Review Article

Extracellular Matrix Remodeling in Human Disease

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Abstract

The extracellular matrix (ECM) is a meshwork of proteins and carbohydrates that supports many biological structures and processes, from tissue development and elasticity to preserve the structures of entire organs. In each organ, the composition of the ECM is distinct. It is a remarkably active three-dimensional structure that is continuously undergoing remodeling to regulate tissue homeostasis. This review aims to explain the role of ECM proteins in the remodeling process in different types of disease. The hardening of the ECM (desmoplasia), as well as its manipulation, induction, and impairment in regulation of its composition can play a role in several diseases, examples of which are chronic obstructive pulmonary disease, pancreatic ductal adenocarcinoma, spinal cord injury, progression and metastasis of breast cancer, and neurodegenerative condition in the brain such as Alzheimer's disease. Remodeling is also associated with diet-induced insulin resistance in many metabolic tissues. A greater comprehension of the way in which the ECM regulates organ structure and function and of how ECM remodeling affects the development of diseases may lead to the improvement and discovery of new treatments.

Keywords: Basement membrane, cytoskeleton, extracellular matrix, remodeling

Introduction

Macroscopically, the extracellular matrix (ECM) has a very important function – it isolates cells from organs. It also affects the hydrostatic pressure in the tissues and organs. At the microscopic level, the ECM is shown as a dynamic molecular system that controls cells by altering proliferation, cytoskeletal organization, cellular differentiation, and receptor signaling. The configuration and location of the ECM proteins and components produces a well-organized topology that contributes to the function of the matrix.[1,2]

The Extracellular Matrix

In the past, the ECM was thought to be a stable structure that changed according to growth and repair needs. More recently, microscopic topology of the ECM has shown that it is continuously remodeled. The remodeling is controlled by a mechanism that forms a balance between matrix production, secretion, alteration, and degradation.[3]

The ECM is an extremely active structure that exists in every tissue. It constantly goes through renewal and repair processes (remodeling). This occurs through particular enzymes that cause ECM degradation and induce changes in the ECM. ECM-cell interactions take place to regulate certain functions such as proliferation, migration, and differentiation.[4]

The ECM is made up of a combination of proteins, proteoglycans, and biological factors that has a vital structural and functional role in cells. The ECM affects cell adhesion and growth, impacts cellular fate, and controls host tissue reactions.[5-7]

Cell interactions and communication allow them to manage their functions, differentiate, develop, and perform the function of tissues. The interaction between cells occurs either chemically or electrically and occurs through the ECM. Cells can communicate mechanically by either one of two mechanisms: First, by responding either to mechanical deformations created by their neighbors or second, by altering the mechanical properties of the ECM of adjacent cells. These methods of communication allow cells to receive and share information and accordingly, to act cooperatively with other proximate cells.[8]

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There are two types of ECM – the first type is the interstitial connective tissue matrix, and the second is the basement membrane (BM). The BM is a form of ECM that has many functions. These functions include isolating the epithelium from the surrounding stroma and regulating cell organization and differentiation using connections with cell surface receptors and proteins in the ECM. The matrix in between the cells is called the interstitial matrix.[9] The interstitial matrix contains many proteins such as fibronectin and collagen I that provide tissues with structural support. The difference between the BM and the interstitial matrix is that the BM is denser and primarily contains collagen IV, laminins, and heparan sulfate proteoglycans (HSPGs). It also consists of other proteins such as nidogen and entactin, which are produced by epithelial cells, endothelial cells, and underlying integrin-expressing myofibroblasts.[9]

The collagen IV network retains the mechanical stability of the cells and is highly cross-linked. Laminin networks, on the other hand, have a noncovalent nature and are more active than the collagen IV network.[10] The two networks are linked by nidogen, which, together with other components, stabilizes the structure of the networks.[11] Furthermore, the association between cells is required to assemble the BM at a particular place.[11]

Integrins and hemidesmosomes are receptors that are expressed in the BM and bind to proteins in the ECM. ECM proteins may also connect to receptors such as dystroglycan, the Lutheran glycoprotein, and sulfated glycolipids.[12]

ECM remodeling is a sequence of quantitative and qualitative alterations that can occur in the ECM during diseases such as cancer metastasis.[13] Remodeling in the ECM is important in the morphogenesis of the intestine, lungs, and mammary and submandibular glands. In fibrosis and invasive cancer, along with many pathological conditions, the ECM composition becomes dysregulated, and its structure is altered and becomes stiff and more abundant.[4] Deposition, degradation, or changes in the ECM components occur during remodeling.[9] The desmoplastic reactions that occur in different types of cancer can alter ECM remodeling and may also increase matrix metalloproteinase.[14] This leads to unbalanced tissue homeostasis and a change in the composition of the ECM,[15] particularly affecting the BM protein type IV collagen.[16]

ECM component breakdown constitutes the primary process of remodeling. This process is vital for controlling ECM abundance, content, and assembly and for secreting growth factors such as biologically active molecules. The ECM can be cleaved by several proteases such as matrix metalloproteinases (MMPs), adamalysins, and meprins.[4] Herein, I review several examples of ECM remodeling in different diseases and discuss their functions, involvement, and properties.

Extracellular Matrix in Disease

Impairment in the regulation of the ECM components results in disease. Abnormal ECM remodeling can cause many pathological conditions such as cancer, osteoarthritis, and fibrosis.[4]

Important features of the ECM must be considered. First, excess ECM breakdown leads to tissue destruction. This highlights the significance of an integral ECM complex in maintaining tissue architecture and homeostasis. Second, excessive ECM manufacturing and deposition, which occur in chronic or severe tissue injuries, can lead to fibrosis without equally sensible degradation of ECM.[3]

MMPs are the main enzymes involved in the ECM breakdown process.[17] Normally, their activity is low, but it becomes elevated in diseased or inflamed tissue and throughout repair or remodeling procedures. MMPs are manufactured as either soluble proteins or as proteinases that are anchored to the cell membrane and cleave ECM components with varied substrate selectivity.[4] Another ECM cleaving mechanism is carried out by the adamalysins protein family. This protein family comprises disintegrins, metalloproteinases (ADAMs),[18] and ADAMs with a thrombospondin motif.[19] ADAMs are "sheddases" – when the transmembrane protein ectodomains are broken down, the complete ectodomains of cytokines, growth factors, receptors, and adhesion molecules are released.[4] This release is accomplished when ADAMs cleave the transmembrane protein ectodomains that are adjacent to the cell membrane.[20] ECM proteins such as collagens can be cleaved by ADAM10, ADAM12, and ADAM15.[4] Furthermore, meprins are another type of protease that can cleave ECM proteins such as collagen IV, nidogen, and fibronectin.[21] Meprins can also aid in the formation of mature collagen molecules by cleaving procollagen I, which assembles into collagen fibrils.[22] Meprins indirectly regulate ECM remodeling through activation of other metalloproteinases.[4] Other enzymes play a vital role in ECM remodeling such as ser proteases, urokinase and tissue plasminogen activator,[23] Ser protease elastase,[24] and ser protease matriptase[25]

Extracellular Matrix Remodelling in the Lung

Chronic obstructive pulmonary disease

The lung contains three main components of ECM, namely, type I collagen, type VI collagen, and elastin. In disease states, inflammatory cells and proteases induce pathological remodeling, and fragments of these proteins are secreted into the circulation. Lung diseases such as chronic obstructive pulmonary disease (COPD) are demonstrated to have a blockage in the airflow of lung tissue, primarily the ECM.[26]

Bihlet *et al*.[26] performed a COPD gene study on the remodeling of lung ECM using healthy controls and COPD patients. Their results show that the breakdown of elastin by the enzyme neutrophil elastase and the turnover of type VI collagen accompany the inflammation induced by COPD and emphysema. Identification of phenotypes that are linked with the development and are responsive to specific medications for clinical trials can be accomplished by a serological assessment of type VI collagen and elastin turnover.[26]

Earlier studies have shown that, in COPD patients, the airway wall components are altered in comparison to normal individuals. In COPD, the deposition of type I, III, and IV collagens, fibronectin, and laminin beta2 is increased.[27] In the airway walls of the lung, structural remodeling results in an increase in ECM protein deposition and scar tissue formation, resulting in tightening of the lumen and airway obstruction, leading to loss of function.[28] ECM turnover is important in tissue homeostasis, a process in which proteins are broken down and new proteins are made. It is a balance between creation and degradation.[29] If this balance is missing, diseases of the connective tissue can occur. In COPD, tissue disruption and fibrosis occur due to increases in both the formation and the degradation of tissue in the peripheral airway wall.[15,30]

Extracellular Matrix in the Pancreas

Pancreatic cancer

Pancreatic cancer (PC) is fatal. In the 1st year of diagnosing PC, 70% of the patients die. Five percent survive the first 5 years. Ninety percent of PC cases are due to pancreatic ductal adenocarcinoma (PDAC).[31] In PDAC, the tumor stroma contains fibroblasts, endothelial cells, and immune cells, as well as desmoplasia. Desmoplasia is hard ECM that contains collagens, fibronectin, proteoglycans, and hyaluronic acid.[32]

The alterations in ECM remodeling from the desmoplastic reactions and the increase in MMP activity in different types of cancer[14] lead to unbalanced tissue homeostasis. This causes a change in the composition and features of the ECM.[15] Types I, III,[33] and IV[17] interstitial fibrillar collagen are vital for alterations in PC-associated tissue homeostasis. ECM degradation fragments that contain specific neoepitopes, known as protein fingerprints, can be released into the circulation due to altered ECM remodeling. These protein fingerprints can act as markers of altered ECM remodeling.[34]

Extracellular Matrix in the Spinal Cord

Spinal cord injury

The ECM regulates nervous tissue maintenance and activity. When an injury occurs, the ECM plays a critical role in important functions such as inflammation, cell survival, axon growth, gliosis, revascularization, and plasticity. Thus, manipulation of the ECM after injury may assist in nervous tissue repair. After spinal cord injury (SCI), there are some endogenous repair systems such as axon growth/sprouting,[35] revascularization, and neural stem cell proliferation and differentiation.[36] However, these processes may fail or succeed only partially. The functional damage and loss of tissue after SCI are known to be permanent.[37] Some strategies are used for protection, regeneration, and repair of the SCI. The first protective strategy aims to save the neural cells by increasing the survival programs intracellularly, decreasing inflammation and bleeding, or stimulating antioxidation. The second strategy is to stimulate axon growth/sprouting through regenerative processes. This occurs by promoting axon growth intracellularly or by decreasing growth inhibition in the injury surroundings. The third strategy enhances electrical stimulation and rehabilitative motor training, which promotes neural plasticity.[38]

The three-dimensional network ECM complex links and maintains both neuronal and nonneuronal cells. These cells produce many ECM components that play a vital role in regulating cell migration, axon guidance, and synaptogenesis of the CNS. The ECM regulates signaling pathways in mature, healthy CNS tissue, either directly or indirectly. Direct regulation occurs through cell surface receptors, while an example of indirect regulation is the ECM acting as a carrier or container for growth factors and other molecules.[39]

The ECM in perineuronal nets (PNNs) is the same as that found in the IS; however, it is denser and hence has more CSPGs and components that inhibit growth (e.g., tenascin R and link proteins).[39] PNNs are found at presynaptic terminals, synaptic boutons, nodes of Ranvier, and around some neurons.[40]

Haggerty *et al*.[41] raised the question of how ECM-based therapies can directly contribute to axon growth. Is it by initiating neuronal growth or by changing the growth-inhibitory influences of scar tissue indirectly? The answer to this question is that collagen, fibronectin, and laminin have a distinctive role in tissue growth and repair.[41]

Collagen has integral axon growth-supportive characteristics[9] and can enhance or expand its regenerative abilities.[42] Yao *et al*.[42] stated that exogenous collagen administered at an injury site encourages axon growth. Diverse structural configurations of collagen produce different effects on axon growth.[43] The effect of collagen on axon growth is in collaboration with growth factors or repair-supporting cells. In injury, the inflammatory response can also be modulated by collagen,[44] which supports axon growth in scar tissue.

Laminin is a classic axon growth supporter.[45] Two forms of laminin are therapeutic for promoting axon growth: the axon growth-signaling peptide sequence Ile-Lys-Val-Ala-Val[46] and polylaminin.[47] When polylaminin was introduced into the injured spinal cord, it was shown to promote axon growth as well as recovery of functions.[48]

The primary ECM protein that is involved in peripheral nerve growth and astrocyte associated white matter regeneration is fibronectin.[49] Lin *et al*.[50] showed that treatment with fibronectin enhanced serotonergic axon sprouting. In addition, it was found that the combination of fibronectin with cells, growth factors, or synthetic materials has an effect on axon growth.[51]

Extracellular Matrix in the Breast

Breast cancer

ECM plays an important role in breast cancer. ECM proteins such as fibrillar collagens, fibronectin, specific laminins and proteoglycans, and matricellular proteins are induced, while

healthy tissues under homeostasis are reduced. These proteins have a major function in the progression and metastasis of breast cancer. They are also vital components of metastatic niches, stimulating stem/progenitor signaling pathways and metastatic growth. The changes in composition, organization, and biochemical properties of the ECM in breast cancer development are due to the increase in ECM remodeling enzymes. In advanced stages of breast cancer, alterations are detected in the ECM that include the stimulation of tumor-promoting ECM components and the loss of tumor-suppressive ECM.[52]

Functional studies on animals revealed that the cancer-associated matrix proteins might alter many processes in cells. Breast cancer cells rely on specific ECM constituents and ECM-mediated signals, if the cells are to go through environmental stresses at different stages of breast cancer progression and metastasis to survive such an environment. Consequently, inhibition of the matrix components or their downstream functions weakens cancer cells and exposes them more to treatment.[52]

It is important to look at the physiology of the tumor framework, specifically in secondary tumor metastasis, when developing cancer treatments targeting the ECM. The ECM is context-dependent and knowing the function of the ECM enhances the search for suitable drugs and reduces the damage to healthy tissues. An understanding of particular matrix isoforms is also important, as some ECM proteins have different splice variants or are changed posttranslationally, and some of them may be tumor specific. An example of this is the lack of certain matricellular ECM proteins in healthy adult tissues and the strong upregulation of others in breast malignancies.[52]

The Extracellular Matrix in the Brain

Extracellular matrix in Alzheimer

The ECM in the brain has an extremely controlled system that comprises collagens, noncollagenous proteins, glycoproteins, hyaluronan, and proteoglycans. In the brain, the ECM performs a vital role in neuronal plasticity and neurite outgrowth. Neurodegenerative conditions in the brain are related to abnormal ECM structure.[53]

Neurodegenerative disease, such as Alzheimer's disease (AD), is brain dysfunction that is caused by the gradual and progressive loss of neural cells and changes in ECM components.[54] A protein associated with the formation of amyloid plaques is called amyloid beta (Aβ) A4 precursor protein (APP). Tau is another protein that is involved in the formation of neurofibrillary tangles.[55] Studies have indicated that HSPGs and CSPGs play a role in AD.[56] It has been shown that heparan sulfate binds to and influences the aggregation, intracellular internalization, and clearance of tau and APP.[57]

Several HSPGs, including perlecan, glypican, syndecan, and agrin, are connected with amyloid plaques in AD.[58] Studies regarding AD have proposed that ECM components, including CSPGs and PNNs, decrease in density in AD and have a neuroprotective role against tau lesions.[59]

Extracellular Matrix in Adipose Tissue

Extracellular matrix in obesity

Many studies including those on humans and rodents have suggested that the remodeling is connected to diet-induced insulin resistance in numerous metabolic tissues.[60]

Adipose tissue reacts strongly to an excess of nutrition. Changes occur through adipocyte hypertrophy and hyperplasia,[61] followed by immune cell infiltration and ECM remodeling.[62] Adipose tissue remodeling is changed in obesity by ECM proteolysis through fibrinolytic coordination and MMPs.[61] Collagen VI expression is high in obese humans.[63] In addition, the ECM and integrins are important regulators of insulin action in the muscle, liver, and adipose tissues.[60]

Two stimuli for ECM remodeling during adipose tissue expansion are hypoxia and inflammation. Halberg *et al*.,[64] in an experiment performed on rodents, stated that HFD feeding causes a doubling of the fat cells accompanied by local hypoxia. Due to the hypoxia that occurs in obese adipose tissue, the local vasculature may not expand correctly to match the increased fat mass.[64] Pathological accumulation of ECM proteins occurs in metabolically dysfunctional adipose tissue. During the development of obesity, collagen deposition increases, and this forms a physical barrier for adipocyte expansion, thus promoting the movement of lipids into other tissues.[62] The removal of collagen VI in obese ob/ob mice leads to unimpeded expansion of adipocytes, glucose tolerance enhancement, and insulin signaling. Furthermore, in mice, overexpression of the α3 chain of collagen VI (endotrophin) stimulated insulin resistance and the deposition of collagens I, III, and VI in the case of HFD.[65]

Thrombospondin 1 is an ECM glycoprotein that is mainly expressed in the visceral adipose tissue, and its expression is elevated in insulin-resistant obese humans.[66] Circulating thrombospondin 1 may induce insulin resistance.[67] ECM remodeling in the obese state is due to increased inflammation and the subsequent upregulation of pro-fibrotic signaling molecules, including transforming growth factor. Williams *et al*.[60] stated that it is not known how the ECM controls insulin function; however, some theories have been proposed to describe it. First, ECM remodeling forms a mechanical wall for (i) glucose and insulin transport in the muscle and liver and (ii) adipocyte hypertrophy in adipose tissue in an overnutrition state. Second, alterations in the composition of the ECM cause downstream changes in signaling of integrin that results in reduced insulin function. In conclusion, the ECM and integrins are important regulators of insulin function, and they present unique therapeutic targets for treating insulin resistance associated with type 2 diabetes mellitus.[60]

Summary

The ECM is made up of proteins, proteoglycans, and biological factors that have a vital structural and functional role in cells.[8] Of particular interest is the role of ECM remodeling and alteration during disease.[13] In COPD, PC and breast cancer remodeling and a change in the composition and features of the ECM occur.[14,26,52] In addition, ECM regulates the mature nervous tissue and re-organizes and becomes involved in nervous tissue repair after injury.[35] In the brain, the ECM has an extremely controlled system that comprises collagens, noncollagenous proteins, glycoproteins, hyaluronan, and proteoglycans.[54] Adipose tissue remodeling is changed in obesity by ECM proteolysis through fibrinolytic coordination and MMPs.[61] Pathological accumulation of ECM proteins occurs in metabolically dysfunctional adipose tissue.[62]

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Conflicts of interest

There are no conflicts of interest.

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