Preface

Stem cells have an astounding capability to self-renew or differentiate under a plethora of seemingly chaotic external and internal inductive signals which may lead to contradicting fate decisions. The current popular view relies on the identification of isolated signals or combinations based on the premise that by varying the signaling milieu, one can effectively control the development of stem cells and enable their medical applications.

The phenomenology of stem cell fate decisions for self-renewal, differentiation, as well as the reprogramming of committed cells into pluripotent cells, results from a complex interplay of a multitude of regulatory elements on the molecular level. One way to formally describe these complex interactions is the application of network models which represent the relevant molecular components and map their interactions (Chapters 1 and 2). Studying the dynamic properties of such networks at different levels will allow for a better systemic understanding of the regulatory principles underlying stem cell fate decisions.

In this book, a perspective is presented from a systems level of the mechanisms regulating stem cell development. Information resulting from the application of systems biology concepts can be incorporated in developing technologies for the realization of stem cell-based applications. The recurrent network motifs of information processing could account for and integrate the "chaotic" signals and thus underwrite the biological "fits" of stem cells. We believe that the network perspective, which has been under-represented in the discussion of stem cell biology and applications, is beginning to attract attention from the research community.

One of the apparent merits of network motifs is prediction. The discovery of the pluripotency gene network suggested that over-expression of the few "pluripotent" genes linked via positive feedback loops may suffice to generate the pluripotent state in differentiated somatic cells. Testing this prediction has led to the development of a new successful technology for the generation of induced pluripotent stem cells (iPSCs) (Chapter 3). The generation of human iPSCs using viral and non-viral approaches, characterization of their pluripotent capabilities and development of culture conditions for their stable propagation are addressed in Chapter 5.

Feed-forward loops are frequently found motifs in biological networks (Chapter 1). Their functions may vary from pulse generators and gating systems to response delaying circuits. The novel integrative nuclear FGFR1 signaling (INFS) mechanism discovered in the recent years constitutes a nexus of a feed-forward-and-gate module which effectively regulates developmental gene activities (Chapter 4). Direct activation of this module via over-expression of the INFS genes should suffice to convert the proliferating stem/progenitor-like cells into their differentiated progeny, thus bypassing the daunting need to identify proper combinations of the many external and internal factors needed for such a transition. This has been shown to work not only *in vitro* in cultured cells (Chapter 4), but recently also *in vivo* whereby the transfer of the INFS genes reinstates an active neuronogenic development in stem cells in the mature brain (Chapter 10).

An important feature of developmental differentiation is the "permanent" — often irreversible — status of the achieved state. Such a state can result from positive feedback regulation whereby the expression of the central genes in the module is activated by their products (Chapter 1). These positive feedback loops may lead to a bi-stable "low" or a "high" signal as discussed in Chapters 1 and 4. Once initiated by external factors, the positive feedback loop that underlies the high activated state remains switched on even if the original activators are no longer present.

We have started untangling the effects of critical signals on stem cell biology only recently. A deeper understanding of these effects will be important for the development of technologies, enabling the testing of diverse developmental networks already implicated by systems biology as well as the development of new network models. Chapter 6 discusses the significance of physicochemical parameters such as oxygen tension, pH and biomechanical forces for the *ex vivo* expansion and differentiation of hematopoietic stem cells. Chapter 7 focuses on recent advances and challenges associated with the scalable culture of embryonic and induced pluripotent stem cells. Enabling bioreactor technologies and associated bioprocesses will also be critical for the realization of the clinical potential of stem cells. Given the important role of the stem cell milieu in guiding their commitment along specific lineages, intense research efforts have concentrated on appropriately designed biomaterials for the engineering of stem cell-based tissue equivalents. The engineering of bioactive scaffolds for vascular tissue constructs utilizing stem cells is presented in Chapter 8. Special microfluidic platforms can be used to further identify the critical signals controlling developmental networks in stem cells. Aspects of the stem cell niche can be recreated in microfluidic devices to obtain a better understanding of the interactions among stem cells and with their environment as described in Chapter 9.

Besides embryonic stem cells and iPSCs, alternative sources of stem/progenitor cells for regenerative medicine are also explored. One such promising source of stem cells is the human umbilical cord blood. Its multi-potent fetal stem-like cells can differentiate into diverse cell lineages including neural cells. Progress in elucidating the mechanisms, control networks and technologies for their neural differentiation and application in preclinical and experimental medical treatment are discussed in Chapter 10.

An understanding of the mechanisms that control the biology of adult stem cells could potentially be used to recruit endogenously produced stem cells for regenerative medicine. Nanotechnology has provided new therapeutic tools such as non-viral vectors for DNA delivery. DNA nanoplex targeting of developmental networks in brain stem/progenitor cells *in vivo* can reinstate the generation of new neurons by an adult brain and thus open a new horizon for the treatment of neurological disorders (Chapter 11).

As discussed in Chapter 12, an important development has been the identification of cancer stem cells, which may aid in improving disease diagnosis. We are just beginning to unravel the mechanisms underlying an aberrant control of the developmental networks in those cells. Successful corrective targeting the deregulated pathways should enable future advances in cancer treatments.

In summary, this book has two interconnected themes: (1) systems approach towards understanding the biology of stem cells and targeting network mechanisms for effective manipulation of stem cell biology and commitment, and (2) the development of technologies through the application of engineering and biological tools for advancing our ability to control aspects of stem cell biology critical for the realization of the clinical potential of stem/progenitor cells.

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