



IMPROVING CHEMOTHERAPY FOR ACUTE MYELOID LEUKEMIA

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Acute Myeloid Leukemia (AML) is a malignancy of hematopoietic stem cells. In AML, myeloblasts start from common myeloid stem cells, proliferate uncontrollably, and have a maturation arrest. AML relapse is due to leukemic stem cells that home into bone marrow niches where they are resistant to chemotherapy. Stromal cells found in the bone marrow microenvironment secrete CXCL12 (SDF-1 α), support proliferation and promote homing of AML cells. Leukemic cells express CXCR4, a receptor which binds with the chemokine CXCL12. Nuclear protein HMGB1 increases the efficiency of the binding of CXCL12 to CXCR4. It is believed that the CXCR4–CXCL12–HMGB1 interaction facilitates homing in the bone marrow and that ultimately promotes chemotherapy resistance and proliferation of AML cells.

O-desulfated heparin (ODSH), a derivative of heparin with low anticoagulant activity, has potential to interrupt the CXCR4–CXCL12–HMGB1 interaction. Interrupting this axis would release leukemic stem cells from bone marrow niches and render them susceptible to chemotherapy.

Receptor-ligand Binding assays were performed using ELISA. Authenticity of binding was assessed by omission of the ligand from the reaction mixture. Preliminary results show that CXCR4, HMGB1 and ODSH all bind CXCL12. Also, ODSH inhibits CXCL12 binding to HMGB1. Cell-free assays performed so far suggest that ODSH may not inhibit the direct binding of CXCL12 with CXCR4, suggesting the interaction between HMGB1, CXCL12, and CXCR4 may possibly be more complex.

The goal of the project is to investigate the therapeutic potential of ODSH on AML. The preliminary studies reported here indicate that ODSH has the potential to interfere directly or indirectly with the CXCL12/CXCR4 and thus prevent homing of leukemic stem cells in the bone marrow to make them susceptible to chemotherapy.

