"Deciphering the Role of RNA Editing in Leukemia Stem Cell Generation and Pediatric Acute Leukemia Relapse"

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SCIENTIFIC ABSTRACT

Acute lymphoblastic leukemia (ALL) relapse is the most common cause of cancer-related mortality in children. Leukemia relapse is driven by leukemia stem cells (LSC) that to inflammatory microenvironments, self-renew and become dormant thereby rendering them resistant to chemotherapy. The goal of this project is to investigate the molecular pathways that propagate LSCs in ALL. Previous work in our lab has shown that activation of adenosine deaminase acting on RNA (ADAR1) editase by inflammatory cytokines promotes generation of LSCs and progression of chronic myeloid leukemia (CML) from chronic phase to a therapy- resistant blast crisis phase. In blast crisis LSC, ADAR1-mediated adenosine to inosine (A-to-I) RNA editing impairs maturation of let-7 microRNAs, thereby providing a block in differentiation and enhancing LSC self- renewal and therapeutic resistance. However, the mechanistic role of ADAR1 in LSC generation in ALL and the inflammatory cytokine drivers of ADAR1 activity have not been elucidated and will be the focus of this project. Our quantitative RT-PCR and intracellular flow cytometry data reveal high expression of ADAR1 in human ALL compared with normal bone marrow (BM) samples. Thus, we have established a robust humanized mouse model of ALL by intrahepatic transplantation of progenitors from human ALL BM into RAG2- /-γc-/- neonatal mice. Transduction of LSC with our lentiviral ADAR1 luciferase reporter will enable in vivo imaging of ADAR1's effects on homing, self-renewal and dormancy. Elucidation of the role of ADAR1 on LSC propagation will inform the development of LSC eradication strategies aimed at obviating relapse in pediatric RAG2- ALL.

LAY ABSTRACT

Acute lymphoblastic leukemia (ALL) is the commonest childhood cancer and leukemia relapse after treatment is an important cause of cancer-related death. Leukemia relapse is caused by a distinct subset of cells called "leukemia stem cells" (LSC) that have the unique capacity to maintain themselves for a long period of time while remaining in a dormant state. This enables them to evade elimination by conventional cancer treatments such as chemotherapy and radiotherapy, which preferentially kill rapidly multiplying cells. This project aims to study the signals and pathways that are important in propagating these LSC. Previous work in our lab in chronic myeloid leukemia (CML) has shown that inflammatory signals activate a family of enzymes called adenosine deaminase acting on RNA (ADAR) which generates LSC and leads to progression of CML from an indolent "chronic phase" to an aggressive "blast crisis" phase that is resistant to treatment. However, the role of ADAR in generating LSC in ALL is not known. Work in our lab showed that there is high expression of ADAR1 in human ALL. Hence we have established a mouse model of ALL by transferring cells purified from leukemia patient's bone marrow into immune-deficient mice. We will perform latest molecular tests that will allow us to track the functional activity of ADAR1 in LSC in live mice that harbor human ALL. This will enable us to understand how ADAR mediates LSC maintenance and dormancy, thereby revealing novel targets that may be utilized in elimination of the LSC that drives leukemia relapse.