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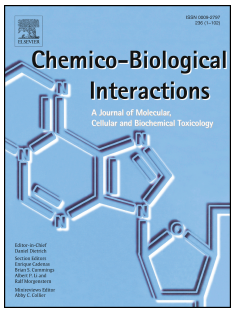

ALDHs in normal and malignant hematopoietic cells: Potential new avenues for treatment of AML and other blood cancers

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ALDHs in normal and malignant hematopoietic cells: potential new avenues for treatment of AML and other blood cancers

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Abstract

Multiple studies have demonstrated that ALDH1A1 is elevated in hematopoietic stem cells (HSCs). As a means to better characterize such cells, we previously developed the fluorescent ALDH1A1 substrate Aldefluor to facilitate HSC identification and isolation. This has proven useful for counting and isolating HSCs from human bone marrow, peripheral blood and cord blood as well as stem cells in other tissues and organisms. Given the high level expression of ALDH1A1, we explored its biology and that of other ALDHs in HSCs and found that ALDH1A1 and ALDH3A1 were important in metabolizing reactive aldehydes (RAlds) and reactive oxygen species (ROS). In murine models, loss of these two isoforms resulted in a variety of effects on HSC biology, increased DNA damage and predisposition to leukemia formation when combined with a genetic driver of HSC proliferation and self-renewal. Loss of ALDH activity may also predispose to marrow failure and AML in Fanconi's anemia (FA). ALDHs also have importance in mediating drug resistance in AML, may be useful in the identification of leukemia stem cells (LSCs) and ALDH activity levels may have prognostic significance. Together these findings suggest that further studying ALDH biology in AML and other blood cancers may provide important insights into malignant transformation and may point the way to the development of novel diagnostics and therapies.