HDAC inhibitor SAHA inhibits in vitro hypoxia-induced CXCR4 up-regulation in AML cells

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Background: Chemokine (C-X-C motif) receptor 4 (CXCR4) and its ligand stromal cell-derived factor-1 (SDF-1) play central roles in invasion and metastasis of solid tumor. On the other hand, high levels of CXCR4 expression correlate shorter survival in acute myeloid leukemia (AML). Recently, it has been shown that O_2 partial pressure (pO_2) in bone marrow of AML patients is lower than healthy volunteers. Reduced pO_2 stabilizes transcriptional factor hypoxia-inducible factor-1α (HIF-1α) which induces various gene expressions including CXCR4. Elevated CXCR4 expression in AML cells increase expression of vascular cell adhesion molecule-1 and very late antigen-4, which enhance interaction between AML cells and niche cells including osteoblast and mesenchymal stem cell, resulting that AML cells resistant to chemotherapy. Therefore CXCR4 inhibition is important therapeutic target in AML treatment. It has been recently reported that histon deacethlase (HDAC) regulates HIF-1α expression, and HDAC inhibitor suppress hypoxia-induced HIF-1α expression. However, effect of HDAC inhibitor in hypoxia-induced CXCR4 increment is totally unknown. Subject: we investigated the effect of HDAC inhibitor suberoyl hydroxamic acid (SAHA) to hypoxia-induced CXCR4 up-regulation. Methods: AML lined cells, U937 and NB4, were treated hypoxia-mimetic agent deferoxamine (DFO) and/or SAHA. Cell surface CXCR4 expression was analyzed by flow cytometry method, HIF-1α and total CXCR4 protein expression were assessed by western blotting, and mRNA expression of HIF-1α and CXCR4 were analyzed by real time RT-PCR methods. To address whether CXCR4 modulation have functional consequences, migration assay using transwell was performed. Results: DFO up-regulated HIF-1α protein, total/cell surface CXCR4 expression and migration activity toward SDF-1. SAHA inhibited SDF-1-induced migration activity via surface CXCR4 inhibition. Although HIF-1α mRNA expression was unchanged by SAHA itself, SAHA inhibited DFO-induced expression of HIF-1α protein, CXCR4 mRNA and total CXCR4 protein. Conclusion: SAHA inhibited hypoxia-induced CXCR4 up-regulation with HIF-1α inhibition. SAHA may restore AML chemoresistance by inhibition of interaction between AML cell and niche cell.