Hematology-2013
OMICS Group Conferences
Accelerating Scientific Discovery
International Conference on
Hematology & Blood Disorders
September 23-25, 2013 Raleigh, USA

Cell adhesion as a therapeutic target in acute lymphoblastic 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 overexpressed 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

Dr. Enzi (Eun Ji) Jiang (Gang) received her M.D. from Norman Bethune College of Medicine, Jilin University, formerly Norman Bethune University of Medical Science, Changchun, China in 1987. She has completed her Ph.D. from Harbin Medical University in 1999 and postdoctoral studies from University of Texas Southwestern Medical Center at Dallas in 2007. Dr. Jiang is working as a senior scientist at Division of Hematology and Oncology, Children's Hospital Los Angeles University of Southern California Keck School of Medicine, Los Angeles, USA. She has published more than 15 papers in reputed journals related to mesenchymal stem cells and leukemia and contributed to a book chapter (Chapter 4: Molecular Pathogenesis of ALL, *Contemporary Management of Acute Lymphoblastic Leukemia*, In Press 2013). Dr. Jiang is serving as an editorial board member for the *Journal of Blood Disorders and Transfusion*. Her research interests include: mouse models of pre-B acute lymphoblastic leukemia and its application in preclinical evaluation of novel anticancer therapy, stem cell niches, integrins, survivin, drug resistance, minimal residual disease, small molecule inhibitors of Wnt signaling pathway, mesenchymal stem cells isolation and application in regenerative medicine such as muscular dystrophy.