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Extracellular Matrix: The driving force of mammalian diseases

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Abstract

Like the major theme of a Mozart concerto, the immense and pervasive extracellular matrix drives each movement and ultimately closes the symphony, embracing a unique role as the fundamental mediator for most, if not all, ensuing intracellular events. As such, it comes as no surprise that the mechanism of just about every known disease can be traced back to some part of the matrix, typically in the form of an abnormal amount or activity level of a particular matrix component. These defects considerably affect downstream signaling axes leading to overt cellular dysfunction, organ failure, and death. From skin to bone, from vessels to brain, from eyes to all the internal organs, the matrix plays an incredible role as both a cause and potential means to reverse diseases. Human malaises including connective tissue disorders, muscular dystrophy, fibrosis, and cancer are all extracellular matrix-driven diseases. The ability to understand and modulate these matrix-related mechanisms may lead to the future discovery of novel therapeutic options for these patients.

Introduction

The human body is an elegantly-structured vessel containing a complex labyrinth of diverse organ systems that complement one another to sustain life. Likewise, each organ within a system is intricately assembled from distinct tissue types composed of specific cellular milieus. These biological fields preserve normal function as well as finely tune an organ's response to altered microenvironments found during disease. When we look closely at the molecular level, we find that tissue homeostasis and the initial cellular insults in disease states share common roots in the extracellular matrix (ECM). The ECM is defined as a compendium of signaling effectors that provides structural and functional support to the cells that it surrounds. It includes organizational proteins, like collagen and elastin, fibronectin [1], hydrostatic regulators and biochemically-relevant signals like proteoglycans and their derivatives [2,3], and hyaluronan [4,5]. The ECM encompasses other functional proteins that maintain cellular activity, regulate the mechano-chemical properties [6] and

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evoke extracellular remodeling and regeneration [7]. This list is not exhaustive, but just a small snippet of the extensive assortment of ECM constituents that act together in a powerful manner to mechanistically designate cellular responses to a variety of stimuli.

To compare the ECM to our vast universe, we can liken it to a river that flows through the valley to provide sustenance and order to the surrounding trees and soil to promote the existence of the native flora and fauna. In times of drought, there is too little water to sustain life. Similarly, in times of excess rain, flooding can cause equally great damage resulting in loss of homeostasis of a perfectly balanced ecosystem. Analogously, the ECM is absolutely required for normal cellular maintenance. However, a paucity or superfluous amount of ECM components or aberrant activity of their respective signaling cascades leads to similar devastation resulting in severe dysfunction and even death, both at the microscopic and organismal level.

Originally, many ECM-related studies focused on its structural capacity. However, as scientists unraveled more of the nuances of ECM-mediated regulation of cellular integrity, new avenues of study opened surrounding the ability of the ECM to modulate normal physiology and disease [8,9]. Notably, the ECM has been the subject of intense investigation across all organ systems from the very outside layer of the skin to the more general organism-wide augmented cellular proliferation seen in cancer. With more enthusiasm than ever before, scientists are discovering novel disease mechanisms, drug targets, and diagnostic markers originating from the ECM as well as unveiling how endogenous ECM components can be utilized as therapeutic modalities.

We aim to underscore the importance of the ECM in diseases encompassing the integumentary, musculoskeletal, cardiovascular, pulmonary, and renal systems as well as its role in the broad cellular dysregulation found in cancer and metastasis [10]. As such, we hope to paint a broad picture of the global importance of the ECM in the human body by focusing on ECM-mediated signaling in each organ system, working from the skin, the external barrier protection to all internal organs, to the remaining connective tissues that supply structure and strength, to the vasculature that mobilizes oxygen and nutrients, and finally to the critical workhorses of the body found in the other major organ systems. We will end with a brief discussion of ECM-driven processes in cancer. Taken together, this information will afford a comprehensive overview of the omnipotence of ECM in human physiology and disease, as nearly every physiologic aberration can be traced back to the matrix. We anticipate that the dissemination of this knowledge of ECM-driven ailments will foster even greater interest in the already remarkable field of matrix biology to promote sophisticated novel scholarship that will pioneer the next frontier of research to defend against destructive diseases.

Covered head to toe: ECM-driven connective tissue disease

We will start our journey by defining the role of the ECM in connective tissue disorders where we can appreciate the necessity for a working matrix by noting the existence of the many types of skin, bone, and cartilaginous diseases that can be attributed to defective ECM components [11] (Fig. 1).

Moving from outside in, we will begin with a discussion of matrix-related skin diseases. Many of these disorders are heritable, deriving predominantly from collagen abnormalities, though some are also caused by mutations in common basement membrane proteins. For example, Ehlers-Danlos syndrome is a genetic disease resulting from mutations in collagen [12,13] or proteins that regulate collagen organization, such as metalloproteinases (MMP) [14]. Hallmarks of this condition involve remarkably elastic skin, hyper-flexible joints, and valvular heart disease.

Other cutaneous disorders triggered by abnormal collagen organization can be found in the blistering diseases, of which epidermolysis bullosa (EB) is the prototype [15–17] (Fig. 1). In the dystrophic subtype of this disease, collagen VII is mutated resulting in aberrant anchoring of the dermis to the epidermis. As such, these patients exhibit tremendously fragile skin and often have sores rivaling severe burns. Of note, other subtypes of this disorder include EB simplex, an autosomal dominant disease that contains mutations in keratin, and junctional EB, an autosomal recessive disorder characterized by mutations in the gene encoding laminin-332 [18] and α6β4 integrin [19]. These mutations result in a phenotype similar to the dystrophic subset of EB, thereby equally adversely affecting quality of life for afflicted patients. As one might expect with diseases resulting in high cellular turnover, all types of these blistering diseases are associated with increased rates of squamous cell carcinoma of the skin, likely caused from acquired mutations after unending rounds of wound formation and healing [20]. Though intensive research is ongoing to provide better treatment options, there is no definitive curative therapy for this disease as of yet. Recent evidence suggests that cell-based therapies might be a promising therapeutic approach [21]. However, we hope that the identification of the underlying genetic bases and abnormal pathways evoked from genetic mutations would lead to application of precision medicine strategies for this group of ECM-driven diseases [17].

Moving inward to the skeleton, a heritable collagen disorder predominantly affecting bone can be found in osteogenesis imperfecta (OI) [22] (Fig. 1). Depending on the type, this disease varies in severity and its mode of inheritance. It is typically characterized by short stature, blue sclera, and brittle bones that are susceptible to fracture. The specific molecular pathology of OI results from mutated collagen I, where glycine is replaced by a bulkier amino acid leading to loss of the collagen triple helix [23]. This structural defect causes the collagen fibrils to form in an improper manner, often resulting in their degradation thereby diminishing the strength of the bones. In the more severe types, death occurs *in utero* or perinatally, while the less severe versions afford some quality of life to those suffering from this disease.

Cartilage can also be affected by matrix-related genetic misfortune as evidenced by hereditary multiple exostoses (HME). HME is stamped by mutations in genes encoding the exostosin-glycosyltransferase 1 and 2 (EXT1/2) proteins. EXT1/2 form a complex to modulate the synthesis of heparan sulfate [24–26]. Mutations of these genes cause a loss of the functional EXT1/2 proteins, phenotypically resulting in the formation of numerous bony growths covered with a cartilage cap. Surgery and physical therapy are the mainstays of treatment; however, these growths can recur following removal and can continue to cause pain and discomfort throughout the patient's life.

Keeping with cartilage, pseudochondroplasia is an autosomal dominant disease illustrated by short stature, limb deformities, and laxity of the ligaments. It can be caused by defects in the cartilage oligomeric matrix protein (COMP), a crucial ECM component responsible for chondrocyte proliferation and migration [27], where this mutated COMP is retained within the chondrocytes, leading to their death. Recent work suggests that the interaction of COMP with collagen IX [28] is also important for disease progression, possibly by causing an accumulation of collagen IX within the chondrocytes.

Our discussion of ECM-driven diseases affecting skin and cartilage would not be complete without the inclusion of disorders caused by abnormal elastic tissue. For instance, fibrillin 1, a glycoprotein that regulates the formation of elastic fibers [29–31], is mutated in Marfan syndrome. Patients affected by this disease tend to be tall and thin with long digits, flexible joints, and an increased risk of mitral valve prolapse. Most dangerously, since the elastic nature of their vasculature is compromised, these patients harbor an increased probability of aortic aneurysm and subsequent fatal vessel rupture.

In line with the theme of structural support for the body, muscle does not survive unscathed in the context of ECM-driven disease. Progressive muscular dystrophies, such as congenital muscular dystrophy (CMD) can be caused by mutations in the basement membrane protein, laminin [32,33]. These mutations impair the connection of the muscle fiber with the ECM, thereby decreasing its strength and stability. However, other types of this disease, such as Becker's muscular dystrophy (BMD) and Duchenne muscular dystrophy (DMD) occur as a result of reduced or absent levels of the cytoplasmic protein, dystrophin [34]. For both BMD and DMD, the inheritance pattern is X-linked recessive. Mechanistically, low or absent expression of dystrophin [35] prevents the attachment of the muscle fiber cytoskeleton to the ECM via a cell membrane connector, resulting in destruction of the muscle over time. Furthermore, dystrophin also mediates calcium uptake and signaling and thus its absence hinders these processes, leading to mitochondrial dysfunction. DMD patients typically present earlier than those afflicted with BMD and have a grim prognosis of death in the early 20s. To date, there is no cure. It is imperative to comment that other muscular dystrophies (Ulrich congenital muscular dystrophy, UCMD) and myopathies (Bethlem myopathy, BM) are linked to mutations in collagen VI [36]. These mutations decrease the contractile strength of the muscle fibers and are associated with mitochondrial and autophagic dysfunction [37–39].

Though not a heritable disease, it is unsurprising that cartilage may become compromised following normal wear-and-tear over a long period of time [40]. These unrelenting insults to the cartilage lead to collagen disorganization [41], resulting in the classic presentation of osteoarthritis, a widespread ailment affecting almost every human if one lives long enough. Likewise, bone does not always age gracefully either, where imbalances in the turnover of the ECM due to abnormal osteoclast and osteoblast function [42] can cause the bone fragility known as osteoporosis.

We would be remiss to not include a brief discussion about intervertebral (IV) disc disease as back pain is one of the most common causes of decreased workplace productivity and affects nearly every living person at one point in his or her life. Much of this disease can be

attributed to loss of glycosaminoglycans, namely aggrecan, in the aging IV disc, leading to decreased hydration, reduced compressibility, and increased probability of disc herniation. However, new research is highlighting the importance of other dynamic factors that contribute to IV disc degeneration [43], including hypoxia, inflammation, and autophagy [44,45].

A gut feeling: Matrix glitches in internal organ systems

The ECM of the organs within the body is crucial for maintaining their homeostasis, and has now reached a high level of complexity in both soft and mineralized tissues [46,47]. If signaling cascades are improperly activated or silenced, major organ dysfunction can occur. No part of the body is immune from this aberrant cellular activity and thus we will briefly discuss some common ECM-related diseases in the major organ systems.

Fibrosis is a damaging process that can occur due to excess formation of connective tissue in response to injury [48], likely due to a combination of factors such as a disproportionate activity of matrix enzymes (i.e. MMPs, ADAMTS) [49,50] that causes matrix degradation and re-organization as well as hyperactive ligand-mediated receptor signaling, most prevalently via TGF-β [51,52]. Fibrosis and inflammation can be also modulated by the activity of mesenchymal cells [53]. Though these fibroses arise via similar mechanisms, there are distinct outcomes for patients depending on the affected organ. For example, pulmonary fibrosis [54] is often a secondary event following other causes of lung dysfunction including infection and autoimmune disease [55]. However, it can also be idiopathic with no known trigger. Eventually, this amplified formation of pulmonary connective tissue impairs breathing by acting in a restrictive manner to normal function by increasing the stiffness of the lung parenchyma and reducing lung capacity.

Hepatic fibrosis [56] occurs via activation of pro-fibrotic stellate cells thereby destroying normal liver architecture with excessive formation of scar tissue. When severe enough, the fibrosis leads to cirrhosis, ultimately causing organ failure and death by limiting normal hepatic inflow and outflow tracts as well as destroying the functional hepatic cells. Likewise, renal scarring typically occurs after an injury to the kidneys. Predictably, this change in kidney structure disrupts normal function leading to end stage renal disease (ESRD). These patients will invariably need dialysis or organ transplant in order to sustain normal electrolyte levels and proper excretion of metabolites. Additionally, as the kidneys are the paramount mechanism of blood filtration, they are also subject to abnormal glycosylation in the setting of diabetes leading to life-altering nephropathy. This occurrence is often a direct result of morphological changes in the matrix as the high level of advanced glycation end products (AGE) [57] found in diabetic patients can further exacerbate renal fibrosis by activating pro-fibrotic cellular pathways to induce collagen crosslinking.

Furthermore, two genetic diseases, Alport and Goodpasture syndromes [58], can also negatively affect renal function. Patients with Alport syndrome typically suffer from hematuria, proteinuria, and hearing loss. Mechanistically, these physical findings are caused by defective collagen IV [59], which prevents the proper structure of the glomerular basement membrane. Notably, collagen IV is also present in other basement membranes (i.e.

inner ear), which explains the other physical symptoms that are observed in these patients. Goodpasture syndrome is also related to collagen IV [60], except in this disease there is an abnormal production of anti-glomerular basement membrane antibodies resulting in autoimmune destruction of these components of glomeruli and alveoli [61]. Not unexpectedly, these patients present with hematuria, proteinuria, peripheral edema, shortness of breath, and hemoptysis.

(A)vascular disaster: Matrix-mediated vessel integrity and formation

The vascular system is also perturbed by matrix dysregulation as demonstrated by atherosclerosis, as well as the less common phenomenon of vessel aneurysm. Both diseases are characterized by defects in the matrix, leading to the accumulation of lipids within the sub-endothelium or weakness and ballooning of the vessel wall, respectively. In the case of atherosclerosis, ECM members, such as collagen, elastin, and versican [62], are ubiquitous components of the atherosclerotic plaque. While this ECM deposition can sometimes stabilize these lesions to prevent them from breaking off and forming thrombi, it can also cause narrowing of arteries subsequently impeding normal circulation resulting in hypertension, myocardial infarction, and stroke. In contrast, aneurysms typically have the opposite problem whereby collagen and elastin are broken down, leading to the loss of integrity of the vessel wall. These vascular defects can occur in any vessel. However, the most deadly aneurysms occur in the aorta and the Circle of Willis in the brain, as their rupture leads to rapid loss of blood and, consequently, death.

Furthermore, matrix components can also modulate angiogenesis [63,64]. In some cases, ECM constituents promote neovascularization by augmenting VEGF-dependent signaling, whereas in others they can assist in decreasing this process through diverse mechanisms, including direct vascular endothelial growth factor receptor 2 (VEGFR2)-antagonism and autophagy [65,66]. For instance, potent inducers of angiogenesis include perlecan [67], a large heparan sulfate proteoglycan, biglycan, a small, leucine-rich proteoglycan (SLRP) [68], and many growth factors including vascular endothelial growth factor (VEGF) [69,70] and fibroblast growth factor (FGF). However, endorepellin and endostatin, the C-terminal fragments of perlecan and collagen XVIII respectively, act in an opposing manner to obstruct new vessel growth by interfering with canonical VEGFR2 signaling [71–74]. Remarkably, both endorepellin and endostatin are potent inducers of autophagy [66,75,76], providing a link between this biochemical process and vessel destruction. Of note, perlecan is also present in avascular tissues where it plays an important role in mediating cartilage development, such that mice lacking perlecan have such unstable cartilage that they die perinatally from diaphragmatic dysfunction [77,78].

The malignant matrix and its guardians

Finally, one of the most unforgiving diseases affecting almost every organ system is that of cancer. These malignancies often start as an insult at the cellular level, progressing to unrestrained cellular proliferation, neovascularization, and metastasis [79]. As such, the ECM has become a hot subject of inquiry for drug discovery and therapeutic design to fight various types of cancer ranging from breast to lung to brain. Many matrix components including epidermal growth factor [80–83] platelet-derived growth factor [84,85], and the

ever-ubiquitous hyaluronan [86–89], interact with cell surface receptors to augment tumor growth. Ongoing studies investigating the role of these factors and cognate receptors have led to novel discoveries, which may prove quite useful for combating carcinogenesis. For example, a functional receptor for progranulin, a protein that is involved in prostate tumorigenesis among other pathologies [90–94] has remained elusive until just recently with the identification of the receptor tyrosine kinase (RTK), EPHA2, as one of its signaling partners in prostate cancer and endothelial cells [95]. This discovery and others like it, will prompt further study to translate these findings from bench to bedside, thereby promoting unique therapeutic design to more effectively target tumor growth and metastasis.

Interestingly, other matrix constituents, such as decorin [96–99] can interfere with these hyperproliferative pathways by suppressing receptor signaling [100,101], resulting in tumor stasis. In this way, the pro-autophagic decorin [102,103], and other matrix members [66,75,76,104] hold a distinctive role as guardians stemming from the ECM. Thus, the ability to modulate these pathways via the matrix is an important facet of outside-in signaling and chemotherapeutic drug design.

Of note, while ECM-mediated regulation of the tumor parenchyma continues to be a large field of study, the tumor microenvironment is becoming increasingly popular, as neo-angiogenesis is the powerhouse for tumor existence. Given this knowledge, the tumor vasculature has become a novel and effective target for curbing cancerous growth. Once again, the matrix is a critical referee for this tumor vascularization [105,106]. As mentioned in the above section, many extracellular growth factors (i.e. VEGF, FGF) and other matrix components (i.e. perlecan) promote angiogenesis [67]. However, there are equally as many ECM components, such as endostatin [76], that act in direct opposition resulting in inhibition of new vessel growth or the complete obliteration of pre-existing vessels. As such, the avenue of approach for anti-angiogenic therapeutics in the context of cancer drug design is well-suited to the extracellular niche.

Conclusion

All of these diseases and more will be discussed in greater detail in this special issue. We continue to be astounded by the leaps and bounds that the field of matrix biology has made in the last decade and we aim to provide the most complete and current information regarding the relevance of the ECM to numerous diseases across all organ systems as no tissue type is exempt from the devastation of dysregulated matrix. We hope that this review whets the appetite for further inquisition into the secrets of the matrix in the context of disease-based research and are looking forward to future discoveries that will advance the field and impact the health of all of humankind.

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Abbreviations used

ADAMTS	a disintegrin and metalloproteinase with thrombospondin motifs
AGE	advanced glycation end products
BM	Bethlem myopathy
BMD	Becker's muscular dystrophy
CMD	congenital muscular dystrophy
COMP	cartilage oligomeric matrix protein
DMD	Duchenne muscular dystrophy
EB	epidermolysis bullosa
ECM	extracellular matrix
EPHA2	ephrin type-A receptor 2
ESRD	end stage renal disease
EXT1/2	exostosin-glycosyltransferase 1/2
FGF	fibroblast growth factor
GFR	glomerular filtration rate
HME	hereditary multiple exostoses
IL	interleukin
IV	intervertebral
KRT	keratin
MMP	matrix metalloproteinase
OI	osteogenesis imperfect
ROS	reactive oxygen species
RTK	receptor tyrosine kinase
SLRP	small, leucine-rich proteoglycan
TGF-β	transforming growth factor β UCMD, Ulrich congenital muscular dystrophy
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2

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Highlights

- The major goal of this review is to demonstrate that the extracellular matrix is the driving force of nearly all mammalian diseases
- Indeed, the mechanism of just about every known disease can be traced back to some part of the matrix
- Matrix-driven causes typically include abnormal amounts or activity levels of a particular matrix constituent
- Additionally, abnormal signaling events can lead to overt cellular dysfunction, organ failure, and death
- The increased knowledge of the matrix-driven events may lead to the future discovery of novel therapeutic options

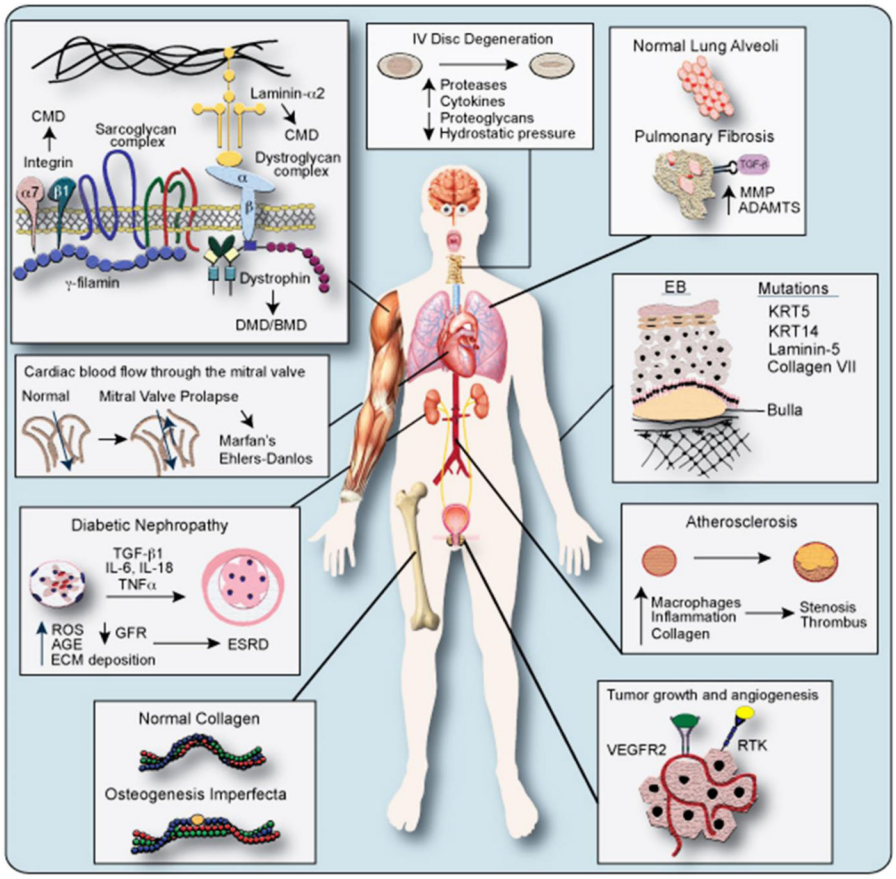

Figure 1.

The extracellular matrix is at the root of most diseases. Members of the matrix are involved in disease pathology affecting nearly every organ system in the human body. The mechanisms of these ECM-driven diseases range from absent factors to aberrant signaling activity to disorganization of structural components of crucial organs and organ vasculature. More details regarding the molecular pathogenesis of disease can be found in the text.