Comment on Paoluzzi et al., page 5350

Bak to death with chemotherapy

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In this issue of Blood, Paoluzzi and colleagues describe preclinical results of combining a BH3 mimetic (AT-101) with standard chemotherapy agents in models of B-cell lymphoma, and demonstrate significant synergy in a schedule-dependent manner of administration.

BH3 mimetics, such as AT-101, are designed to interfere with various antiapoptotic proteins such as bcl-2, bcl-XL, and mcl-1, thus activating Bax and Bak; these mimetics ultimately promote apoptosis through a complicated pathway (see figure). When a malignant lymphocyte is exposed to chemotherapy, modulation of the cellular apoptotic threshold through this pathway could significantly enhance cytotoxicity.

Therefore, the targeting of antiapoptotic proteins represents an exciting paradigm to treat lymphoma. Bcl-2, in particular, plays a critical role in normal lymphocyte development, and, through the t(14;18) translocation, in the pathogenesis of follicular lymphoma. A subset of diffuse large B-cell lymphoma cases also overexpresses bcl-2 through amplification; this molecular subtype responds less well to conventional chemotherapy. In mantle-cell lymphoma cell lines, significant synergy was observed with AT-101 in combination with the proteasome inhibitor carfilzomib, but not bortezomib. Pretreatment with AT-101, particularly at a high dose, improved activity of rituximab.

The article by Paoluzzi and colleagues in this issue of Blood details an elegant series of experiments designed to explore appropriate dose and schedule of AT-101 alone and in combination with a variety of other agents. They demonstrated that duration of exposure was not a critical determinant of cytotoxicity, but dose was critical. In mantle-cell lymphoma cell lines, significant synergy was observed with AT-101 in combination with the proteasome inhibitor carfilzomib, but not bortezomib. Pretreatment with AT-101, particularly at a high dose, improved activity of rituximab.

There are several limitations to these studies. The human in vivo mechanisms of therapeutic agents, particularly rituximab, may not be recapitulated well in these artificial model systems. Moreover, perhaps the major disease of interest, follicular lymphoma, lacks predictive cell lines and murine models, and it is unclear if any of the findings would extend to that histology. The chosen agent, AT-101, a pure negative enantiomer of gossypol, may be inferior in efficacy and more toxic than other BH3 mimetics, including a modified version, apogossypol. Finally, these interesting results with AT-101 may not extend to other members of the BH3 mimetic class of drugs, as specificity of these small molecules for the individual BH3 family members varies significantly.

Despite these considerable limitations, the studies provide an important framework in developing rational clinical trials that combine small-molecule inhibitors with standard agents for lymphoma, and suggest key features of the biology of lymphoma and cellular apoptotic pathways. Given the small numbers of patients available for clinical trials, and the substantial expense of conducting such trials, taking hints about trial design from carefully conducted cell line and murine experiments is now a crucial first step. As the phase 1 and 2 trials are developed with this exciting class of agents, it is hoped that...
appropriate correlative studies will be performed
to both validate the model systems and deter-
mine the degree to which the putative target is
affected by the agent under evaluation.

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Comment on Babich et al, page 5282

Slipping out the Weibel-Palade body

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In this issue of Blood, Babich and colleagues disclose an elegant mechanism that
serves to selectively release cargo from WPBs.

Weibel-Palade bodies (WPBs) are versa-
tile storage organelles within endothelial
cells that release their inflammatory and
prothrombotic content into the circulation in
response to a large number of agonists.1 Using
real-time analysis of fluorescently tagged von
Willebrand factor (VWF) and VWF propolypeptide, Babich et al nicely show that a
proportion of WPBs transiently fuse with the
plasma membrane during a “lingering kiss.”

Fusion pores of approximately 12 nm in diam-
ereter are generated that facilitate the selective
release of low–molecular-weight components
like IL-8 from these organelles. An important
physiological implication of these findings is
that endothelial cells can selectively release
proinflammatory cytokines like IL-8 and
cotaxin-3 while retaining prothrombotic
VWF. The selective release of small-core and
membrane proteins comes at a cost, though;

- The pH within WPBs during a lingering kiss
crease in intracellular pH results in the rapid
disappearance of VWF tubules (see figure).
- The morphological characteristics of these
collapsed WPBs have not been determined.

In their visually appealing article, Babich
and coworkers show that lingering kisses
account for 10% to 25% of all fusion events
following stimulation with histamine.
A large number of agonists can provoke re-
lease of WPBs. Clinically, this is exploited
by the administration of desmopressin
(DDAVP) to patients with von Willebrand
disease or mild hemophilia A. Under these
conditions, the release of WPBs is induced by
cAMP–dependent signaling pathways that
result in only modest activation of sig-
naling molecules involved in regulation of
WPB exocytosis.1 It will be interesting to
determine whether, under these conditions,
transient fusion of WPBs with the plasma
membrane will occur at a higher frequency
than observed following stimulation
with histamine.

Overall, the findings of Babich et al highlight
yet another fascinating aspect of the
biology of the uniquely shaped WPB. Their
study provides an excellent starting point
to further explore the regulation and physio-
logical significance of release of WPBs with
different proinflammatory and vasoregula-
tory cargo.

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