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Arsenic in leukemia

A RSKy business

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Commentary to: Galvin JP, Altman JK, Szilard A, Goussetis DJ, Vakana E, Sassano A, Platanias LC. Regulation of the kinase RSK1 by arsenic trioxide and generation of antileukemic responses. Cancer Biol Ther 2013; 14:411-6; PMID:23377826; http://dx.doi.org/10.4161/cbt.23760

It has been known for many years that arsenic trioxide (As_2O_3; ATO) is an effective therapy for acute promyelocytic leukemia but has little activity against other forms of the disease. ATO has diverse modes of action, but is well known to generate high levels of reactive oxygen species in cells which are believed to be causal in many of its biologic actions.[1] ROS can both activate and suppress signaling through multiple intracellular pathways based on the amount and duration of ROS production.[2] As the basal activity of the MEK1/2-ERK1/2 pathway is often high in acute myeloid leukemias, and that ATO is known to stimulate MEK1/2-ERK1/2 signaling in leukemia, the authors investigated whether knock down of the downstream effector of ERK1/2, RSK1, could enhance the anti-leukemic activity of ATO.[3,4]

The authors demonstrated that ATO rapidly activated RSK1 and that inhibition of RSK1 using a small molecule inhibitor of the kinase, BI-D1870, enhanced both the growth suppressive effects of ATO and the apoptotic response of cells to ATO; these effects correlated with reduced colony formation and with reduced phosphorylation of the toxic BH3 domain protein BAD. The authors confirmed their data using siRNA knock down of RSK1. Most importantly, the authors demonstrated that RSK1 inhibition enhanced ATO toxicity in primary acute myeloid leukemia cells but not in non-transformed normal myeloid hematopoietic progenitors cells of various lineages. This argues for tumor cell specificity effects of this drug combination.

The concept that one therapeutic agent can activate pathways normally associated with cell survival has been well established over the past 15 years, and that inhibition of these survival pathway(s) causes a profound apoptotic response.[5-8] In APL cells inhibition of MEK1/2 was shown to enhance ATO toxicity and the findings in the present manuscript generally support the concept that this mechanism applies to other leukemic cell types.[3,4] It would have been of interest had the authors presented data using a MEK1/2 inhibitor in combination with ATO in their studies and compared such findings to JNK pathway inhibitors, particularly as both ERK and JNK can regulate RSK phosphorylation.[9] The present manuscript did not investigate in detail the molecular mechanisms by which ATO and RSK interact to cause death, though altered BAD phosphorylation will undoubtedly be one mechanism. ATO kills through mitochondrial dysfunction but also through elevated levels of DNA damage. Thus, for example, the expression of BIM is also regulated by the ERK1/2-MEK1/2 pathway as is the expression of MCL-1. And the levels of ERCC1 and XRCC1 can also be regulated by ERK1/2-MEK1/2 signaling. Clearly, such assessments will be part of a future study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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