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MULTI-AUTHOR REVIEW

Emerging functions of matricellular proteins

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Cells in multicellular organisms employ a variety of mechanisms to coordinate their individual functions with the needs to the whole. Over the past two decades, the extracellular matrix has become recognized as more than just a structural framework to arrange cells in the proper three-dimensional context to form tissues and organs. Many of the cell surface receptors for specific matrix components are signaling receptors, and their ligation alters signal transduction pathways that control cell shape, survival, movement, and gene expression [1]. Rigidity or elasticity of the matrix provides additional information that controls cell behavior through a process known as mechanotransduction [2]. Matrix proteins also contain binding sites for diffusible growth factors, and specific matrix components can be essential cofactors for presentation of growth factors to their signaling receptors [3]. Such binding sites in the matrix also provide a repository for storing growth factors in the matrix, which can limit their diffusion and allow gradients to be established that provide guidance cues for tissue morphogenesis and regeneration. Together, these signals from the extracellular matrix create a context that tells cells which differentiation programs to execute, identifies neighboring cells to each other, and creates permeability barriers that define what solutes and macromolecules can pass between cells.

Each tissue contains characterisitic structural matrix components that grossly define this context [4]. For example, epithelial and endothelial cells reside on a basement membrane composed of type IV collagen, perlecan, specific laminins, and nidogen that provides a permeability barrier and maintains cell polarity. Cartilage and bone contain characterisitic collagens, noncollagenous matrix proteins, and proteoglycans that provide structural integrity and direct mineralization. Tissues that require elasticity such as blood vessels contain elastin and fibrillins that confer this mechanical property. Soft tissues contain hyaluronan and proteoglycans that maintain the high water content needed for tissue flexibility and compressibility.

The gross composition of extracellular matrix changes during embryonic development to direct organogenesis and differentiation of stem cells to their adult phenotypes. In the adult, specialized matrix niches also support the tissue-specific stem cells needed for tissue homeostasis [5]. Following injury, changes in matrix compostion direct regeneration of tissues, and specific alteration of this matrix program in cancer can be sufficient to suppress a malignant phenotype [6].

In addition to these diverse functions of the major structural components of extracellular matrix, it is increasingly clear that some nonstructural proteins are present in the matrix only at specific times, and that rather than being stable structural elements, these proteins tend to be rapidly turned over. These proteins characteristically contain binding sites for some major structural elements in the matrix, binding sites for specific cell surface receptors, and in some cases domains that enzymatically alter other matrix components and that sequester or modulate the activities of specific growth factors. Such proteins have been classified as matricellular proteins [7, 8]. The prototypical matricellular proteins were thrombospondin-1, tenascin-C, and secreted protein acidic and rich in cysteine (SPARC).

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Thrombospondin-1, one of five members of the thrombospondin family, remains the most intensely studied matricellular protein and illustrates how our understanding has advanced from biochemical studies and genetic studies in mice and human disease to development of therapeutic strategies that are now being validated in animal models and human clinical trials. Several aspects of thrombospondin research were reviewed in previous multi-author reviews [9–13].

Thrombospondin-1 is typical of matricellular proteins in that it has context-dependent effects on cells. It can either stimulate or inhibit adhesion, migration, or growth of cells. Initially, this caused much confusion to understand why different laboratories reported conflicting results, sometimes for a single cell type. This paradox has been resolved in part by recognizing that cells express several receptors for thrombospondin-1 that engage different signal transduction pathways. Furthermore, cells may express two receptors for thrombospondin-1 but require different signals to activate each receptor to recognize thrombospondin-1, or signaling through a single thrombospondin-1 receptor may be positive in isolation but become negative if a second receptor is engaged by its ligand [14]. Such context-dependence for activity is not unique to thrombospondin-1, and this concept should facilitate our understanding of the functions and mechanism of action for other matricellular proteins.

Another general property of matricellular proteins exemplified by thrombospondins is that most are not essential for development. Thus, transgenic mice are available that lack one or more of the five thrombospondin genes [15–18]. Although these null mice are viable, a number of functions of matricellular protein genes have been revealed when these mice are stressed in specific ways. Thrombospondin-1 and thrombospondin-2 null mice have abnormal injury repair responses and respond differently to oncogenic stress [11, 13, 19]. Correspondingly, expression of matricellular genes is frequently induced acutely in response to injury and may be altered in a sustained manner in some chronic diseases. In parallel to these findings, polymorphisms or mutations in these genes that alter the expression or stability of the encoded matricellular proteins have been found to alter the risk for various diseases in human populations [20], and the case of thrombospondin-5 (also known as cartilage oligomeric matrix protein) to be causative for the inherited disorders pseudoachondroplasia and multiple ephiseal dysplasia [10]. Thus, although many matricellular genes are not essential for development, they serve critical functions in adult animals for responding to specific stresses, and as such they could be useful targets to treat major dieases including cardiovascular disorders, inflammation, and cancer.

The current series focuses on recent advances in several members of the matricellular peotein family that were discussed at a 2010 FASEB Summer Research Conference on Thrombospondins and other Matricellular Proteins in Tissue Organization and Homeostasis. This meeting brought together world leaders in matricellular protein research to discuss emerging concepts in the structure, function, and human genetics of matricellular proteins, their role in the pathogenesis of disease, and opportunities for translation of this knowledge to develop new therapeutics.

Tenascin-C is another original member of the matricellular protein family [21]. Tenascin-C is not an essential gene for viability in mice, but it is also induced upon tissue injury and plays important roles in inflammatory and fibrotic processes associated with cardiovascular disease and cancer. Here, Midwood et al. review recent advances in the biology of tenascin-C from the perspective of these two diseases and the emerging evidence that tenascin-C plays an important role in guiding stem cell fate choices. Importantly, this research has yielded translational applications, and tenascin-C antibodies have entered clinical trials for treatment of glioblastoma patients and show promise in animal models for imaging atherosclerotic plaques.

SPARC is a matricellular protein that functions primarily to modulate tissue remodeling in adult animals. SPARC plays an important role in collagen matrix assembly, which is reflected by decreased collagen content and fiber size in the skin of SPARC null mice [22]. Endothelial cells are an important cellular target of SPARC, and the protein is generally recognized to be an angiogenesis inhibitor. This may have clinical relevance given the strong correlation between SPARC expression and cancer progression and survival [23]. Several mechanisms have been described to account for the anti-angiogenic activity of SPARC, but a number of questions remain unanswered. Rivera et al discuss recent advances in defining the mechanisms by which SPARC regulates endothelial cell responses to angiogenic growth factors and evidence that vascular pericytes are a second cellular target through which SPARC controls physiological and pathological angiogenesis.

The CCN family of cysteine-rich matricellular proteins contains 6 members in vertebrates [8, 24]. These multidomain proteins are related to thrombospondins in that they contain a thrombospondin type 1 repeat. CCN1 (also known as Cyr61) and CCN2 (also known as connective tissue growth factor) are essential for development in mice, with *Ccn1* null embryos dying at E9.5 and *Ccn2* nulls dying as neonates. Like other matricellular proteins, CCN1 engages several cell surface receptors, and its activities are correspondingly context-dependent. Lau reviews recent

advances in understanding signaling responses to CCN1 and its emerging functions in wound healing and fibrosis, inflammation, vascular disease, and cancer. CCN2 is a well-recognized modulator of fibrosis in adult animals and of developmental chondrogenesis, but recent studies are expanding the range of cellular targets and physiological processes it regulates. Hall-Glenn et al. discuss emerging functions of CCN2 in bone, cartilage, and lung development and current controversies concerning its role in the vasculature.

Thrombospondin type 1 repeats also characterize the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) superfamily of matricellular proteins [25]. This is a large family of secreted multidomain proteins that contain a metalloprotease domain that cleaves specific substrates in the extracellular matrix or on the cell surface. Several members of this family have known substrates, and defects in their genes give rise to inherited diseases. Hubmacher and Apte review evidence that mutations in several less characterized ADAMTS family members, including ADAMTS10 and ADAMTSL2, phenocopy inherited diseases that affect microfibril function such as Marfan syndrome, which is caused by mutations in the structural matrix protein fibrillin-1. Fibrillin-1 is a major constituent of microfibrils, a key component of elastic matrices. Microfibrils serve as a scaffold that regulates bioavailability of growth factors in the TGFβ superfamily, and a link between mutations in ADAMTS proteins that interact with fibrillin-1 and bioavailability of these growth factors is proposed as a mechanism.

Periostin is a relatively new member of the matricellular protein family. Based on expression in the periosteum and phenotypes of the periostin null mouse, the first defined function for periostin was in remodeling of bone and teeth during development and in response to mechanical stress [26]. Kudo reviews recent studies that provide mechanistic insights into the function of periostin in mechanotransduction and expand its role beyond the skeleton to heart disease and cancer.

Together, these reviews exemplify the diversity in function of matricellular proteins. Advances in defining their cell biology and physiology are revealing unexpected roles in the pathogenesis of inherited disorders as well as in common diseases of an aging population. Some of these insights are being applied to develop new imaging modalities and therapeutics. Further research may also yield mimics or antagonists of specific matricellular proteins that could be applied in the emerging field of regenerative medicine.

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