REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Where do lymphomas meet leukemias ? a look at the underlying aberrant DNA damage response and p53 pathway activation!

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12:00 Noon
Seminar Room

The field of DNA repair has recently undergone a major transformation, due to the ability to better characterize the factors involved in the repair of cellular DNA breaks, and to an improved ability to induce and monitor chromosomal breaks. B cells are developmentally programmed to undergo ordered DNA breaks and generate a large and diverse range of antigen receptor variable regions. Thus, these cells offer an ideal system to examine physiological DNA repair mechanisms. We have earlier shown that these double strand breaks are strictly dependent on the activation of AID (activation induced cytosine deaminase). I have generated Immuno-FISH assays to visualize and functionally analyze the DNA damage response in these cells. In an unexpected and interesting finding we found that 53BP1 is recruited to switch regions of IgH locus in the absence of AID induced DNA double strand breaks. We also show that secondary structures that are formed at transcribing switch region within IgH locus recruit 53BP1 prior to the breaks and perhaps target AID to these structures. These results indicate that 53BP1 acts as a scaffold protein to initiate synapses between distant chromosomal regions (unpublished).

In yet another studies, we found that lineage restricted p53 activation leads to different fates for hematopoietic stem cells. MDS (Myelodysplastic Syndrome) is a pre-leukemic hematopoietic stem cell (HSC) disorders. It is characterized by block in differentiation of HSCs. 5q- syndrome is the first hematologic disorder associated with a specific chromosomal deletion and is the only subtype of MDS defined by a specific molecular abnormality. In an in vitro model for 5q- syndrome, we found that p53 accumulates selectively in the erythroid lineage of primary human hematopoietic progenitor cells following expression of shRNAs targeting RPS14 in HSCs. Induction of p53 led to lineage-specific accumulation of p21 and consequent cell cycle arrest in erythroid progenitor cells. Pharmacologic inhibition of p53

rescues the erythroid defect, while nutlin-3, a compound that activates p53 through inhibition of HDM2, selectively impaired erythropoiesis. In bone marrow biopsies from patients with DBA or del(5q) myelodysplatic syndrome there is an increase accumulation of p53 in the nucleus . Besides, our finding that erythroid progenitor cells have increased sensitivity to HDM2-mediated p53 accumulation has implications for the pathogenesis and treatment of human diseases beyond the 5q- syndrome and DBA (many congenital or acquired bone marrow failure syndromes). These findings also suggest that p53 plays an important role in deciding the fate of stem cells.