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CSCs and pluripotent/multipotent stem cells

This month's special issue of *Laboratory Investigation* focuses on cancer stem cells (CSCs) and pluripotent/multipotent stem cells. These two types of stem cells differ in origin but share common biological features such as self-replication and multipotency. The CSC theory states that organ-specific stem cells may be the origin of cancer and that cancer develops from maturation disorders of these stem cells. Additionally, signals such as Notch, Wnt, and Shh are related to both oncogenesis and stem cell development. Furthermore, when cancer cells are cultured *in vitro*, it appears that CSCs exist, because only a small number of cells have proliferative ability and form stem cell–like colonies. This special issue presents 13 papers that enhance our understanding of CSCs and pluripotent/multipotent stem cells, with an emphasis on therapeutic implications.

Why focus on CSCs?

A tissue stem cell has two important properties: it can divide to produce the same cell type as itself (self-renewal ability) and it can differentiate into various types of other cells (multipotency). Cancer is hypothesized to originate from a small number of CSCs. The development of flow cytometry and immunodeficient mice led to discovery of CSCs in acute myeloid leukemia in 1997.[1] Subsequently, CSCs expressing stem cell markers such as CD44 and CD133 were found in cancers of the breast, brain, pancreas, head and neck, and colon—in work that was based on the CSC hypothesis that originated from research on leukemia. In this special issue of *LI*, Sarkar and colleagues report a novel CSC biomarker for assessing colon cancer risk.

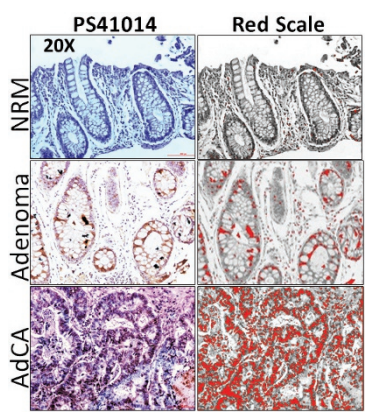

Figure 1 Immunostaining of a patient's screening colonoscopy sample with the PS41014 antibody, which is specific for the cancer stem cell biomarker DCLK1-S. For more information, see the paper by Sarkar *et al* (Lab Invest 2017;97:1246–1262).

The CSC hypothesis also explains the mechanisms of cancer development and metastasis and may therefore lead to the discovery of new drugs. Hardin and colleagues focus on the evolving concept of CSCs, especially on the involvement of noncoding RNAs during epithelial-to-mesenchymal transition of CSCs and the role of exosomes in the CSC microenvironment. Xu *et al* report possible involvement of pluripotent gene activation, i.e., upregulation of the *c-Myc*, *Oct-4*, *KLF-4*, *Nanog*, and *Gli-1* genes, during the reprogramming of hepatic progenitor cells in nonalcoholic steatohepatitis–associated hepatic carcinogenesis. Zhao and co-workers show how CSCs can be used to demonstrate preclinical proof of concept for drug discovery; they describe a novel low-molecular-weight compound that impairs the stemness of glioma cells as determined by measurement of CSC colony formation and sphere formation.

How do we integrate studies of pluripotent/multipotent cells into pathology?

Like CSCs, pluripotent/multipotent stem cells are promising tools for pathobiology studies such as disease modeling "in a dish." Watanabe *et al* provide an up-to-date summary of applications of induced pluripotent stem cells (iPSCs) as a novel model system for the study of human disease. Patient iPSCs differentiate into cell types relevant to their disease and identify abnormalities caused by the patients' unique genetic background. Yagi *et al* examine the epigenetic foundation of iPSCs in association with pediatric tumor development. Matsushita and Dzau discuss in depth the relationship between adipogenesis of mesenchymal stem cells (MSCs) and the comorbidities of obesity. MSCs indeed show promise as a tool for evaluating the potential of effective and safe therapies for obesity, dyslipidemia, and hypertension.

In addition to availability of stem cells for disease modeling, stem cells are now used as raw material for production of cellular therapy products used to regenerate damaged tissue or organs because of their ability to differentiate into various cell types. Higuchi and co-workers present a state-of-the art review of stem cell–based therapies administered in clinical trials to patients with ischemic heart disease. Matsushita and Dzau review the potential role of MSCs in treatment of diabetes and the angiogenic and anti-inflammatory potential in a clinical setting, and Webber and co-workers demonstrate the immunosuppressive effect of dermal MSCs in a murine model.

Numerous technical advances, such as improved differentiation methods, development of three-dimensional

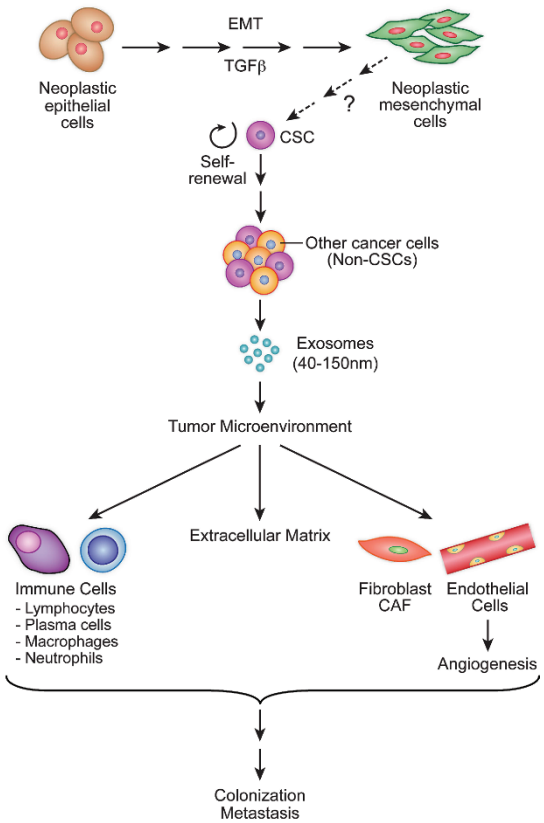

Figure 2 Diagrammatic illustration of epithelial-to-mesenchymal transition and interaction of cancer stem cells with the tumor microenvironment. Reprinted from the paper by Hardin *et al* (Lab Invest 2017;97:1142–1151).

culture systems, and the use of extracellular matrix with human stem cells have further accelerated the field. Kojima and colleagues describe a method for efficiently producing trophoblasts and intestinal organoids from human iPSCs (see also ref. 2). Urbanek *et al* present the novel insight that differentiation of liver-derived mesenchymal stromal cells to osteoblasts is mediated in part by the Notch pathway. Uehara and colleagues reveal the role of extracellular matrix in the maintenance and differentiation of hematopoietic stem cells in specialized bone marrow microenvironments known as niches. They found that laminin-322 secreted from osteoblasts regulated osteoclast differentiation. Teshigawara and co-workers discuss human intermediately reprogrammed stem cells (iRSCs), yet another resource for cellular therapy products. iRSCs can be converted into both pluripotent stem cells and somatic cells via a change in culture conditions.

The story of Prometheus in Greek mythology reminds us of tissue regeneration. Prometheus was punished by being chained to a rock on top of Mount Caucasus, and his liver was eaten by an eagle each day and regenerated at night. At present, liver transplantation is a routine medical practice because of the strong regenerative capability of hepatic stem cells. This special issue on CSCs, iPSCs, and regeneration will, we believe, provide clues toward a further understanding of the complex mechanisms of cancer and the therapeutic implications for future translational innovation.

1. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 1997;3:730–737.
2. Uchida H, Machida M, Miura T, *et al*. A xenogeneic-free system generating functional human gut organoids from pluripotent stem cells. JCI Insight 2017;2:e86492.