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Review

Extracellular matrix: Forum introduction

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The extracellular matrix (ECM) is now appreciated as a key regulator of cell and tissue behavior [1,2]. Support for this notion has been derived from correlative studies demonstrating large changes in the composition and distribution of extracellular matrix components during tissue development, differentiation and in response to hormone/growth factor/cytokine influences. In addition, a variety of functional studies demonstrate ECM-dependent cellular responses *in vitro* while genetic approaches clearly demonstrate critical requirements for genes encoding ECM components or modifiers of ECM, e.g., metalloproteases, in a wide variety of processes *in vivo* [3,4].

ECM produces these effects in multiple ways. One of these is via direct interactions with cell surface ECM receptors of various types, including integrins and syndecans. As a result of these interactions, cytoskeletal elements are reorganized which, alone, can strongly influence responses such as apoptosis [5]. In addition, interactions with these receptors activate a complex array of intracellular signal transduction cascades that modulate a variety of cellular functions including secretory activities and gene transcription. In this regard, the ECM must be considered to act in a continuum with the cell surface, cytoskeleton and, ultimately, the nucleus. ECM also serves as a reservoir of growth factors and cytokines. These key molecules may bind to either polysaccharide or protein constituents of ECM. In some cases, biochemical neutralizers of growth factor activities, e.g., noggin [6], bind strongly to ECM. These interactions further help limit the range of activities of growth factors and cytokines.

In most cases, even individual ECM components are, in fact, complexes of non-identical proteins, e.g., laminin, collagens. These complexes normally function in the context of much larger macromolecular complexes including many other ECM components. Therefore, it is not surprising that the composition of ECM is usually quite dynamic. This not only reflects differential expression of genes encoding ECM components, but also various post-transcriptional processes. In the cases of proteoglycans, structural nuances of the glycosaminoglycan chains are often critical for protein binding activities. Thus, differences in the expression or activities of glycosyltransferases and sulfotransferases alter the function of proteoglycans. Moreover, secreted polysaccharide-degrading enzymes may modify these same polysaccharides after assembly into the ECM and can release bound growth factors/cytokines. In other examples, different isoforms of ECM polypeptide constituents are generated either by alternative mRNA splicing or differential expression of discrete genes encoding similar proteins. Additional variety or control of function is provided by the action of secreted or cell surface-associated metalloproteases that hydrolyze specific ECM components at specific sites [3]. These activities can have several consequences. New sites may be opened for the addition of newly synthesized ECM components, the ECM may be loosened allowing for new cell growth/proliferation or migration, or growth factors/cytokines may be released. Similar proteolytic enzymes also can act at the cell surface to trigger release of ectodomains of ECM, receptors, growth factor receptors or even growth factors themselves [4].

Finally, given that most cellular responses to ECM require engagement of cell surface receptors, factors that interfere with cell surface receptor interactions, e.g., mucins, also play key roles in regulating these events. Mucins also play complex roles since they not only limit certain cell-cell, cell-ECM interactions, but also can bind to other cell sur-

face receptors, e.g., selectins, or, in the case of transmembrane mucins, interact directly with intracellular signal transducers. As is the case for cell surface receptors, transmembrane mucins may be released by the action of cell surface proteases allowing for rapid modulation of mucin-dependent events.

In this miniseries, authors will consider the role of ECM in reproductive processes and cancer. A select group of topics has been chosen that, in some cases, will broadly consider the role of ECM in a specific biological context, i.e., prostate and prostate cancer. Other contributions will focus on the functions of specific ECM components or ECM receptors in particular contexts. These include the roles of syndecans in mammary epithelia, the functions of integrins in embryo implantation and the role of mucins in early embryonic development and certain cancers. Collectively, the reader should gain a perspective on the complex regulation of ECM expression and function in important, representative reproductive and endocrine systems.

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