REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Alteration of metabolic pathways driven by pro-apoptotic Bax and Bak in early thymopoiesis initiates the stage specific T-cell Leukemia

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T cell differentiation in the thymus depends on a continuous supply of bone marrow derived progenitors. A selective subset of progenitors settles in the thymus and initiates T lineage development. Commitment to the T-lineage fate depends on different metabolic pathways, environmental signals and transcription factors, via multiple prethymic and intrathymic steps. Our recent findings (Blood, 2010; 116, 5237) established that in mice in which the two major pro-apoptotic Bcl-2 family members, Bax and Bak, are deleted (BaxBak DKO mice), T cell differentiation is disrupted with the accumulation of early T-cell progenitors (ETPs) in the thymus. To elucidate this distorted T cell differentiation we reconstituted mice with DKO hematopoietic cells. Interestingly in this reconstitution assay, the progenitors from DKO mice display a marked competitive advantage with aberrant differentiation. Notably, the increased ETPs without BaxBak are associated with broad alterations of the AKT pathway, mitochondrial membrane potential, ATP levels and glycolytic rate. These mice develop an aggressive neoplastic disorder, T cell lymphoblastic leukemia (T-ALL). To determine whether our mouse tumors reflect a subset of human disease, we performed a Gene Set Enrichment Analysis using a gene signature derived from the relative expression of up-regulated genes in DKO tumor samples against a dataset of human T-ALL samples. We demonstrated a significant correlation between the expression profile of our BaxBaxDKO mouse lymphoma and early T cell specific LYL1-associated human T-ALL. The knowledge of this stage specific leukemic transformation without BaxBak has potential to develop the new therapeutic targets.