Section II

MORPHOGENETIC PROCESSES

Complex, multicellular organisms can recruit, reorganize, and reshape groups of cells to form functionally specialized tissues and organs—a process collectively referred to as morphogenesis. Morphogenetic processes must be carefully choreographed in time and space in the developing organism so that the right cells are relocated and interact in the right place at the right time, and so that the reshaping of the multicellular structure into a tissue or an organ is specified for a particular function.

Examples of changes in cell organization in embryonic development include the spatial ordering of cell lineages within the blastocyst or during terminal differentiation processes such as neurogenesis, dynamic cell movements during gastrulation and epithelial-to-mesenchymal transitions, the formation of branching tubes in many epithelial and endothelial organs, and the segregation of cells and formation of boundaries in tissues. These processes are discussed in the chapters in this section, with an emphasis on the molecular mechanisms involved at the gene and protein levels, the signal transduction pathways induced between and within cells, and insights into the cell-biological processes involved in structurally and functionally reorganizing cells within specialized three-dimensional (3D) structures.

In the mammalian embryo, the first significant changes in cell organization and signs of overt morphogenesis occur in the blastocyst (Chapters 12 and 13). The initial series of cell divisions from the fertilized zygote give rise to a polarized, transporting epithelium (the trophectoderm) that will form the placenta, which surrounds a fluid-filled lumen (the blastocoel), and a compact group of pluripotent cells, the inner cell mass (ICM), that will form the different cell lineages of the embryo. The formation of the trophectoderm appears to be regulated by pathways common to other 3D epithelial cysts and tubes (Chapter 7). Recent studies have shown that lineage specification within the ICM is controlled by networks of transcription factors and cell-to-cell signaling between small groups of cells within the ICM and the overlying cells of the trophectoderm (Chapter 12). Subsequent morphogenetic changes involve dynamic changes in cell–cell boundaries, cell movements, and continued inductive and inhibitory signaling between groups of cells, which give rise to the primitive streak and eventually lead to gastrulation (Chapter 13). Another example of lineage specification and morphogenesis is development of the mammalian brain from neural stem and progenitor cells (Chapter 8); cell division and transcriptional control specify lineage specification and cell fate, and some of the regulators at the cellular level have similarities to mechanisms orienting cell divisions and polarity in epithelial cells (Chapter 7).

The aforementioned examples highlight another aspect of morphogenesis—namely, the choreography between the timing of cell divisions, the juxtapositioning of cells relative to each other and regulation of intercellular signaling that is required for the development of tissues and organs. In the chapter on somitogenesis (Chapter 11), Saga discusses the mechanisms underlying the control of this choreography in the paraxial mesoderm that undergo cyclic processes during somite formation. In the mouse, a "segmentation clock" organizes the collective behavior of cells and their patterning into segmented somites through different growth factor signaling pathways and transcriptional regulation. Whether some other "clocks" regulate different morphogenetic processes is not known.

The segregation of different cell types and the formation of cell boundaries are important in tissue and organ morphogenesis. Mesenchymal cells are generally more motile, which allows them to migrate to different sites in the body cavity where they convert to epithelial cells and contribute to the formation of secondary epithelia. This provided additional complexity in compartmentalization in metazoans that led to the formation of functionally different tissues and organs. A common mechanism involved in the formation of mesenchymal cells is the conversion of cells in an epithelium via the process of epithelial–

mesenchymal transition (Chapter 9). This conversion requires correct temporal and spatial patterning of cells within the epithelium, the localized activation of signaling pathways that enables those cells to disengage from the epithelium (e.g., changes in cell adhesion to other cells and the extracellular matrix) and then to migrate out through the surrounding interstitium (which requires the adoption of a motility phenotype), and remodeling of the extracellular matrix by secreted matrix metalloproteinases.

The formation of tissues requires that groups of cells, which may be structurally and functionally different and derived from different progenitors and locations within the embryo, form precise interactions and patterns required for proper tissue organization. How different cell types form these boundaries is another important aspect of morphogenesis. This is a classical problem that has been studied by separating cells from tissues and then allowing them to reaggregate, and recent studies have identified several changes in cell behavior required for a boundary, including contact inhibition of cell migration, cell–cell contact repulsion by extracellular signals, and changes in cortical tension of cells (Chapter 10).

Branching morphogenesis is an important event in the formation of the vasculature and of epithelial tubes in the kidney, lung, and mammary gland. It is one of the most studied processes in development, because it is easily identified and followed, and directly amenable to genetic and morphological analyses in a wide variety of organisms from insects to mammals (Chapter 6). It can also be reconstituted in vitro with cells derived from different tissues (Chapter 7). This powerful combination of genetic and cell-biological approaches has lead to significant advances in defining pathways of gene regulation, signal transduction between and within cells, and cellular reorganization of proteins involved in forming complex, branched structures. A striking finding, which was known for many years but not understood at the molecular level, is that initiation of branching is induced by reciprocal signaling between different groups of cells involving growth factors that induce intracellular signaling pathways that in turn switch on new patterns of gene expression (Chapter 6). Converting these signals and gene expression into 3D tubular structures is complex and is difficult to study in vivo—how do cells transform from a solid mass to a closed cell monolayer surrounding a fluid-filled cavity, how are apical and basolateral plasma membranes formed and orientated correctly to face different biological compartments separated by the epithelial monolayer? These more cell-biological studies are technically easier with epithelial cells that can be reconstituted into 3D epithelial cysts and tubes in vitro, and the advent of siRNA has enabled a "genetic" approach to test mechanisms. These studies indicate that changes in lipid organization, the activation of Rho family GTPases, polarity complexes (Crumbs, PAR, and Scribble) and their downstream effectors including the cytoskeleton, and the endocytotic and exocytotic vesicle trafficking pathways cause the redistributions of plasma membrane and cytoskeletal proteins that give rise to hollow 3D structures (Chapter 7).

Although recent studies have provided significant advances in identifying genetic regulation and signaling pathways involved in morphogenetic processes, relatively less is known about how changes in intercellular organization, cell–cell boundaries, and cell movements are controlled and specified, and these areas remain significant challenges and opportunities for the future.

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