities, and this may raise the question of whether the use of “dirty” drugs in AML may exemplify a return to the past with less specific and “1-size-fits-all” therapies. In reality, incorporation of drugs with off-target activities in combination with more specific inhibitors may prove to be a sound strategy if we broaden the “1 target-1 drug” concept to a more comprehensive definition of therapeutic targeting that includes complex networks of mechanisms whose interplay and concurrent (de)regulation shift the equilibrium from normal to malignant hematopoiesis in individual patients with unique molecular features.

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REFERENCES


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Comment on Machlus et al, page 921

Platelet production: new players in the field

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In this issue of Blood, Machlus et al report a novel potential positive feedback mechanism whereby the platelet-borne inflammatory cytokine chemokine ligand 5 (CCL5; also known as regulated on activation, normal T cell expressed and secreted [RANTES]) can stimulate megakaryocytes to produce platelets.
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