Mitochondrial Homeostasis in AML and Gasping for Response in Resistance to BCL2 Blockade

Michael R. Savona1,2 and Jeffrey C. Rathmell2,3

Summary: Understanding resistance to BCL2 inhibition is a critical scientific and clinical challenge. In this issue of Cancer Discovery, two laboratories use unbiased approaches of large loss-of-function CRISPR/Cas9 screens to discover targetable liabilities in cell signaling and metabolism to acute myeloid leukemia resistant to BCL2 inhibition.

See related article by Chen et al., p. 890 (2).
See related article by Nechiporuk et al., p. 910 (3).

Apoptosis is a carefully regulated cell death program initiated by noxious stimuli, inflammation, or cellular structural dysfunction orchestrated via the interactions of intra- and extra-mitochondrial proteins with competing roles in normal homeostasis. In apoptosis, the BH3-only protein BIM activates formation of mitochondrial membrane pores by interacting with BAX, cytochrome C is released through these mitochondrial pores, and caspase activation ensues (1). B-cell lymphoma 2 (BCL2) is a critical intramitochondrial protein that inhibits apoptosis by negatively regulating apoptosis by sequestering BIM. BIM binds to the hydrophobic groove of the BH3 binding site of BCL2, which depletes available BIM to activate BAX. This biological structural insight led to the development of BCL2 inhibitors, which were successfully modeled to competitively bind to the BH3 binding site for BIM; ergo, “BH3 mimetics.” Two studies in this issue provide new insight into the use and resistance to these drugs (refs. 2, 3).

The advent of BH3 mimetics and BCL2 inhibition has heralded transformational changes in treatment algorithms for hematologic malignancies, and led a slew of new approvals for acute myeloid leukemia (AML)—the first seen in decades (4, 5). Venetoclax (ABT-199; AbbVie) is a second-generation selective BCL2 inhibitor which has modest activity in relapsed/refractory AML as a single agent (6), but in combination with the low-dose cytosine arabinoside (LDAC) or the DNA methyltransferase inhibitors (DNMTi) 5-azacitidine or decitabine led to remission in 55% to 67% of untreated elderly patients with AML deemed noncandidates for high-intensity chemotherapy in recent clinical trials (4, 5). These responses have provided hope to patients with AML and physicians hoping to provide efficacious, low-toxicity therapies. Still, most patients with AML treated with venetoclax-based regimens ultimately relapse, and a large number of patients, typically those previously treated with DNMTi or those with TP53 mutations, never respond at all (4, 5). This explains the urgency to understand venetoclax resistance and further liabilities in this “hallmark of cancer.”

Resistant BCL2 mutations have arisen in patients with venetoclax-treated chronic lymphocytic leukemia (CLL; ref. 7), although never noted in AML, and mechanisms of venetoclax resistance in wild-type BCL2 remain unclear. Just as BIM preferentially binds BCL2 (1), NOXA is an activator of apoptosis that preferentially binds to induced myeloid leukemia cell protein 1 (MCL1), another antiapoptotic factor in the BCL2 family of proteins. Whereas BCL2 upregulation is nearly universal in CLL (8), the heterogeneity of expression of antiapoptotic factors in AML is far more diverse. Some AMLs are BCL2-, MCL1-, or BCL-XL–dependent, and often multiple antiapoptotic proteins are upregulated in variable fashion with proportional sensitivity to selective inhibitors of antiapoptotic proteins (9, 10). Early observations revealed MCL1 was frequently upregulated in response to venetoclax treatment (9). This led to the hypothesis that sequential treatment with venetoclax followed by selective inhibitor of MCL1 or combination treatment with both agents may be an effective treatment strategy. Although this has yet to come to bear in the clinic, there are sufficient data to illustrate this approach is effective in synergistically removing AML cells in vitro and in xenografts (10). Though safe in early preclinical combination studies, safety concerns with potential dual inhibition of BCL2 and MCL1 have yet to be abated (10, 11), and despite a relatively bland safety signal with venetoclax in the clinic, neutropenia is not subtle, and can be significant (4, 5). Also, the predicted emergence of BCL-XL or other antiapoptotic protein–driven resistance remains a concern. So, although development of MCL1 inhibitors in the clinic is ongoing, a deeper understanding of venetoclax resistance from an unbiased perspective would be useful.

In this issue of Cancer Discovery, two laboratories harness the power of genome-wide CRISPR/Cas9 to conduct unbiased screens to best identify liabilities and synergies in

1Division of Hematology & Oncology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee. 2Vanderbilt Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, Tennessee. 3Vanderbilt Center for Immunobiology, Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee.

Corresponding Author: Michael R. Savona, Vanderbilt University School of Medicine, 2200 Pierce Avenue, 777 Preston Research Building, Nashville, TN 37232. Phone: 615-936-9246; E-mail: michael.savona@vanderbilt.edu. Cancer Discov 2019;9:831–3

doi: 10.1158/2159-8290.CD-19-0510
©2019 American Association for Cancer Research.
Neurotrophin receptors (NTRK1/2/3 or TRKA/B/C) are transmembrane receptors with tyrosine kinase activity, which are known to couple RAS/MAPK, PI3K, or PLCγ signaling pathways in cancer (12). The importance of this pathway in the absence of functional p53 is unclear, but the activity in TP53 knockout venetoclax resistance is noteworthy.

Using a similar screening strategy, Chen and colleagues identify a gene encoding for a key mitochondrial protein, CLPB, to be negatively selected in the CRISPR/Cas9 screen, preferentially overexpressed in AML CD34+ cells versus normal donor CD34+ cells, and non-core essential in normal homeostasis. CLPB interacts with OPA1 to buttress mitochondrial cristae under stress and is a lethal target in venetoclax resistance. Deletion of CLPB alone restored biosynthesis of amino acids and venetoclax sensitivity in venetoclax-resistant AML and represents a new liability to address in the development of new therapy for AML.
Whereas only selective BCL2 blockade is available in the clinic, MCL1-selective inhibitors are in clinical trials (NCT02979366, NCT02675452, NCT03218683) and BCL-X and BCL-W-specific inhibitors are in development. Neither of these studies specifically addresses the consideration of alternating (or combining) direct antiapoptotic protein-selective inhibitors in the face of resistance, nor the role of MCL1 or BCL-X in contributing to metabolic alterations. Yet, indirectly addressing the consequences of venetoclax resistance by targeting mitochondrial structure and NTRK signaling is novel. Resistance to venetoclax is dependent on alternating energy use (13–15), and the powerful approaches suggested here further improve the current understanding of how targeting energy use and mitochondrial structure may lead to enhancement of venetoclax response. The challenges with the heterogeneity of AML cell metabolism across variable patient samples, the disruptions in mitochondrial homeostasis relevant in response and resistance, and therapeutic windows of emerging approaches to venetoclax resistance remain. The methods by which we wield venetoclax, a powerful new tool in our arsenal against AML, are currently being refined. It will be important in future studies to establish how relationships between energy use and structure drive resistance to venetoclax, and how these events can be targeted with selective therapies.

Disclosure of Potential Conflicts of Interest

M.R. Savona has received research support from Astex, Boehringer Ingelheim, Celgene, Incyte, Millennium, Sunesis, and TG Therapeutics; has equity in Karyopharm; and has consulted for Astex, Celgene, Karyopharm, Millennium, and TG Therapeutics. No potential conflicts of interest were disclosed by the other author.

Published online July 1, 2019.

REFERENCES

Mitochondrial Homeostasis in AML and Gasping for Response in Resistance to BCL2 Blockade

Michael R. Savona and Jeffrey C. Rathmell

*Cancer Discov* 2019;9:831-833.

<table>
<thead>
<tr>
<th>Updated version</th>
<th>Access the most recent version of this article at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><a href="http://cancerdiscovery.aacrjournals.org/content/9/7/831">http://cancerdiscovery.aacrjournals.org/content/9/7/831</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cited articles</th>
<th>This article cites 15 articles, 9 of which you can access for free at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><a href="http://cancerdiscovery.aacrjournals.org/content/9/7/831.full#ref-list-1">http://cancerdiscovery.aacrjournals.org/content/9/7/831.full#ref-list-1</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Citing articles</th>
<th>This article has been cited by 1 HighWire-hosted articles. Access the articles at:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><a href="http://cancerdiscovery.aacrjournals.org/content/9/7/831.full#related-urls">http://cancerdiscovery.aacrjournals.org/content/9/7/831.full#related-urls</a></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>E-mail alerts</th>
<th>Sign up to receive free email-alerts related to this article or journal.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reprints and Subscriptions</td>
<td>To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at <a href="mailto:pubs@aacr.org">pubs@aacr.org</a>.</td>
</tr>
<tr>
<td>Permissions</td>
<td>To request permission to re-use all or part of this article, use this link <a href="http://cancerdiscovery.aacrjournals.org/content/9/7/831">http://cancerdiscovery.aacrjournals.org/content/9/7/831</a>. Click on &quot;Request Permissions&quot; which will take you to the Copyright Clearance Center's (CCC) Rightslink site.</td>
</tr>
</tbody>
</table>