CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140402

Project Title:
Novel Targets for Acute Myeloid Leukemia Treatment

Award Mechanism:
Individual Investigator

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Acute myeloid leukemia (AML) is the most common acute leukemia affecting adults. Despite continuous treatment, the majority of the patients relapse within 5 years. Leukemia stem cells (LSCs) may be responsible for the relapse of disease following a remission brought about by conventional chemotherapy, and new molecular targets and therapeutic approaches need to be identified to effectively inhibit LSC activity. Our research has indicated that the inhibitory receptor LAIR1 supports the self-renewal and survival of human leukemia cells. We found that LAIR1 is highly expressed on cells from AML patients and that LAIR1+ primary human AML cells are enriched for AML stem cell (AML-SC) activity. Interestingly, the deletion of lair1 in the mouse does not cause defects in normal hematopoiesis or in hematopoietic stem cells. In contrast, the disruption of lair1 in human and mouse leukemia cells blocked leukemia development. Importantly, we demonstrated that LAIR1 protects AML cells through the SHP-1/CAMKI pathway. This experimental finding is strongly supported by the clinical data. Here, we propose three aims to test our hypothesis that LAIR1, as a representative of the ITIM-containing receptors, is essential to the AML-SC activity through the SHP-1/CAMKI pathway. In Aim 1, we will investigate the function of SHP-1 in LAIR1 signaling AML-SCs. In Aim 2, we will dissect how CAMKI transmit the LAIR1-intitiated signaling in AML-SCs. In Aim 3, we will test whether blocking LAIR1 activation inhibits the SHP-1/CAMKI signaling. Importantly, while loss of LAIR1 is detrimental to AML development, there is no apparent effect of knockout of lair1 on normal hematopoiesis. Therefore LAIR1 signaling may represent an ideal target for treating AML. Our proposed blockade of ITIM-receptor signaling through signaling inhibition in combination with conventional therapies may prove to be an effective strategy for elimination of LSCs and lead to complete remission of patients.