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POSTER ABSTRACTS

636.MYELODYSPLASTIC SYNDROMES-BASIC AND TRANSLATIONAL

Downregulation of Mitochondrial Complex II (MC II) in Myelodysplastic Syndromes

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Myelodysplastic syndromes (MDS) are a group of diseases of hematopoietic stem cells (HSCs) that occur in the aging population and following therapy for unrelated cancers. The standard of care for MDS involves hypomethylating agents (HMAs) that invariably result in resistance and disease progression. We previously determined the role of mitochondrial metabolism in MDS pathophysiology, whereby suppression of mitochondrial activity leads to the accumulation of oncometabolites that competitively inhibit α-ketoglutarate-dependent dioxygenases (2OGDDs). Consequently, hypermethylation of epigenomes and hypoxia-inducible factor 1A (HIF1A) activation ensues a pseudohypoxia state that drives MDS pathogenesis.
Our recent informatics analyses of primary MDS samples identified a patient subset with high TGF-β signaling in which mitochondrial complex II (MC II) genes were downregulated. MC II, or succinate dehydrogenase (SDH) is the smallest complex of the oxidative phosphorylation system that oxidizes succinate to fumarate and thereby donates electrons to reduce FAD to $FADH_2$ and the ubiquinone pool. Its downregulation results in the accumulation of Krebs cycle intermediate metabolites that can act as antagonists for 2OGDDs. To understand whether SDH dysregulation alone can contribute to MDS pathobiology, we generated a doxycycline-inducible and reversible mouse model (SDH-KD) that expresses shRNAs against the SDH subunits (SDHA, B, and D) in HSCs. These mice showed a gradual buildup of intracellular succinate in c-Kit $^+$ bone marrow (BM) cells and the peripheral blood, and a corresponding decrease of fumarate levels after induction for 2 weeks, 4 weeks, and 2 months. We found that knocking down *Sdh* was sufficient to induce pancytopenia and trilineage dysplasia in SDH-KD mice, while intracellular iron granules that surround the nucleus of erythroblasts, similar to ring sideroblasts commonly observed in MDS patients were also detected in BM and spleen smears. Of note, removing doxycycline and restoring *Sdh* expression rescued macrocytic anemia among other MDS phenotypes. Furthermore, treating SDH-KD mice with HMAs restored mitochondrial respiration and reversed HIF1A activation through the upregulation of SDH subunits. Using another MDS model, *Mll* $^{PTD/WT}$/ *Vav1*-Cre/Runx1 $^{Flox/Flox}$, we found that HMA-treated HSCs differentiate towards CD11b $^+$Gr1 $^+$ mature myeloid cells and that this requires *Sdh* expression.
In conclusion, our results indicate that pseudohypoxia- and TGF-β signaling-associated changes in metabolic regulation caused by SDH downregulation underlie MDS pathogenesis. Elucidating the role of MC II in MDS pathobiology may provide alternative targets that can be combined with HMA or luspatercept therapy for MDS.

Disclosures No relevant conflicts of interest to declare.

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