Simultaneous targeting of LSD1 and PRMT5 through chimeric inhibitors as a novel therapeutic approach against leukemia

ShT-04.3-3

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The lysine-specific demethylase 1 (LSD1) catalyzes the removal of mono- and dimethyl modifications of Lys4 of histone H3 (H3K4me1/2), which are essential marks of transcriptional activation. LSD1 has been shown to play a central role in the insurgence of solid and blood cancers. In particular, it is highly expressed in acute myeloid leukemia (AML), a hematopoietic malignancy caused by abnormal proliferation and differentiation of blasts. In AML, LSD1 is crucial for the maintenance of cancer cell stemness, inhibition of cell differentiation, and prevention of apoptosis. Similar to LSD1, the protein arginine methyltransferase 5 (PRMT5), a methyltransferase that catalyzes the symmetric dimethylation of arginine residues, acts as an oncoprotein in AML. Indeed, PRMT5 activity was shown to support AML growth in vitro and in vivo. Given the involvement of both LSD1 and PRMT5 in AML, the simultaneous inhibition of these enzymes may represent a successful approach to treating this malignancy. Notably, we have identified a synergistic interaction between an LSD1 inhibitor and a PRMT5 inhibitor in multiple AML cell lines. The two inhibitors combined promote AML differentiation and eventually growth inhibition and apoptosis. To leverage this synthetic lethal interaction, we developed a series of dual-targeting LSD1/PRMT5 inhibitors that could inhibit both enzymes in vitro in the submicromolar to nanomolar range while being selective over PRMT1 and PRMT7. Among, the prepared compounds, two of them impaired leukemic cell viability with higher potency compared to single-target inhibitors and induced apoptosis and myeloid differentiation. In addition, we were able to solve the X-ray co-crystal structure of one of the designed inhibitors with LSD1, thus elucidating its binding mode and providing a structural basis for the rational design of further inhibitors.