

PREFACE

Stem cell research is one of the most fascinating and exciting research areas considering the therapeutical potential of stem cells. Manipulation of endogenous stem cells or the application of exogenous stem cells has the great promise to rejuvenate diseased and aged tissues in regenerative therapies. To fulfill this promise, we first need to identify tissue stem cells, define their physiological lineage relationship to differentiated cells, and characterize their functional control by intrinsic regulators and extrinsic factors from the microenvironment. In the past three decades, tremendous progress has been made: from the successful culture of embryonic stem cells and the early discovery of hematopoietic stem cells and stem cells in rapidly renewing skin and intestinal tissues to the more recent identification of neural, mammary, muscle, lung, and germ stem cells as well as hepatic and kidney progenitors. Recent studies have also shed light on the molecular make-up of stem cells and the complexly controlled balance between stem cell self-renewal and differentiation by endogenous transcriptional regulators, microRNAs and their overall epigenetic state, as well as by signaling and cellular communication from and to the microenvironment.

These insights have led to the establishment of stable stem cell cultures and culminated in recent efforts to engineer three-dimensional intestinal, skin, and other tissues. They further guide attempts at differentiation of embryonic and induced pluripotent stem cells and at direct reprogramming of differentiated somatic cells. Finally, our greatly improved understanding of stem cell control and function directly overlaps with studies of cancer biology and aging, as recently discovered cancer stem cells share many regulatory mechanisms with normal tissue stem cells that go awry in cancers and that also become dysregulated in aging tissues.

In this volume of *Current Topics in Developmental Biology on Stem Cells in Development and Disease*, 14 contributions from leading stem cell researchers provide a comprehensive overview about our current knowledge of physiological stem cell functions in 11 different mammalian organ systems and of the mechanisms that contribute to aging and cancer. In Chapter 1, Posfai et al. review embryonic and other pluripotent stem cells in the pre- and postimplantation embryo. They comprehensively discuss the latest insights on the sequential lineage specifications in the early developing embryo. Furthermore, they dissect the similarities and differences of *in vivo* pluripotency

development with their stem cell population counterparts propagated *in vitro*. All these developmental aspects are then placed in the context of the major signaling pathways known to play critical roles in the regulation of pluripotency.

Chapters 2–4 are focused on the discussion of well-characterized stem cell systems in the rapidly renewing tissues of the bone marrow, intestine, and skin. In Chapter 2, Goodell and colleagues summarize the main results of many important recent studies on hematopoietic stem cell regulation with a focus on epigenetic control. They thoroughly discuss the latest insights on general principles of epigenetic regulation and the specific epigenetic mechanisms that impact embryonic hematopoietic development and that control the balance between hematopoietic stem cell maintenance and lineage commitment. This review further highlights epigenetic controls in the context of aging and hematopoietic malignancies. In Chapter 3, Tan and Barker review intestinal stem cells and discuss the controversial relationships and hierarchy of different stem cell populations that have been identified within the crypts. They summarize the main competing theories and conflicting results of many important recent studies and offer an integrative discussion of a unifying theory. In Chapter 4, Tadeu and Horsley review the latest insights on epithelial skin stem cells of the epidermis, hair follicles, and sweat glands. They detail the intrinsic and extrinsic controls of adult skin stem cell niches and discuss their relevance for epithelial skin cancer progression and pathology.

In subsequent chapters, other well-established and more recently discovered stem cells and progenitors of several organ systems are discussed. In Chapter 5, Fu et al. review the lineage relationship of different stem and progenitor cell populations of the mammary gland. With an insightful discussion, they provide reconciliatory explanations to new competing theories regarding lineage relationships within the epithelial mammary gland. It continues with a thorough overview of the molecular control of mammary stem and progenitor cell regulation by steroid hormones and other molecular players and finally ties together the latest insights regarding implications for breast cancer. In Chapter 6, several established and novel features of satellite stem cells are reviewed by Chang and Rudnicki in a comprehensive discussion of many recent insights, including: the emerging concept of satellite stem and progenitor cell heterogeneity, novel findings regarding the embryonic origin of muscle stem cells, and the requirement of Pax7 in satellite cells. Finally, this chapter discusses age- and disease-related decline of muscle stem cell function and provides an outlook on potential stem cell

transplantation therapies. In Chapter 7, Rolando and Taylor summarize the latest insights on the developmental origin of adult hippocampal neuronal stem cells with a focus on controlling signaling pathways and transcription factors. Then, they dissect the heterogeneous nature and function of adult neurogenic stem cells and niches and, in this context, the role of important signaling pathways. Finally, this chapter discusses recent insights into the role of adult hippocampal neuronal stem cells in epilepsy, aging, and depression. In Chapter 8, Leeman et al. review recently discovered lung stem and progenitor cells. They summarize the identification of several different lung epithelial stem cells, the role of lung stromal and endothelial cells, and their relevance for lung cancers. Discussed are further recent advances toward cell-based therapies by applying bone marrow-derived mesenchymal stem cells and directed differentiation of induced pluripotent stem cells. In Chapter 9, Yang and Oatley review spermatogonial stem cells in physiological and pathological conditions. They first discuss the origin of spermatogonial stem cells, then the molecular mechanisms regulating their maintenance, and the latest insights into germ cell tumor formation. In Chapter 10, Shin and Kaestner describe recently discovered hepatic progenitor cells. They discuss competing and controversial theories regarding the cellular origin and precise identity of these stem cell-like cells. In Chapter 11, Kopan et al. review the role of nephrogenic progenitors in kidney morphogenesis and dissect extrinsic regulatory influences by stromal signals, in addition to intrinsic transcriptional controls. They then discuss the impact of these latest insights on renal hypoplasia and the general control of cessation of nephrogenesis.

In Chapter 12, Rezza et al. provide a niche-centric view on the general intrinsic regulation of stem cells and their extrinsic control by the microenvironment. A dissection of the cellular organization of adult stem cell niches is followed by an extensive discussion of established and novel molecular regulators in adult stem cell niches. It closes with a brief discussion of stem cell niche dysfunction in aging and cancer. The final Chapters 13 and 14 establish in greater detail the stem cell and niche-related processes and molecular mechanisms that are dysregulated in cancers and during aging, respectively. Atlasi et al. in Chapter 13 first provide a general discussion of the historical perspective, the definitions, and the emerging concept of cancer stem cells. In addition, they analyze the control of cancer stem cells by signaling pathways with a focus on Wnt/ β -catenin signaling, and discuss the similarities of germ cell tumors with embryonic pluripotent stem cells. Finally, Jung and Brack review in Chapter 14 the dynamic changes in stem

cells during aging that are only recently beginning to be uncovered. They discuss the molecular players in cellular aging and the extrinsic regulation mediating aged cellular and tissue homeostasis. They finally provide important examples of aging mechanisms in major well-known stem cell systems.

This volume of *Stem Cells in Development and Disease* is a collection of 14 timely and comprehensive reviews on the current knowledge and recent insights of stem cell functions in several different organ systems. New biotechnological breakthroughs in the past decade have brought tremendous advances that have greatly increased our understanding of stem cell functions, which ultimately brings us closer to the prospect of applying stem cell therapies to human disease. It is my hope that reading the diverse chapters in this volume will provide the different stem cell fields with new ideas and fresh perspectives.

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