Power Cut: Inhibiting Mitochondrial Translation to Target Leukemia

Marcus Järås[1] and Benjamin L. Ebert[1,*]
[1]Division of Hematology, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
*Correspondence: bebert@partners.org
DOI 10.1016/j.ccr.2011.10.028

In this issue of *Cancer Cell*, Skrtic et al. demonstrate that inhibition of mitochondrial ribosomes with tigecycline, a known antimicrobial, selectively kills leukemia cells. This finding highlights the metabolic susceptibility of leukemia cells to mitochondrial translational inhibition and identifies a compound with significant efficacy in an in vivo preclinical model.

Advances in cancer genomics are providing tremendous insights into the genetic basis of acute myeloid leukemia (AML), but the development of novel pharmacologic therapies has not proceeded as rapidly (Ley et al., 2010; Mardis et al., 2009). The identification of novel mutations, epigenetic dysregulation, and aberrant gene expression patterns has yielded profound insights into the pathogenesis of AML. However, many of the molecular lesions highlighted by these studies, such as loss-of-function mutations in tumor suppressor genes, are not straightforward therapeutic targets. An alternative strategy for the identification of therapeutic targets is to identify tumor cell dependencies that are not necessarily directly related to somatically mutated genes through unbiased screens.

In this issue of *Cancer Cell*, Skrtic et al. (2011) performed a chemical screen using two AML cell lines and FDA-approved drugs in the hopes of facilitating rapid clinical translation of any findings. Salinomycin, recently reported to target breast cancer stem cells, was a top hit. The next hit was tigecycline, a broad-spectrum antibiotic currently in clinical use. In validation studies, tigecycline induced cell death in a panel of murine and human leukemia cell lines. Importantly, tigecycline showed antileukemia selectivity for 13 out of 20 primary AML patient samples relative to normal hematopoietic cells. Both $CD34^+CD38^-$ cells, which are enriched for leukemic stem cells, and the bulk leukemia cell population was sensitive to tigecycline.

To identify the mechanism whereby tigecycline inhibits the viability of eukaryotic cells, the authors performed a genome-wide haploinsufficiency profiling (HIP) screen in yeast (Giaever et al., 1999). Interestingly, yeast grown under respiratory conditions, in which oxidative phosphorylation is used for energy production, were sensitized for tigecycline relative to yeast grown in rich media favoring glycolysis. In the HIP screen, yeast strains haploinsufficient for proteins involved in mitochondrial ribosomes were most potently sensitized to tigecycline treatment, a result that was also replicated for chloramphenicol, a known inhibitor of both mitochondrial and bacterial translation. The sensitivity of both mitochondrial and bacterial ribosomes to tigecycline treatment highlights the common origin of mitochondrial and bacterial ribosomes according to the endosymbiotic hypothesis, which posits that mitochondria are descendants from bacterial ancestors that survived endocytosis in eukaryotic cells (Gray et al., 2001). Hence, the development of tigecycline for inhibition of prokaryotic ribosomes relative to mammalian cytosolic ribosomes may have optimized the molecule for selective inhibition of mitochondrial ribosomes as well.

Exploring the effects of tigecycline on mitochondrial ribosome function, the authors found that tigecycline treatment preferentially inhibited the translation of proteins synthesized in mitochondria relative to proteins translated by cytosolic ribosomes. Moreover, the pharmacologic effects of tigecycline on leukemia cells could also be achieved by genetic inhibition of mitochondrial translation. Using RNA interference to knock down expression of the mitochondrial elongation factor Tu (EF-Tu), which is needed to transport aminoacyl-tRNAs to the mitochondrial ribosome, mimicked the selective effect of tigecycline on leukemic cells, independently demonstrating a previously unrecognized enhanced dependency of leukemic cells for mitochondrial protein synthesis.

Because the mitochondrial translation machinery is also essential for normal cells, the authors searched for differences between leukemic and normal cell mitochondria that could explain the higher sensitivity of leukemic cells for tigecycline. Compared with normal cells, leukemia cells were found to have a larger mitochondrial mass, a greater mitochondrial DNA copy number, and a higher rate of oxygen consumption. The reason for these findings remains to be elucidated, but leukemic cells may need greater energy production to support a higher growth and proliferation rate. Mitochondria generate adenosine-triphosphate (ATP) through oxidative phosphorylation. This process takes place in protein complexes along the respiratory chain of the mitochondrial membrane, building up an electrochemical proton gradient that generates the mitochondrial membrane potential. Administration of tigecycline to leukemic cells, but not normal cells, disrupted the membrane potential in an oxygen-dependent manner. The authors further demonstrated that protein complexes in the respiratory chain translated by mitochondrial ribosomes were predominantly suppressed following tigecycline treatment, suggesting that the lower oxygen consumption is a consequence of the inhibition of mitochondrial protein synthesis, rather than a direct inhibition of the respiratory chain.

The finding that AML cells are hypersensitive to inhibition of mitochondrial

translation adds to our understanding of cancer cellular metabolism. While Skrtic et al. describe a dependency for ribosomal translation and oxidative phosphorylation in leukemia cells, the Warburg hypothesis, a cornerstone of cancer cellular metabolism, postulates that cancer cells, unlike normal cells, favor glycolysis for energy production, even under aerobic conditions (Warburg, 1956). This reprogramming of energy metabolism in cancer cells is now considered to be a distinct hallmark of cancer cells (Hanahan and Weinberg, 2011; Hsu and Sabatini, 2008; Luo et al., 2009). The shift in cancer cell metabolism termed "aerobic glycolysis" may be partially an adaptation to lower oxygen levels in tumors, but may also be a direct consequence of activation of certain oncogenes such as *MYC* and *RAS* (Hsu and Sabatini, 2008). In leukemia, inhibition of fatty acid oxidation was recently shown to sensitize leukemia cells to apoptosis induction, but whether this finding is linked to pathways affected by tigecycline remains to be elucidated (Samudio et al., 2010). The full relationship between dependencies on mitochondrial metabolism and glycolytic flux in leukemia cells remains to be determined, but both represent attractive therapeutic targets for the treatment of cancer.

Tigecycline is an FDA-approved drug with known pharmacokinetics and toxicity, facilitating preclinical studies. The authors administered the drug to mice engrafted with primary AML cells and found a reduction in the leukemic burden relative to controls, which demonstrates that AML cells are therapeutically accessible in vivo. Interestingly, combining tigecycline with daunarubicin, a cytotoxic drug in clinical use for AML, had an additive or synergistic antileukemic effect, suggesting that combining the two should be considered for future clinical trials. Similar results were obtained for the combination of tigecycline with Ara-C, another cytotoxic chemotherapeutic agent in routine use for the treatment of AML. Since tigecycline is already used in patients as an antimicrobial, and the toxicity profile is known, clinical trials in AML could be initiated expeditiously to determine the efficacy of tigecycline for the treatment of this challenging disease.

REFERENCES

Giaever, G., Shoemaker, D.D., Jones, T.W., Liang, H., Winzeler, E.A., Astromoff, A., and Davis, R.W. (1999). Nat. Genet. *21*, 278–283.

Gray, M.W., Burger, G., and Lang, B.F. (2001). Genome Biol. *2*, S1018.

Hanahan, D., and Weinberg, R.A. (2011). Cell *144*, 646–674.

Hsu, P.P., and Sabatini, D.M. (2008). Cell *134*, 703–707.

Ley, T.J., Ding, L., Walter, M.J., McLellan, M.D., Lamprecht, T., Larson, D.E., Kandoth, C., Payton, J.E., Baty, J., Welch, J., et al. (2010). N. Engl. J. Med. *363*, 2424–2433.

Luo, J., Solimini, N.L., and Elledge, S.J. (2009). Cell *136*, 823–837.

Mardis, E.R., Ding, L., Dooling, D.J., Larson, D.E., McLellan, M.D., Chen, K., Koboldt, D.C., Fulton, R.S., Delehaunty, K.D., McGrath, S.D., et al. (2009). N. Engl. J. Med. *361*, 1058–1066.

Samudio, I., Harmancey, R., Fiegl, M., Kantarjian, H., Konopleva, M., Korchin, B., Kaluarachchi, K., Bornmann, W., Duvvuri, S., Taegtmeyer, H., and Andreeff, M. (2010). J. Clin. Invest. *120*, 142–156.

Skrtic, M., Sriskanthadevan, S., Jhas, B., Gebbia, M., Wang, X., Wang, Z., Hurren, R., Jitkova, Y., Gronda, M., Maclean, N., et al. (2011). Cancer Cell *20*, this issue, 674–688.

Warburg, O. (1956). Science *123*, 309–314.

The Two Faces of NF-κB Signaling in Cancer Development and Therapy

Ulf Klein[1,2,3,*] and Sankar Ghosh[4,*]
[1]Department of Pathology and Cell Biology
[2]Department of Microbiology and Immunology
[3]Herbert Irving Comprehensive Cancer Center
[4]Department of Microbiology and Immunology
Columbia University, New York, NY 10032, USA
*Correspondence: uk30@columbia.edu (U.K.), sg2715@columbia.edu (S.G.)
DOI 10.1016/j.ccr.2011.10.026

Constitutive activation of NF-κB signaling can promote oncogenesis, providing a rationale for anticancer strategies that inhibit NF-κB signaling. Two recent publications in *Genes & Development* provide evidence that, in contexts where prosurvival signals derive from other oncogenes, NF-κB activity instead enhances sensitivity to cytotoxic chemotherapy, thereby exerting a tumor-suppressor function.

The nuclear factor-κB (NF-κB) signaling cascade is a major transducer of external signals, controlling the expression of a broad range of genes involved in cell survival, growth, stress response, and inflammation (Hayden and Ghosh, 2008). NF-κB signaling is tightly regulated and aberrant activation of this pathway has been associated with the pathogenesis of solid tumors (Ben-Neriah and Karin, 2011). Recent studies have shown that B cell lymphomas frequently harbor genetic