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TITLE
Interleukin-8 Secretion due to Leukemia induced Endothelial-cell Activation promotes AML Expansion and Chemoprotection

HYPOTHESIS:
Our working hypothesis is that AML induces ECs to secrete interleukin-8 (IL-8) which directly contributes to enhanced proliferation of non-adherent AML cells. Furthermore, using an IL-8 inhibitor will negatively influence AML expansion and improve effect of chemotherapy.

BACKGROUND/AIMS:
Chemotherapy regimens are often used to manage acute myeloid leukemia (AML); however, the majority of cases eventually relapse. Therefore, a deeper understanding of the mechanisms governing AML growth and relapse is necessary to develop effective therapies. Previously, we demonstrated a novel mechanism whereby AML-induced endothelial cell (EC) activation leads to subsequent leukemia cell adherence, quiescence and chemoresistance, identifying these cells as potential mediators of relapse. In this study, we focus on the effect of AML induced EC activation on AML expansion and therapy.

METHODS:
Using a unique in-vitro AML-EC co-culture model, we analyzed the effect of EC activation induced by AML interaction. A structural pocket that is druggable was identified using the crystal structure of IL-8. The DOCK (UCSF) program was then used to perform an in-silico screen of 139,735 compounds in a NCI small molecule library. An IL-8 inhibitor was identified and tested for its anti-leukemic activity.

RESULTS & CONCLUSIONS
AML-EC interaction induced EC activation resulting in secretion of IL-8, which is normally produced during EC activation immune response. The soluble factor IL-8 enhanced expansion of non-adherent AML cells both during direct interaction with AML as well as treatment with EC conditioned media. We further identified an IL-8 inhibitor (Inh 4) that can bind to the active site of IL-8 and interrupt IL-8-CXCR2 signaling in AML. Proliferation studies showed that IL-8 inhibition affected AML growth. We show that EC activation also induces the secretion of IL-8 leading to significant expansion of non-adherent leukemia cells. These findings identify EC activation as a double-edged sword that can chemoprotect adherent AML cells, while enhancing the expansion of non-adherent AML cells. This demonstrates that EC directly contributes to the grim survival rate and high relapse in AML patients and therapies aimed at reducing these effects may provide a strategy for better overall patient care.