Cell differentiation
Plasticity and commitment – developmental decisions in the life of a cell
Editorial overview

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Introduction

The development of all metazoan organisms requires that multiple tissue-types emerge during their embryogenesis. Thus cell-fate diversification is an ancient problem that has ultimately been solved by all multicellular organisms in a fantastic variety of ways. The development of nearly all cell lineages entails the initial formation of a multipotent progenitor or stem-cell population, proliferation of this stem-cell population and commitment of these progenitor cells to distinct cell fates. In some cases, stem cells for particular cell types remain in the adult organism, providing a continual source for the generation of replacement tissues, whereas for other cell types the stem-cell population is only present during the early development of the organism. In this issue of *Current Opinion in Cell Biology*, we have assembled several articles that focus on stem-cell diversification and individually address aspects of the following questions: what are the signals that drive the generation of multipotent stem cells; what are the factors that endow a stem cell with the plasticity to give rise to multiple other types of cell; what are the signals and transcription factors that drive a stem cell to give rise to progeny cells committed to a particular cell fate; and is this decision to differentiate along a developmental program irreversible?

Stem cells and lineage diversification

During the past couple of years, remarkable advances have been made in the identification of pluripotent stem cells capable of contributing to several different tissue types in adult mice. Margaret Goodell (pp 662–665) critically reviews the recent claims that both neural and hematopoietic stem cells can contribute to a number of other mesodermal cell types in the adult mouse. Goodell cautions that these recent claims regarding the potency of stem cells need to be validated by future studies. In particular, Goodell emphasizes that the purity of the input 'stem' cells be rigorously tested by a prospective analysis of stem-cell markers and characteristics.

Probably one of the best-studied stem cells are those of neural origin. Sean Morrison (pp 666–672) discusses the origin of stem cells in both the CNS and the PNS, and the factors that instruct these cells to assume either a neuronal- or glial-cell fate. Morrison discusses recent findings indicating that neural stem cells change their sensitivity to neurogenic factors over time and that some glial cells with apparently restricted developmental potential can acquire stem-cell properties *in vitro*. Morrison reviews recent evidence that Notch signals promote gliogenesis, whereas BMP signals promote neurogenesis. Lastly, several recent studies are discussed that have demonstrated that the neurogenic bHLH genes simultaneously promote neurogenesis while blocking gliogenesis.

Two cell lineages whose formation seems to be inextricably connected are cells that give rise to the blood and vasculature. Shin-Ichi Nishikawa (pp 673–678) discusses the evidence that endothelial cells of the vasculature and hematopoietic cells originate from a common precursor, the hemangioblast. In addition to deriving from a common precursor, endothelial cells can in some instances give rise to hematopoietic cells. Nishikawa discusses how conversion of endothelial cells into hematopoietic cells requires the transcription factor, RUNX1, as this process is disrupted in mice lacking this regulator. In addition, Nishikawa reviews recent evidence indicating that the transcription factors SCL and LMO2 are necessary both for lineage commitment of hematopoietic cells and for the differentiation of endothelial cells during vascular remodeling.

Peter Bailey, Tamara Holowacz and Andrew Lassar (pp 679–689) discuss the origin of skeletal-muscle stem cells in the embryo and the adult. The progenitor tissue for most embryonic skeletal muscle is the somite, a transient condensation of pluripotent paraxial mesoderm cells. Bailey, Holowacz and Lassar discuss both the signaling molecules and the transcription factors that modulate the conversion of somitic cells into skeletal muscle. Knockout experiments in mice have established that the myogenic bHLH genes, MyoD and Myf-5, play a key role in skeletal-muscle induction. The authors discuss what is currently known about the upstream transcriptional regulators of MyoD and Myf-5, and summarize recent work identifying Pax-3 as a key regulator of MyoD in the trunk. In addition the authors summarize recent exciting findings indicating that hematopoietic stem cells may be a source for skeletal muscle in the

adult. The authors summarize parallels in the establishment of muscle stem cells in the embryo and the adult, and discuss the evidence that another Pax family member, Pax-7, plays a crucial role in the establishment of muscle satellite cells. Finally, the authors review fascinating recent findings suggesting that Msx1 may play a crucial role in reversing the terminally differentiated state of skeletal muscle in regenerating limbs.

Nearly irreversible decisions: preferential inactivation of the parental X chromosome

One example of a nearly irreversible cellular decision is the stable inactivation of one of the pair of X chromosomes in female mammals. Although the maternal and paternal X chromosomes are randomly inactivated in the embryo proper of developing mice, the paternal X has been found to be preferentially inactivated in extraembryonic tissue from this species. Khanh Huynh and Jeannie Lee (pp 690–697) discuss the elegant studies during the past several years that have elucidated the mechanism of X-chromosome inactivation. This entails the expression of a non-coding RNA, termed Xist, on the inactive X chromosome and conversely the expression of an antisense transcript from this region, termed Tsix, on the active X chromosome. Huynh and Lee discuss evidence supporting a model in which Xist expression is necessary for silencing the inactive X chromosome and Tsix expression acts in a regulatory role to block the upregulation of Xist on the active X chromosome. Huynh and Lee discuss the factors that may regulate the expression of Xist and Tsix and thereby control X inactivation. Furthermore, Huynh and Lee propose that imprinting becomes relaxed in some extraembryonic tissues and that the imprinted X may be transmitted as pre-inactivated. This provocative hypothesis suggests additional levels of control and complexity in X-inactivation.

Tissue interactions that control cell fate

Paul Trainor and Robb Krumlauf (pp 698–705) discuss how cells are allocated to different fates in the cranial neural crest. This structure arose during the evolution of vertebrates, where it gives rise to a number of different cell types including nerve, ganglia, cartilage, bone and connective tissue. Cells of the cranial neural crest migrate from the dorsal regions of the hindbrain into the branchial arches, where they will form cartilage or bone tissue. The skeletal structures formed from the cranial neural crest are different in each branchial arch. For instance, neural crest that populates the first arch forms Meckel's cartilage, whereas neural crest that populates the second arch forms Reichert's cartilage. Thus, distinct cell-fates are assumed by the cranial neural crest along the anterior/posterior axis. Trainor and Krumlauf review recent evidence indicating that cranial neural crest cells are developmentally plastic and that the developmental program of these cells depends upon signals from the cranial mesenchyme. In addition, these authors discuss how patterning signals from the cranial mesoderm act to control expression of Hoxa2, which itself modulates the expression of transcription factors that control either chondrogenesis, such as Sox-9, or intramembranous bone formation, such as Cbfa1.

Transcription factors that coordinate several aspects of organogenesis

Eye formation in vertebrates has been intensively studied during the past decade. The eye is a complex organ consisting of numerous cell types, each of whose development is dependent upon sequential tissue interactions. Ruth Ashery-Padan and Peter Gruss (pp 706–714) review how a cascade of tissue interactions is necessary to promote the formation and maturation of the optic vesicle and the lens. Interestingly, one of the transcription factors whose expression is controlled by such tissue interactions is Pax6, a transcription factor that has a crucial role at differing stages of eye formation. Ashery-Padan and Gruss discuss the multiple roles that Pax6 plays during vertebrate eye formation, initially being required for biasing the surface ectoderm to form a lens, secondarily being required in the formation of neural retinal cells and subsequently being required for proper differentiation of the lens. Thus, Pax6 is re-utilized at various times and in various tissues to promote the proper development of both lens and retina. The re-utilization of transcription factors at different stages of development, even within a single cell lineage, seems to be a recurring theme in the development of metazoa.

The regulatory pathways that control cartilage and bone formation are discussed in the article by Benoit de Crombrugghe, Veronique Lefebvre and Kazuhisa Nakashima (pp 721–727). With the exception of some cranial bones, most of the skeleton forms via endochondral ossification of a cartilage template. In this process, immature chondrocytes within an initial cartilage template undergo a maturation process, to generate hypertrophic chondrocytes. The latter cells lay down an extracellular matrix that is eventually invaded by osteoblasts, which produce bone tissue. De Crombrugghe, Lefebvre and Nakashima discuss both the signaling molecules and the transcription factors that regulate the induction and maturation of cartilage and bone. The authors summarize elegant work, much from the de Crombrugghe laboratory, demonstrating the importance of members of the Sox family of transcriptional regulators in the induction and maturation of cartilage. In addition the authors discuss recent compelling data that the transcription factor Cbfa1 plays a dual role in both chondrocyte maturation and osteoblast function.

Evolutionary comparison of cell-lineage specification

The identity of vulval cell types in the nematode has provided an important paradigm for understanding how cell–cell interactions can control cell fate. Ralf Sommer (pp 715–720) reviews how EGFR/RAS/MAPK signals and

Notch signals are integrated to control the formation of particular vulval cell fates. Interestingly, the stereotyped development of cell lineages in nematodes has changed during evolution. Sommer discusses evolutionary changes in vulval development of differing nematode species and speculates as to how these changes occurred.

In summary, we think that the articles in this issue of *Current Opinion in Cell Biology* shed considerable light on some of the intricate strategies employed to generate cell-type diversity in metazoa. We thank the authors for their contributions to this issue and hope that you will enjoy reading these provocative reviews.