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POSTER ABSTRACTS

602.MYELOID ONCOGENESIS: BASIC

ID2 Promotes Leukemogenesis and Chemoresistance of Acute Myeloid Leukemia By Modulating Cellular Oxidative Metabolism

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Acute myeloid leukemia (AML) relies on quiescent leukemia stem cells (LSCs) to evade chemotherapy and drive disease relapse. Recent research indicates that a specific subset of LSCs, characterized by elevated oxidative phosphorylation and/or increased senescence, is responsible for chemotherapy resistance and relapse. While numerous genes associated with LSC maintenance and resistance have been identified, the underlying molecular mechanisms remain elusive. Inhibitor of DNA binding (ID) proteins, a group of Helix-Loop-Helix (HLH) transcription regulators, play a dominant role in regulating other HLH proteins (E proteins) required for the normal development of hematopoietic, muscle, neuronal, and other cells. Our previous investigation revealed that ID2 protects quiescent hematopoietic stem cells (HSCs) activation and exhaustion. Analysis of TCGA data sets demonstrated that high levels of ID2 expression are linked to reduced overall survival in AML patients, suggesting ID2 may be required to maintain some LSCs. Consistent with murine cell findings, we found that knocking down (KD) ID2 expression in human cord blood cells resulted in a loss of CD34+CD38- progenitors. Similarly, ID2-KD in AML cell lines (UT-7, MB-02, and M-07e) significantly reduced their leukemogenic potential in NSG mice, indicating that ID2 is essential for AML cell growth *in vivo*. Conversely, overexpressing ID2 in the human AML cell line M-07e enhanced their leukemic potential and burden in NSG mice, supporting the notion that ID2 may preserve LSC quiescence. Experiments with primary AML-Patient Derived Xenograft (AML-PDX) cells, which are more clinically relevant, also showed reduced leukemic potential in transplanted NSG mice upon ID2 knockdown. Additionally, ID2-KD cells displayed significantly lower levels of reactive oxygen species (ROS) and mitochondrial activity compared to control cells in both AML cell lines and PDX cells. As ROS-low cells are more susceptible to cytarabine (AraC), we investigated whether ID2-KD renders AML cells more susceptible to AraC. Indeed, MB-02-ID2-KD and UT7-ID2-KD cells showed increased sensitivity to AraC, while M-07e cells overexpressing ID2 exhibited resistance to AraC. Furthermore, AraC effectively eliminated ROS-low cells, but ROS-high cells remained resistant, supporting previous findings. To further investigate the effect of ID2-KD in AraC resistance *in vivo*, UT7-ID-KD and MB-02-ID2-KD transplanted NSG mice were treated with AraC and monitored for their overall survival, and it was observed that ID2-KD transplanted mice have significantly higher overall survival compared to the control cell transplanted mice. In conclusion, it can be said that ID2 plays a critical role in maintaining normal murine and human HSCs, and it likely contributes to leukemia development and chemotherapy resistance. Therefore, targeting ID2 may offer a promising therapeutic approach to selectively tackle LSCs, followed by chemotherapy and bone marrow transplantation to achieve complete remission.

Disclosures No relevant conflicts of interest to declare.

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