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Arsenic Trioxide and the PI3K/AKT Pathway in Chronic Lymphocytic Leukemia

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Summary

Simultaneous targeting of the PI3K/AKT pathway increases arsenic trioxide (ATO)-dependent cytotoxicity of chronic lymphocytic leukemia (CLL) cells, while it has no significant effects on normal lymphocytes. Combinations of ATO with small molecules that target the PI3' kinase and/or AKT may provide a novel approach for the treatment of CLL.

In this issue of *Clinical Cancer Research*, Redondo-Muñoz et al (1) report on the effects of arsenic trioxide (ATO) on chronic lymphocytic leukemia (CLL) cells. Arsenic trioxide has important antineoplastic properties *in vitro* and *in vivo* (2,3). This agent has been used extensively in the treatment of acute promyelocytic leukemia in humans, but a major limitation for its use in other hematological malignancies and solid tumors is the requirement of very high, toxic, concentrations for the induction of apoptosis in non-APL cells (2,3). Redondo-Muñoz et al provide evidence that ATO-induced apoptosis of CLL cells involves inactivation of the kinase AKT and a blockade of the transcriptional factor NF-kB, as well as upregulation of PTEN and downregulation of XIAP. Notably, ATO treatment of CLL cells was found to induce activation of the JNK kinase, which is essential for the inactivation of AKT and NF-kB and for mitochondrial damage and leukemic cell death (Fig. 1). These findings extend previous work that had shown a critical and essential role for JNK in the induction of ATO-dependent apoptosis in APL cells (4). In addition, they place JNK activation upstream of reactive oxygen species (ROS) in CLL cells, as demonstrated by experiments in which a pharmacological inhibitor of JNK, or JNK gene silencing, was found to inhibit ROS production by CLL cells. Importantly, the authors of this report also demonstrate that combinations of ATO with two different PI 3' kinase inhibitors, LY294002 and API-2, result in enhanced apoptosis as compared to treatment with ATO alone. This suggests that combinations of ATO with PI 3' kinase inhibitors may provide a novel approach to sensitize CLL cells to lower concentrations of ATO that could be achievable *in vivo*.

The findings of the study of Redondo-Muñoz et al (1) may have important long-term clinical-translational implications regarding the treatment of CLL. Beyond identifying and characterizing a mechanism by which ATO-dependent inhibition of AKT leads to apoptosis of CLL cells, they raise the possibility of future clinical trials involving combinations of ATO with PI 3'K inhibitors. Currently, there is an intense interest in targeting the PI 3' kinase pathway for the treatment of various cancer types and there is ongoing rapid development of agents for that purpose, with several pre-clinical and early clinical studies under way (5). The findings of Redondo-Muñoz et al (1) are promising, as induction of substantial levels of apoptosis of CLL cells was seen when PI 3'K inhibitors were combined with low

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concentrations of ATO (2 μM). There are several PI3'K- (PX-866, XL147, NVP-BKM120, GDC-0941) or dual PI 3'K/mTOR-(SF-1126, NVP-BEZ235, NVP-BGT226, XL765) kinase inhibitors currently in Phase I/II clinical trials for solid tumors (5), while one PI 3'K inhibitor (CAL-101) is currently in Phase I studies in hematological malignancies, including CLL (5). Depending on the outcome of such clinical trials, it is conceivable that combinations of ATO with one or more of these agents could also be explored in future clinical trials in CLL. A particularly important observation in the Redondo-Muñoz study (1) was the fact that while arsenic trioxide had very potent pro-apoptotic effects on CLL lymphocytes, it had very minimal effects on normal peripheral blood lymphocytes. This was seen at final concentrations of arsenic trioxide of 3 μM (1). This finding suggests some potential specificity of arsenic trioxide toward malignant cells as compared to normal lymphocytes, although such mechanisms remain to be investigated and precisely defined in future studies.

Future studies should also determine the effects of arsenic trioxide on effectors of the mTOR pathway downstream of PI 3'kinase/AKT activation in CLL cells. Previous studies have shown that arsenic trioxide can paradoxically increase mTOR activation and engagement of downstream mTOR effectors in BCR-ABL expressing cells (6) or AML cells (7); and that combinations of ATO with the mTORC1 inhibitor rapamycin result in increased apoptosis and enhanced suppressive effects on primary leukemic progenitors (6,7). As arsenic trioxide exhibits suppressive effects on the engagement of PI3'K-AKT in CLL cells, it is likely that it will be eventually also found to suppress downstream effectors of the mTOR pathway, but this will need to be directly examined in future studies. Potential synergistic effects of combinations of ATO with mTOR inhibitors on malignant CLL lymphocytes should also be examined, especially as there are already ongoing clinical efforts to evaluate the effects of mTOR inhibition in the treatment of CLL (8,9).

In recent years, there has been a renewed interest towards the clinical use of arsenic trioxide for the treatment of other hematologic malignancies beyond APL (10). The work of Redondo-Muñoz et al (1) provides the basis for further pre-clinical work that may ultimately lead to clinical trials examining different combinations of inhibitors with arsenic trioxide for the treatment of CLL. Beyond combinations with inhibitors of the PI 3'K/AKT/mTOR pathway, it is possible that targeting other key cellular cascades may prove to be of value. In particular, targeting of MAP kinase pathways in CLL with specific inhibitors may provide an additional approach to enhance the antileukemic effects of ATO (Fig. 1). Previous studies have that treatment of primary chronic myelogenous leukemia (CML) cells with combinations of arsenic trioxide with p38 MAP kinase inhibitors (11); or treatment of acute myelogenous leukemia (AML) cells with combinations of arsenic trioxide and MEK/ERK inhibitors (12) result in enhanced antileukemic responses *in vitro.* It would be interesting to examine whether similar enhancing/synergistic effects occur in CLL cells, as this could provide the rationale for further work and possible clinical evaluation of combinations of arsenic trioxide with different MAPK inhibitors.

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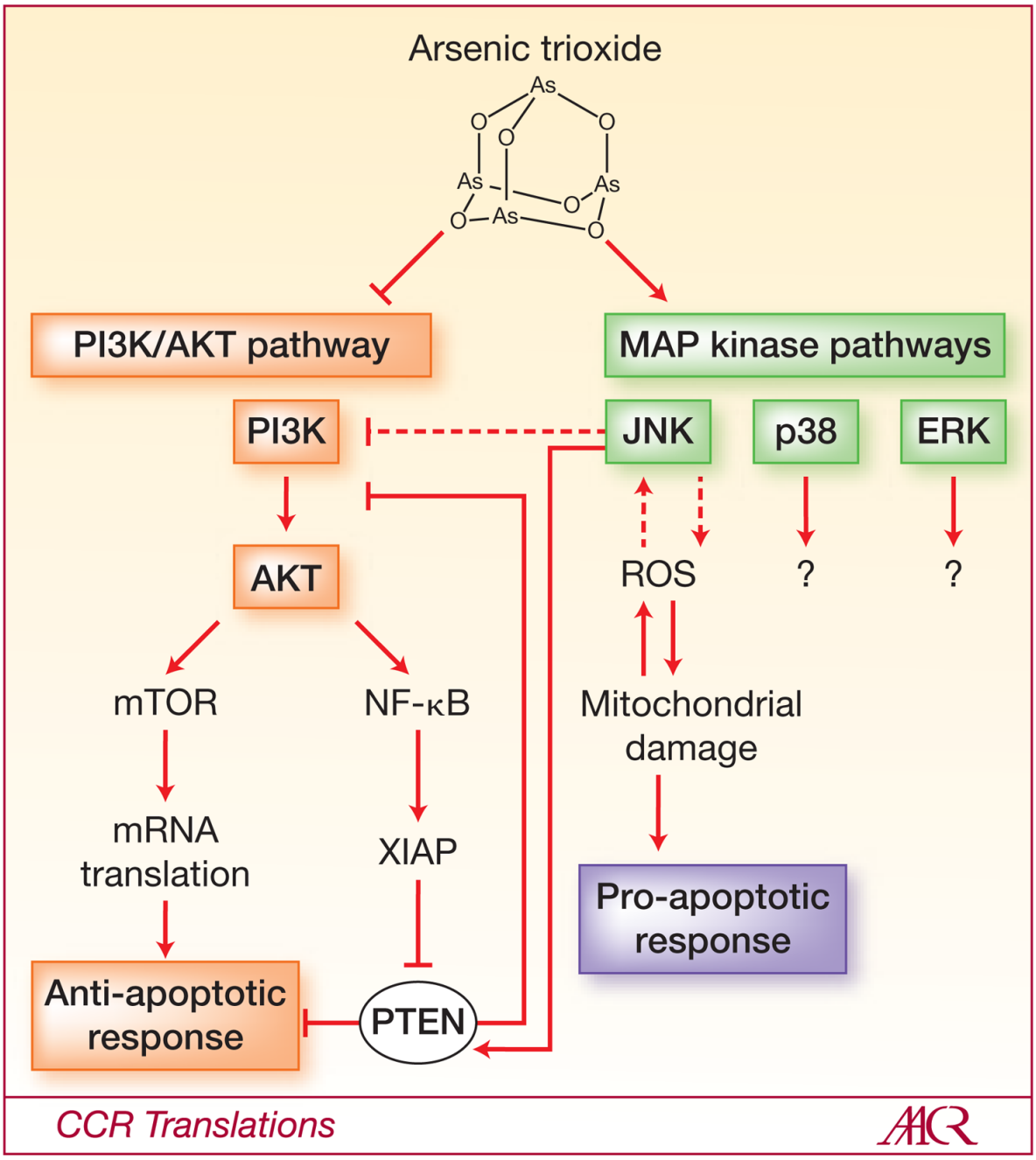

Figure 1.
Targeting of signaling pathways by arsenic trioxide in chronic lymphocytic leukemia cells. Activation of the JNK MAPK pathway is required for induction of apoptosis of CLL cells. Arsenic trioxide treatment of leukemic cells also results in inhibition of the PI 3'K/AKT pathway; and pharmacological targeting of this pathway enhance the antileukemic effects of arsenic trioxide. The potential involvement of other MAPK pathways, such as the p38 MAPK and MEK/ERK pathways which play important roles in control of growth and survival of other types of leukemic cells, in the regulation ATO-dependent responses in CLL cells remains to be defined.