Section I

GENOME, EPIGENOME, PROTEOME, AND SIGNALING

For an embryo to develop into an adult requires an amazingly complex series of events in which the blueprints for development laid down in the genome are transcribed dynamically in time and space. Based on extensive mutational analysis in model organisms, we have an increasingly detailed understanding of the main conserved genetic pathways involved in setting up cell lineages and determining embryonic patterning. Developmental biology is now moving from single-gene analysis to a more systems-wide approach aimed at understanding the full genetic, epigenetic, and proteomic networks that drive developmental decisions.

Embryonic stem cells have been a popular system to study regulatory networks, because they provide a model of early development in which cell numbers are not limiting for large-scale biochemical and genomic analyses. Understanding the mechanisms promoting pluripotency and sustaining self-renewal can provide fundamental understanding of the earliest developmental decisions in the mammalian embryo. In addition, of course, this information has been key to the ability to reprogram adult cells to pluripotency (Chapter 1). Determining the genome-wide binding sites of lineage-specific transcription factors by technologies such as ChIP-ChIP and ChIP-Seq, and integrating this information with genome-wide transcriptional profiling and functional analysis, continues to provide new insights into the genetic hierarchies that drive pluripotency and lineage differentiation. However, this is only one level of control. It is increasingly apparent that epigenetic modifications of DNA itself and of its associated histone proteins play important roles in modulating accessibility of the DNA for transcription. Two examples of epigenetic control that can serve as models with broad implications are X-inactivation (the process by which one of the X chromosomes in female mammals becomes heritably inactive in somatic cells) and genomic imprinting (the process by which certain genes are differentially expressed when inherited from mother or father) (Chapter 2). In these processes, gene or chromosome inactivation is often initiated by *cis*-acting long noncoding RNAs followed by histone modifications and DNA methylation changes and by stable gene inactivation.

Reversing the hierarchy of gene inactivation changes is key to reprogramming cell fate to pluripotency or direct transdifferentiation of cells. A necessary step toward understanding how transcriptional control networks are established during development is an integrated understanding of the interactions among transcription factor binding, chromatin modifications, and DNA methylation changes across the genome. However, understanding these networks is only the beginning, as control at the posttranscriptional level also occurs in a number of different ways. Recently, the importance of microRNAs (miRNAs) has become apparent. miRNAs are short RNAs that can bind to complementary sequences in the 3′-UTR of mRNAs and promote either translational repression or mRNA degradation. A single miRNA can bind multiple targets, thus potentially regulating a coordinated set of genes, and so perhaps control developmental decisions and lineage pathways (Chapter 3). The overall importance of the entire repertoire of noncoding RNAs remains to be revealed, but it is likely that they play key roles in the subtle and dynamic processes that typify developmental systems.

Studying development at the levels of transcriptional and translational control cannot fully explain how the cellular machinery works to organize cells into tissues and organs. A cell responds to its environment and its neighbors via cell-signaling pathways in which extracellular ligands bind to receptors and transduce signals to the interior of the cell. The response to the signal can take many forms but often involves protein modifications such as phosphorylation that alter the properties and

interactions of proteins in the cell. Surveying the different signaling pathways used in development can help reveal some of the common features underlying cell–cell communication (Chapter 5). Given the complexity of protein modifications and protein–protein interactions within a cell, it is increasingly important to be able to monitor cell behavior in terms of the activity of proteins in time and space. Improved approaches for proteomic and protein–protein interaction analysis in even small amounts of tissue have led to new insights into stem cell and developing systems (Chapter 4). This analysis brings new levels of complexity to the network analysis of cell lineages and emphasizes the need to develop better algorithms for interrogating and integrating information at all levels from DNA to protein, to cells, to organ systems. The techniques of modern systems biology will bring new tools to help developmental biologists over the coming years, but these tools can only bring new insights when the underlying biology of the system is clearly understood, as exemplified in the chapters in Sections II and III.

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