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MerTK receptor Tyrosine Kinase is a therapeutic target in acute myeloid leukemia

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Abstract

Although cure rates for acute lymphoblastic leukemia (ALL) in children are high (85~90%), chemotherapeutic drug resistance still remains a major problem and leads to death in 50-95%. Even survived, patients often suffer from late-term secondary toxic effects of current treatments. Therefore, novel therapy modalities with less toxicity are needed to develop for ALL patients. A preclinical model has been established by evaluating new therapies in NOD/SCID or NSG xenograft model engrafted with primary ALL cells. The immunophenotype and morphology of the original patient's disease can be retained after a serial of passages in this mouse xenograft model. Response to drugs of interests can be monitored by *in vivo* bioluminescent imaging and accurately reflects the outcome of ALL patients receiving the novel therapy. Interaction between leukemia cells and their microenvironment has been considered as a new therapeutic target. Bone marrow (BM) stromal cells provide chemoprotection to ALL, thus contributing to drug resistance due to the lack of efficacy of current therapies. In fact, more than 80% of the sites of first relapse in childhood ALL is bone marrow with only ~20% of 5-year survival rate. Integrin α4 mediates adhesion of normal and malignant B-cell precursors to BM stromal cells. According to gene expression profile, integrin α4 is over expressed in ALL patients and inversely correlated with the survival outcome. Therefore, our group tested whether interference with α4-mediated stromal adhesion could be a new ALL treatment strategy. For this purpose, two models of leukemia were used, one genetic (conditional α4 ablation of BCR-ABL1-induced murine leukemia) and one pharmacological using antibody, like Tysabri to target α4 of primary pre-B ALL. Conditional deletion of α4 sensitized murine leukemia cells to chemotherapeutic agent Nilotinib. Adhesion of primary pre-B ALL cells was α4-dependent and inhibiting α4 sensitized primary ALL cells towards chemotherapy, VDL. Combination of chemotherapy with Tysabri prolonged survival of NOD/SCID recipients of primary ALL suggesting adjuvant integrin α4 inhibition as a novel strategy for pre-B ALL.

Biography

Doug Graham completed his PhD in 1994 from the Department of Immunology at the University of North Carolina and his MD in 1996 from the University of North Carolina. He then completed his Pediatric Residency and Pediatric Hematology/Oncology Fellowship at the University of Colorado Anschutz Medical Campus. Currently, he is Associate Professor of Pediatrics at the University of Colorado and a Pediatric Oncologist at Children's Hospital Colorado. Dr. Graham also serves as the Leader of the Research Emphasis Area in Biology of Cancer at Children's Hospital Colorado where he oversees basic science and clinical research in pediatric oncology.