Preface: Stem Cells and Oncogenesis

The title Stem Cells and Oncogenesis encompasses a range of topics that have become central in cancer research in recent years and have provided fundamental insights into the tumorigenic process. In essence, all of these topics address the roles played in cancer by mechanisms regulating cell differentiation states. Among these are the nature of intracellular heterogeneity within tumors and the mechanisms by which differentiation events contribute to it, the identity and functions of cancer stem cells (CSCs), the identity of cells of origin of different cancers, and the functions of molecular regulators of stem cell identity and differentiation in various tumor types.

The CSC model in particular has become a central reference point in recent years, providing an important theoretical framework for much of the research in the field. The model applies the principles of normal stem cell biology to the process of tumorigenesis, proposing that differentiation-like events occur within cancers, that CSCs are positioned at the apex of a differentiation hierarchy in tumors, and that their special abilities in self-renewal and plasticity provide a driving force for tumor development and progression. Beyond the broadening of the conceptual understanding of tumor biology provided by these ideas, the model carries potentially dramatic implications for cancer therapy.

The intense research in this field in recent years has indeed uncovered the immense importance of differentiation-like events in cancer and of the pathways regulating them. At the same time, the CSC model itself has evolved and expanded. The idea that a rigid differentiation hierarchy exists within tumors, such that CSCs can differentiate into non-cancer stem cells but not vice versa, has been challenged by experimental findings. Cell plasticity, reflected in the ability of cells to dedifferentiate and transdifferentiate, is more common among cancer cells, as well as in normal tissues, than previously appreciated. Tools for analysis of genetic and epigenetic clonality within tumors have matured, and recent studies have begun to dissect whether and how particular clones and their cells of origin drive tumor growth. Interactions between tumor cells and their environment that affect cancer cell differentiation states, are being uncovered.

This special issue presents reviews that cover some of the most central topics in the field, touching on a variety of conceptual questions and discussing some of the important tumor types in which the most progress has been made. A review by Gregory Driessens analyzes methods for identifying CSCs in different tumor types, with a discussion of the relative strengths of clonal analysis through lineage tracing and of implantation-based methods. The review highlights recent findings regarding CSCs in tumors of the skin and intestine. A review by Dinorah Friedmann-Morviski focuses on CSCs in gliomas, including dramatic recent discoveries regarding cell plasticity in such tumors. Both reviews discuss important issues regarding the cell of origin of cancers and highlight findings illustrating how processes of dedifferentiation and transdifferentiation contribute to changes in the phenotypes of tumor cells relative to the cell of origin.

A review by Reba Condiotti, Wenjun Guo, and myself focuses on CSCs in breast carcinoma, the first solid tumor type in which such cells were identified. This review analyzes the types of CSCs identified in the disease and the nature of their stemness. Several differentiation axes seem to be operating within breast cancers, including the axis of epithelial versus mesenchymal identity and the axis of basal versus luminal identity. The review discusses how these axes may govern CSC identity and analyzes the links between CSCs and normal mammary stem cells.

A review by Luigi Ombrato and Ilaria Malanchi discusses one of these differentiation axes in depth: the epithelial-to-mesenchymal transition (EMT). EMT is one of the most important coordinated differentiation programs acting in epithelial cancers, and major questions regarding the manner by which this program confers stem cell traits on carcinoma...
cells, and how such abilities are related to its roles in metastasis, have arisen. The review presents a gradient model in which different levels of EMT confer distinct abilities on cancer cells.

A review by Carlos Sebastián focuses on one of the most dynamic and exciting topics in the cancer field: regulation of metabolism. The review describes recent findings highlighting the importance of metabolic reprogramming in the control of CSC identity and function. Current understanding of cancer cell metabolism, as well as of the importance of its regulation in normal stem cells, is integrated in this review to provide a coherent view of the state of the art in this field.

A review by Yusuke Saito and Daisuke Nakada focuses in depth on one of the most important pathways regulating energy and metabolism: the Lkb1/AMPK pathway. Specifically, the role of this important pathway in hematopoietic and leukemic stem cells is discussed in light of recent exciting findings. A review by Aviya Goldshtein and Michael Berger also discusses aspects of leukemia development, with a specific focus on the roles of the NOTCH pathway in T-cell acute lymphoblastic leukemia and its importance in controlling aberrations in normal T-cell differentiation, which contribute to the tumorigenic process.

This collection offers an up-to-date view of the field, and the reviews convey the high level of excitement and dynamism that currently rule it.

Guest Editor:
Ittai Ben-Porath
Department of Developmental Biology & Cancer Research
Institute for Medical Research ¬– Israel-Canada
The Hebrew University-Hadassah Medical School
Jerusalem, Israel