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Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders

CATALASE BLOCKING ENHANCES DRUG SENSITIVITY TO BCL-2 INHIBITORS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Chronic lymphocytic leukemia (CLL) is an incurable disease with a highly variable clinical behavior. Although targeted therapies, such as the BCL-2 inhibitor Venetoclax, have high initial response rates, relapse remains a challenge. Recently, we showed that low levels of the catalase antioxidant enzyme identify an indolent CLL, leading us to hypothesize that catalase downregulation could induce escalated levels of reactive oxygen species (ROS) that promote cell death signals, thus accounting for less aggressive behavior and higher therapy sensitivity of cancer cells.

To verify our hypothesis, we manipulated catalase activity using the specific inhibitor 3-amino-1,2,4-triazole (ATZ) in MEC1 CLL cell line and primary cells from CLL patients. Moreover, in MEC1 cells we targeted catalase using siRNA technology. We analyzed ROS levels using CM-H2DCFDA fluorescent probe while we measured apoptosis with PI-Annexin V staining and flow cytometry.

First, we observed that in vitro spontaneous apoptosis of primary CLL cells was associated with a significant increased accumulation of ROS (Pearson r = 0.7552; p = 0.0186), thus suggesting a functional role of ROS in inducing apoptosis in CLL cells. Importantly, blocking catalase either with ATZ or siRNA induced escalated ROS levels and increased apoptosis in leukemic cells (Figure 1A). To extend our findings to a therapeutic setting, we analyzed the ability of catalase to modulate cell survival in vitro in the presence of Venetoclax. Remarkably, inhibiting catalase with ATZ in combination with Venetoclax significantly potentiated apoptosis in CLL cells compared to those induced by each single agent (Figure 1B). Moreover, Bliss analysis of drugs' independence reveals a synergy between ATZ and Venetoclax in inducing apoptosis in CLL cells. To further investigate the therapeutic relevance of catalase, we analyzed a cohort of treatment-naive CLL patients before Venetoclax therapy. Remarkably, higher pretherapy catalase mRNA levels were associated with a lower percentage of lymphocyte reduction within 24 hours of treatment initiation (Pearson r = 0.1815; p = 0.2515), suggesting a possible role of catalase in response to therapy.

These data support the hypothesis that catalase might play a critical role in regulating susceptibility to spontaneous as well as BCL-2 inhibitor-induced apoptosis in CLL, thus influencing the behavior of cancer cells and contributing to resistance. Moreover, this study provides the rationale for developing novel precision therapies targeting redox pathways that, alone or in combination with currently used therapies, could overcome resistance in CLL and other B-cell malignancies where BCL-2 inhibitor is used, such as mantle cells lymphoma.

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