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The biology of the extracellular matrix: novel insights

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Abstract

Purpose of review—Extracellular matrix (ECM) has both structural and regulatory roles. This update reviews the representative recent developments in diverse aspects of ECM biology relevant to inflammation, tissue destruction, fibrosis, and regeneration.

Recent findings—Biological regulation by ECM is emerging as a major research area, driven by several new directions. Sensing of mechanical cues provided by ECM was found to be crucial in regulating cell differentiation. Transforming growth factor-β (TGF-β) is a pivotal agent in fibrosis and inflammation. A combination of structural biology and cell biology provided novel insights on the mechanisms of its activation by cellular traction and ECM. Improved understanding of how fibrillin microfibrils and associated proteins regulated TGF-β sequestration and activation was achieved by analysis of inherited connective tissue disorders having TGF-β dysregulation as an underlying pathologic mechanism. Insights on microRNA-mediated ECM regulation suggest a key role for miR-29, for which potential therapeutic roles are emerging. Advances in understanding the ECM turnover by proteinases provided novel insights on cell regulation and identified useful disease biomarkers.

Summary—As a crucial modulator of cell behavior, ECM has exceptionally strong relevance and translational implications for human disease, opening novel opportunities for mechanistic understanding of disease pathogenesis as well as treatment.

Keywords

fibrosis; inflammation; microRNA; TGF-β; tissue engineering

INTRODUCTION

Extracellular matrix (ECM), the material around and between cells, is a composite material with a highly regulated tissue-specific composition. In tissues with an obvious mechanical role such as cartilage, bone, and tendons, it is a quantitatively major component that confers gross mechanical properties. ECM composition and organization in such tissues reflect evolutionary adaptation to mechanical load. In epithelia, basement membranes are specialized ECM assemblies that provide a supporting substratum for epithelial sheets and maintain cell polarity. Here, ECM has an important role as an organizer. Indeed, by incorporating specific molecular components in varying concentrations and geometries, a range of tissue-specific structural demands can be met. Furthermore, even a single tissue type is often regionally specialized; a recent study [1] of anatomically distinct cartilages, for

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example, highlighted their differing compositions. The structural significance of ECM is clearly evident from inherited connective tissue disorders such as osteogenesis imperfecta and the Ehlers–Danlos syndromes.

Reduced to the simplest mechanical elements, ECM comprises several secreted proteins that form macromolecular structures as their functional embodiments (fibrils, microfibrils, or fibers). This category includes collagens, fibronectin, elastin, and fibrillins. Enzymes that modify these molecules posttranslationally, such as lysyl oxidase, which forms intermolecular cross-links, and proteinases, which cleave peptide bonds, such as the matrix metalloproteinases (MMPs), are also ECM components. Another category of molecules does not directly contribute to the formation or function of structural complexes, but modulates cell–matrix interactions and cell functions. These are termed matricellular proteins, for example, thrombospondins and tenascins. The glycosaminoglycan (GAG) hyaluronan is a major nonproteinaceous component of ECM, and several ECM core proteins are modified by linkage of various types of GAG chains to form proteoglycans. Hydration of these carbohydrate-rich components exerts a swelling pressure against the surrounding fibrous network, providing tissue turgidity and compressibility and facilitating molecular transport. For a recent systems-level bioinformatics view of ECM composition and function, Cromar *et al.* [2] defined 357 proteins constituting the core of the ECM and 524 gene products with related functions.

ECM constitutes the cellular microenvironment for all cells outside the circulation and is recognized as a major regulatory or instructive influence on cell behavior. Most cells are surrounded by, and attached to, a dynamic pericellular matrix with considerable regulatory potential. There is considerable interest in the diverse ways in which ECM directly signals to cells or modulates soluble signals. One mechanism is signaling via matrix adhesion molecules and receptors such as integrins and discoidin-domain receptors [3]. Another is through its role in sequestration and activation of growth factors, such as those of the transforming growth factor-β (TGF-β) superfamily [4] and by modulating morphogen gradients. In tissue engineering, there is considerable current interest in how mechanical or physical properties of ECM such as elasticity or stiffness influence cell behavior [5].

Of numerous intriguing developments in this vast field in the last year, we selected some in areas of rheumatology relevance as well as other fields for this update.

EXTRACELLULAR MATRIX BREAKDOWN, INFLAMMATION, AND BIOMARKERS

In recent years, there has been considerable interest in aggrecan breakdown in cartilage matrix by ADAMTS proteinases, collectively referred to as aggrecanases. Aggrecan, a large aggregating proteoglycan, is highly hydrated and thus is the principal compression-resisting cartilage ECM component. Its loss is recognized as a crucial early step in arthritis. Wylie *et al.* [6] investigated the distribution and activation of ADAMTS5, a crucial aggrecanase in osteoarthritis, in a mouse explant model of inflammatory arthritis. They suggested that synovial ADAMTS5, as well as proprotein convertase-mediated activation of secreted ADAMTS5 bound to ECM, could contribute to cartilage destruction [6]. ADAMTS5 was also found to contribute to versican proteolysis in fibroblast pericellular matrix, and reduced versican turnover in *Adamts5*-deficient fibroblasts led to a striking myofibroblast conversion [7■].

In contrast to the prevailing notion of enzymes as key mediators of ECM breakdown, Antipova and Orgel [8■] published a provocative study showing that antibodies to the collagen-binding, small, leucine-rich proteoglycan biglycan induced nonenzymatic

decomposition of collagen fibrils. The proposed mechanism was antibody-induced dissociation of biglycan from collagen fibrils, disrupting their structure. This could result in increased susceptibility of collagen to enzymatic breakdown, and altered cell–matrix interactions such as exposure of cryptic sites in the fibrils. Differential protein profiling of synovial fluid from rheumatoid arthritis (RA) vs. osteoarthritis patients demonstrated a greater relative abundance of fibronectin, cartilage acidic protein-1, and cartilage oligomeric matrix protein (COMP) in osteoarthritis fluid, whereas RA fluid had a higher content of MMPs and neutrophil-associated proteins [9].

ECM is a source of diagnostic and prognostic biomarkers, as proteolysis releases intact or fragmented ECM components as soluble ligands. Along these lines, a panel of monoclonal antibodies was developed against COMP fragments, and ELISA was done to monitor the serum levels in patients and mouse models of osteoarthritis and RA. The new ELISA was reported as a sensitive biomarker for cartilage catabolism [10]. Collagen V is a fibril-forming collagen that associates with collagen I, the dominant collagen type in most tissues. A new assay detecting an MMP-cleaved collagen V fragment was reported as a biomarker of ECM turnover, and patients with ankylosing spondylitis were shown to have higher levels of tissue breakdown [11]. The same group reported that liver fibrosis in rats was associated with a biomarker for MMP-2/MMP-9 mediated proteolysis of collagen VI, which is functionally associated with skeletal muscle and whose anomalies result in myopathies. This biomarker could also be useful for inherited and inflammatory myopathies. MMP-2 levels were increased by the promoter SNP G1575A, and this was associated with increased risk of cardiovascular disease in patients with systemic lupus erythematosus [12].

MICRORNA REGULATION OF EXTRACELLULAR MATRIX AND ITS IMPLICATIONS

MicroRNAs (miRs) regulate biologic processes by suppression of translation or induction of degradation of mRNAs. miRs typically regulate clusters of genes involved in a process. There is currently a strong focus on the miR-29 family, which suppresses major ECM genes, including collagens, elastin, and fibrillins [13]. miR-29b overexpression was associated with aging vasculature [13], as well as aneurysm development in a mouse model of Marfan syndrome (MFS) [14]. Its inhibition prevented early aneurysm development in this model, as well as in a mouse elastase infusion model of abdominal aortic aneurysm [15■■]. In contrast, miR29 antagonism could upregulate these major ECM components [13]. Reduced miR-29b was noted in a mouse model of pulmonary fibrosis and associated with upregulation of several ECM genes [16]. A development with translational potential was miR-29 inhibition to enhance elastin expression in patients with elastin haploinsufficiency [17]. There is now compelling evidence to support miR-29 antagonism or agonism in specific clinical settings.

EXTRACELLULAR MATRIX AND THE STEM CELL NICHE

The microenvironment of stem cells (niche) is a key determinant of pluripotency, self renewal, and asymmetric cell divisions from which arise differentiated progeny. Two recent publications showcased the role of ECM. Nakamura-Ishizu *et al.* [18■] found that tenascin-C (Tn-C)-deficient mice failed to reconstitute bone marrow after ablation and had reduced ability to support transplanted donor hematopoietic stem cells (HSCs). Expression of Tn-C in supporting niche cells (stromal and endothelial cells) was dramatically upregulated during hematopoietic recovery after myeloablation [18■]. Tn-C was found to signal HSCs in an integrin-α9-dependent manner, which led to changes in cyclins and cyclin-dependent kinase inhibitors [18■]. Fujiwara *et al.* [19■■] showed that stem cells in the hair follicle bulge deposited nephronectin in their basement membrane to regulate mesenchymal differentiation

toward smooth muscle. Tissue inhibitor of metalloproteinases-3 (TIMP-3) associates with ECM and targets several ECM-degrading metalloproteinases. It is highly expressed by osteoid cells in the endosteal region of bone marrow and its over-expression led to alteration of bone-marrow-derived lineages [20]. However, whether this effect was dependent on the inhibition of metalloproteinases was not elucidated.

EXTRACELLULAR MATRIX AND THE CANCER METASTASIS NICHE

The ECM protein, periostin, was found to be a crucial determinant of metastatic success of cancer stem cells [21■■]. Infiltrating tumor cells were reported to induce periostin production by resident fibroblasts at the metastatic site as a prerequisite for colonization [21■■]. Furthermore, a matrix proteoglycan, versican, produced by myeloid cells was found to be crucial for colonization of lung by breast cancer cells in a mouse experimental model [22]. Versican facilitated mesenchymal-to-epithelial transition of tumor cells by reduction of Smad-2 phosphorylation, resulting in enhanced cell proliferation and metastatic burden. The authors proposed targeting versican as a novel way of treating metastatic lung cancer.

EXTRACELLULAR MATRIX IN GROWTH FACTOR SEQUESTRATION AND ACTIVATION

TGF-βs have complex roles in fibrosis, inflammation, and cellular metaplasia. They are tethered to the ECM via latent TGF-β-binding proteins (LTBPs), which are anchored to fibrillin microfibrils [23]. Using cells isolated from fibrillin-1 and fibrillin-2 knockout mice, it was shown that fibronectin was required for ECM incorporation of LTBP1, whereas LTBP3 and LTBP4 deposition required fibrillin-1 [24]. ADAMTS proteins are also known to be functionally related to fibrillin microfibrils and, potentially, to TGF-β regulation [25]. Saito *et al.* [26] recently identified the ability of ADAMTSL6β to improve microfibril assembly in a mouse model of MFS and demonstrated a concomitant reduction in TGF-β signaling.

TGF-β is activated by integrin-mediated physical forces, molecular displacement or proteolysis. An elegant biophysical study [27■■] showed that distorting the large latent complex via single-molecule force spectroscopy resulted in the release of active TGF-β1. The cells seem to pull at the latency-associated peptide within the large latent complex/LTBP, `squeezing out' active TGF-β against a counterforce provided by LTBPs attached to ECM. This study, together with the recent determination of the crystal structure of the latent complex of LTBP1 and TGF-β1 [28■■], represented a landmark in understanding integrin-mediated TGF-β activation. The enhanced activation of TGF-β in MFS, which results from fibrillin-1 mutations, has been instrumental in devising novel therapies [4]. Thus, other mechanisms of activation are also of interest. The metalloprotease ADAMTS1 and granzyme B were recently identified as novel mediators of TGF-β activation. Granzyme B cleaved the small leucine-rich proteoglycan biglycan and decorin to release TGF-β [29], whereas the ADAMTS1 thrombospondin type 1 motif was shown to activate TGF-β via a nonproteolytic displacement mechanism [30■].

Perlecan is a ubiquitous heparan sulfate proteoglycan, found in basement membranes and cartilage, which binds multiple regulatory factors, for example, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and IL-2, to concentrate them and form morphogen gradients. Recent analysis of perlecan knockout mice revealed that cartilage perlecan was essential for vascularization of the perichondrium; specifically, cartilage perlecan promoted the activation of VEGF/vascular endothelial growth factor receptor (VEGFR) by binding to the VEGFR of endothelial cells [31].

MECHANICAL SIGNALING BY EXTRACELLULAR MATRIX AND IMPLICATIONS FOR BIOMATERIALS

Analysis of the integrin repertoire of human mesenchymal stem cells and its modulation during stem cell differentiation on matrices of varying stiffness showed that osteogenic or adipogenic differentiation generally altered the integrin pattern [32]. In tumors, stiffness provided by ECM is now accepted as crucial in regulating cell behavior. Using a creative approach, Pathak and Kumar [33] described cell behavior on so-called micro-polyacrylamide channels, in which matrix stiffness and pore size (confinement) were independently controlled. They found that cells confined to narrow channels, as probably found in dense fibrillar ECM, migrated faster compared with wider channels and changed their typical biphasic response to ECM stiffness into a steady increase in migration speed with stiffness. This behavior was linked to nonmuscle myosin II and potential polarization of traction forces in narrow pores [33]. Such external influences seem to have a long-term effect on cell behavior, probably through the induction of stable cellular pathways. Culture of lung fibroblasts on stiff substrates revealed their incipient cell plasticity through conversion to myofibroblasts, but also a phenomenon termed mechanical memory [34], that is, myofibroblast phenotype was retained for several subsequent passages on soft substrates.

The biology of cell–matrix interactions relates directly to tissue and organ engineering. `Bio-inspired' artificial matrices strive to achieve the scale, composition, and material properties of ECM to guide cell differentiation, migration, and survival [35■]. Achieving nanoscale scaffolds is also emerging as crucial. A modified electrospinning technique resulted in a porous nanofibrous biomaterial conducive for cell invasion and nutrient diffusion; when modified with chondroitin sulfate, this scaffold was optimized for cartilage formation [36]. In a study on skin epidermal stem cells, Trappmann *et al.* [37■■] found that on collagen-I-coated, acrylamide-based gels, the differentiation of the cells corresponded to the stiffness of the material. However, on polydimethylsiloxane matrices of the same stiffness range (0.1–2.3 MPa), the proportion of cells expressing a keratinocyte marker did not change with stiffness. They attributed the different responses to differences in the porosity of the materials, which translated into different collagen-anchoring densities. They concluded that cells respond to the mechanical feedback they derive from the ECM rather than the ECM stiffness itself.

CONCLUSION

This selection from the recent literature demonstrates the breadth and complexity of ECM research, and emphasizes the functional continuity of ECM with the cell and the considerable crosstalk that results (Fig. 1). The cell–matrix interface, in particular, provides a crucial signaling nexus that regulates all aspects of cell behavior. Whereas the traditional emphasis of the ECM field on its structural relevance has by no means diminished, there is now a strong focus in several new areas. Collectively, this research offers a platform on which to build a strong translational pipeline, such as by modifying chemical signals to cells, and bioengineering of artificial organs using mechanical and adhesive cues.

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KEY POINTS

- Extracellular matrix has both structural and regulatory functions in relation to cells and tissues.
- Extracellular matrix has proved to be particularly crucial for the regulation of TGF-β.
- The stem cell niche comprises extracellular matrix as a key component.

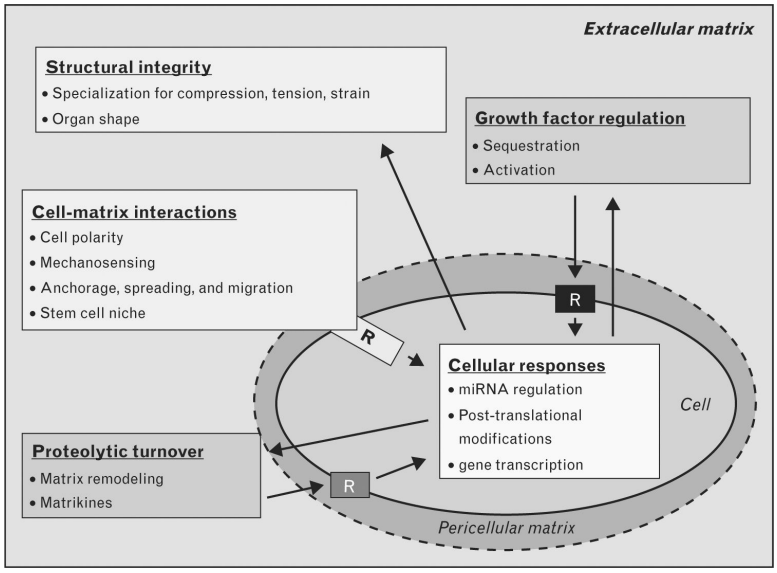

FIGURE 1.

Functions of extracellular matrix (ECM) and crosstalk at the cell–matrix interface. The cartoon shows the various functions of ECM and exemplifies those that result in feedback to the cell.