Extracellular Matrix in Development

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Preface

The Extracellular Matrix in Development

The biological diversity of various interactive events during development reflects the wide-ranging signals associated with the extracellular matrix (ECM). Matrix components are the source of numerous developmental clocks and, by interacting with cell-surface matrix receptors, provide inductive or permissive signals that tell cells which direction to move, where to stop, and which genes to express when. This volume of the Biology of Extracellular Matrix series explores how the ECM influences development through examples of underlying mechanisms related to developmental processes. The chapters are organized into three broadly defined sections. Part I explores basic questions of how information content in the ECM is organized and how ECM molecules influence cellular and tissue movements in early embryonic events, including gastrulation. Chapters in Part II use the well-studied developmental processes neural crest cell migration and branching morphogenesis to illustrate how ECM provides developmental instructions that initiate and control functional interactions that direct tissue organization and morphogenesis. Also addressed is the importance of ECM in the stem cell niche and how ECM molecules might be used to modulate stem cell differentiation in tissue engineering. One of the most fruitful areas of developmental biology is the use of model organisms to study cell–matrix interactions and the regulatory processes operating during organ and tissue development. The chapters in Part III look at three model systems, moving from the simple *Hydra* to zebra fish and mice, to understand the lexicon of developmental signals associated with the ECM. These three animal systems span a great range of complexity and phylogenetic distance, yet illustrate numerous common principles of cell–matrix interactions in development.

The information code within the ECM is complex. In the first chapter, Cadwallader and Yost illustrate how placement of the sulfate groups on unique sugar side chains of heparan sulfate (HS) proteoglycans influences developmental processes. The collective actions of HS chain biosynthesis result in a mature HS chain with a mix of sulfated and non-sulfated residues. The unique placement and

spacing of sulfate and epimerization modifications create the HS fine structure, which provides specificity for biological regulation. Cadwallader and Yost show how the HS fine structure functions much like a zip code (a "Glycode") to regulate specific growth factor binding. Important players in the sulfation pathway are the *O*-sulfotransferases (OSTs), enzymes that function in the Golgi to add sulfate groups to urinoic acid residues. The authors discuss the importance of each of the OSTs in development based upon studies in model organisms.

One of the surprise findings from the application of live-cell imagining techniques to developing embryos is the extensive cell motion throughout the developing organism. In Chap. 2, Czirok, Rongish, and Little use high-resolution imaging along with sophisticated image analysis to document how tissue movements sweep the ECM to distant positions during early embryogenesis. By studying micro-assembly dynamics of fibronectin and fibrillin-2 in avian embryos, they show that the ECM moves as a composite material, whereby distinct molecular components as well as spatially separated layers exhibit similar displacements. These movement patterns are shared among embryos at equivalent stages of development. The authors discuss the implications of how the large-scale co-movement of cells and the surrounding ECM impacts the establishment and maintenance of ECM-bound morphogen gradients.

Gastrulation, the morphogenetic process that forms and positions the three primary germ layers, is mediated by coordinated tissue movements that are driven by integrated cell behaviors influenced by the ECM. Using the *Xenopus* embryo as a model, Dzamba and DeSimone (Chap. 3) explain the important role of fibronectin (FN) in amphibian gastrulation, where the protein provides a critical substratum for cell adhesion and migration. But beyond these traditional roles, the authors illustrate how FN and other ECM proteins regulate cell polarity and contribute to morphogenetic behaviors through mechanical signaling and by influencing tissue force generation. Although ECM is usually thought of as a static structure, the authors point out that the ECM is very dynamic. Its composition and physical structure is constantly changing during development, which, in turn, is an important way that ECM affects cell behavior.

Chapter 4 addresses how the ECM influences one the most important mechanisms in embryonic development—branching morphogenesis. It has long been known that cell interactions with the interstitial matrix and the basement membrane associated with epithelial cells play a critical role in the branching process. In this chapter, Daley and Yamada highlight several general biological principles by which cell–ECM interactions regulate epithelial morphogenesis, including ECM-mediated or ECM-induced alterations in tissue shape and stimulation of dynamic cell motility, proliferative outgrowth and expansion of the epithelium regulated by growth factors and proteolytic degradation of the ECM, and basement membrane roles in coordinating organization of epithelial tissue architecture. They conclude with a discussion of the implications of this knowledge for the rational design of bioengineered scaffolds in regenerative medicine strategies, as well as their potential relevance to epithelial cancer progression.

Cardiovascular development requires spatial and temporal signals that coordinate cell migration and gene expression in the numerous cell populations that make up the heart and blood vessels. In Chap. 5, Astrof explores how signaling by various growth factors is integrated into precise developmental programs via the extracellular matrix. In the developing vertebrate, connecting the heart to the vascular tree of the embryonic circulation requires asymmetric remodeling that is essential for the separation of arterial and venous circulations. This requires coordinated communication between cells of mesoderm, endoderm, surface ectoderm, and the neural crest. Astrof examines the important interactions between neural crest cells and the surrounding tissues that are critical to development of the cardiac outflow tract and aortic arches. The chapter also contains a detailed discussion of the specific ECM molecules that modulate neural crest development in vivo.

Recent interest in developmental and regenerative biology has been focused on adult and embryonic stem cells that have the ability for self-renewal and, through their pluripotency, possess the ability to mature into tissue cells of many different lineages. Regulating stem cell fate has traditionally relied on presenting growth factors and small molecules in developmentally appropriate ways. In Chap. 6, Choi, Holle, and Engler describe how ECM influences stem cell behavior independent of chemical signals. ECM can impact the immediate cellular microenvironment through changes in stiffness, topography, binding properties, and porosity. These physical properties imparted by the ECM influence cell shape and gene expression. In this context, Choi and colleagues discuss recent advances in nano- or microfabrication techniques, biomechanical and biophysical driven stem cell differentiation, and the mechanisms whereby cells feel their ECM environment.

Because of its ability to regenerate, the *Hydra* is one of the most studied organisms in regenerative biology. Its simple body plan (two layers of epithelial and an intervening ECM) and radial symmetry make it ideal for exploring cell–cell and cell–matrix interactions in development and regenerative processes. In Chap. 7, Zhang and Sarras review the biogenesis of *Hydra* ECM during regeneration and development. They detail the biochemical composition of *Hydra* ECM and the important role of the basement membrane and interstitial collagens in maintaining differentiation of the epithelial cells. *Hydra* ECM is resynthesized and assembled during regeneration, and this process is required before morphogenesis and pattern formation can happen. A major message of this chapter is that ECM biogenesis is essential for *Hydra* morphogenesis, which illustrates the key position ECM plays in regulation of cellular differentiation.

Numerous model organisms have been used to illustrate the importance of ECM in development. Frogs, mice, chicks, and numerous invertebrates have all contributed to our understanding of various steps in the developmental process, but each is limited in how much information it can provide. Although in its infancy as a model to study ECM and interacting proteins, the zebra fish offers numerous advantages that circumvent some problems associated with other animal models. In Chap. 8, Mundell and Jessen review the steadily increasing number of zebra fish studies showing developmental roles for matrix proteins, their receptors, and their modifying enzymes. They provide a framework for the reader to gain an

appreciation for the different ECM proteins, integrins, and metalloproteases present in zebra fish and their potential contributions to embryonic development.

Hyaluronic acid (HA) is present throughout the body where it is present in all tissues. In Chap. 9, Roughley and Moffatt discuss HA's role in skeletal biology, where it plays an important role in chondrogenesis and osteogenesis. HA and its fragments play a major role in endochondral bone formation and possibly intramembranous bone formation through the regulation of chondrocyte, osteoblast, and osteoclast differentiation and action. In the growth plate, its abundance increases from the proliferative to the hypertrophic zone, where it is thought to contribute to cell hypertrophy in addition to its more conventional role in proteoglycan aggregate formation within the ECM. Using mouse models to inactivate hyaluronan synthase (HAS, the enzymes that produce HA in cells), the authors show how loss of HA impairs bone growth and chondrocyte organization. They also discuss how HAS gene mutations lead to other disorders, including malignancies.

Obviously, each of the topics covered in this volume represents significant and distinct areas of matrix biology that merit expanded discussion. To broaden the scope, however, would require a much larger book than is possible for this series. It is hoped that the topics covered in this current volume will provide the reader with a basic understanding of the importance of ECM in influencing fundamental mechanisms of development.

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