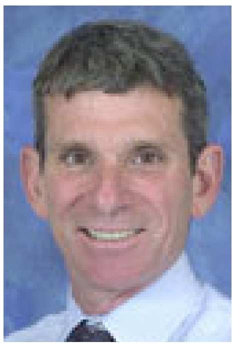
Spatial Analysis of Hematopoietic Stem and Progenitor Cells in the Bone Marrow

Presenter: Leslie Silberstein, Harvard Medical School, Boston, MA



Dr. Silberstein is currently Professor of Pathology at Harvard Medical School and Director of the Joint Program in Transfusion Medicine at Children's Hospital, Boston, Brigham and Women's Hospital, and the Dana-Farber Cancer Institute, integrating research, clinical practice and education with a focus on development of cell-based therapies. Additionally, he is Director of the Center for Human Cell Therapy (CHCT) at the Immune Disease Institute, whose mission is to rapidly translate novel cell therapy protocols from the laboratory to the clinic, providing cell therapy resources for the Harvard community and its affiliated hospitals. Dr. Silberstein is also a Senior Investigator at the Immune Disease Institute and Head of the Harvard Stem Cell Institute's Translational Research Program.

Abstract

Sustained production of all mature blood cell types relies on the continuous proliferation and differentiation of a rare population of self-renewing, multipotent hematopoietic stem cells (HSCs). HSC maintenance and lineage differentiation are strictly regulated by distinct microenvironments, termed niches, defined by cellular components, soluble regulators, and by the extracellular matrix.

Upon entering the differentiation pathway, HSCs progress from primitive, multi-lineage potential progenitors through more restricted progenitors, finally giving rise to fully functional mature blood cells. Therefore the BM constitutes an extremely complex and diverse environment harboring a vast array of hematopoietic cells at all stages of differentiation, distinct populations of stromal cells of mesenchymal origin as well as cells involved in bone metabolism and a intricate vascular network. A detailed understandying of the spatial organization of BM tissue underlying the sophisticated regulation of hematopoiesis, has not been achieved to date due to limitations of conventional imaging techniques. Among the best characterized multi-step developmental pathways ocurring in BM cavities is the one leading to B cell production. Thus, as an initial validation for the use of Laser Scanning Cytometry (LSC) to study BM tissue sections, we have analyzed the anatomical localization of progenitor B cells at distinct stages of development. Analysis of whole femoral longitudinal sections showed that B lymphopoiesis in BM is not strictly spatially compartmentalized, however, early B cell progenitors reside preferentially in niches/microenvironments in the periphery of the BM cavity near bone surfaces. These studies lead the way to the current focus of our work which is to investigate hematotopoietic stem and progenitor (HSPC) localization in BM cavities. Preliminary data generated using LSC suggestive of a non-random preferential localization of HSPCs to metaphyses of long bones, will be presented. Our future effort will be directed to identify HSPC niche cellular constituents. A comprehensive description of niche-derived signals regulating unique properties of HSPCs will certainly prove relevant in human HSPC transplantation and cellular therapies.