Chapter 10

The Role of Extracellular Matrix Proteins in the Urinary Tract: A Literature Review

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Abstract

The extracellular matrix (ECM) is a noncellular component with a crucial role on tissue morphogenesis, differentiation and hemostasis within all tissues and organs. With advancement in the technology and increased data on ECM components, it was realized that many conditions in urinary tract have a close relation with the composition of ECM in the affected tissue. According to some basic research studies, ECM composition may give us important information about the prognosis and progression of disease in addition to the cause and pathophysiology of the diseases such as congenital ureterovesical and ureteropelvic junction obstruction. Afterwards, with better understanding of ECM one can develop new treatment and follow-up models. This chapter will summarize the evidence-based role of ECM in urinary tract conditions.

Keywords: urinary tract, extracellular matrix, immunohistochemistry, ureteropelvic junction, ureterovesical junction

1. Extracellular matrix

The extracellular matrix (ECM) is a noncellular component within all tissues and organs, and it is essential for the scaffolding of cellular constituents and also it plays a crucial role on tissue morphogenesis, differentiation and hemostasis [1]. It is an anchoring platform for epithelia, forms the basement membrane, and also surrounds capillaries and neural cells, and is part of the connective tissue [2].

In general, ECM molecules can be classified as fiber-forming and non–fiber-forming molecules [3, 4]. Collagens, elastins, laminins and fibronectins are the main fiber-forming ECM proteins. Proteoglycans which are main non–fiber-forming molecules fill the majority of the extracel-

lular interstitial space and they have a wide variety of functions that reflect their unique buffering, hydration, binding and force–resistance properties.

2. Fiber-forming ECM elements

2.1. Collagen

Collagens are the most abundant proteins in ECM and the whole human body [5]. Collagens have many functions, which depend on the type and tissue they are in. Depending on the tissue, collagen fibers can provide tensile strength, can regulate cell adhesion, can support chemotaxis and migration and can direct tissue development [6]. Generally in normal physiologic states, different types of collagen fibers form a heterogeneous mixture but usually there is a dominant type of collagen in every given tissue.

The five most common collagen types are the following:

Type I: skin, tendon, vascular ligature, organs and bone (main component of the organic part of bone)

Type II: main collagenous component of cartilage

Type III: main component of reticular fibers

Type IV: forms basal lamina and basement membrane

Type V: placenta, cell surfaces and hair

A majority of collagen molecules are in the form of triple strands, which form supramolecular complexes like fibrils and networks depending on the type of collagen. Network collagens are incorporated into the basal membrane and fibrous collagens form a skeleton for the collagen fibril bundles in the interstitium [1].

2.2. Elastins

Elastins are the main ECM element, which gives tissues elasticity and allows a tissue to stretch and return to its original state if needed. Their tight association with collagen fibrils crucially limits their stretchability. Fibroblasts and smooth muscle cells secrete elastin in the form of its precursor, tropoelastin. Secreted tropoelastin molecules assemble into elastin fibers. Elastin fibers are covered by glycoprotein microfibrils. The most common glycoprotein covering elastin fibers is fibrillin. The presence of fibrillins is also essential for the integrity of elastin [1].

2.3. Laminins

Laminins are glycoproteins that form heterodimers containing 1 α, 1 β and 1 γ chain. They are synthesized in podocytes and endothelial cells. Laminin trimerization occurs inside the cell in the endoplasmic reticulum. Once trimerization completed they are secreted into the extracel-

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lular space and they polymerize to form a supramolecular network. Laminin polymerization initiates basement membrane formation and sends signal to adjacent cells [7].

2.4. Fibronectins

Fibronectins are glycoproteins that establish connection between cells and collagen fibers in the ECM. It is secreted as a dimer form, which are joined by two disulfide bonds. Fibronectin fibers have several binding sites through which they form a connection with other fibronectin dimers, collagen fibers, heparin and cell-surface integrin receptors [1].

Fibronectins have vital importance for mediating cell attachment and function and they have an important role in the organization process of the interstitial ECM. During tissue development, fibronectins are important for cell migration, and also studies showed that they have roles on cardiovascular disease and tumor metastasis [6].

3. Non–fiber-forming ECM molecules

3.1. Proteoglycans

Proteoglycans are heavily glycosylated proteins. They contain glycosaminoglycan (GAG) chain, which is linked with a protein core covalently. They are classified by their size (large and small) or the nature of their GAG chains. The main classes of proteoglycans are heparan sulfates, keratan sulfates and chondroitin sulfates. Their extreme hydrophilic nature and ability to adapt extended conformations make them easier to form hydrogel, and structures formed with these molecules can withstand high compressive forces.

Proteoglycans and their most common locations:

Heparan sulfate: basement membranes and components of cell surfaces.

Chondroitin sulfate: cartilage, heart valves and bone.

Keratan sulfate: cornea and bone.

3.2. Hyaluronic acid

Hyaluronic acid is a polysaccharide, which does not contain protein core and it consists of alternating residues of D-glucuronic acid and N-acetylglucosamine. Hyaluronic acid forms a coat around chondrocytes and they provide resilience of articular cartilage tissue. In extracellular space, hyaluronic acid also provides the ability to resist compression by absorbing significant amounts of water and providing a counteracting swelling force.

4. ECM remodeling and matrix metalloproteinases

Each tissue has an ECM with a unique composition, which is formed by biochemical and biophysical interaction between the various cellular components (e.g., fibroblast and

endothelial elements) and the evolving cellular and protein microenvironment [1]. There is a constant turnover of ECM in the body and it is being regulated with either enzymatically or nonenzymatically which makes ECM a dynamic structure.

Matrix metalloproteinases (MMPs) are a large family of endopeptidases, which are calcium-dependent zinc-containing enzymes. They are responsible for the degradation of the ECM in which they assist the tissue remodeling and they play a central role in tissue homeostasis [8]. They are present in both pathologic and normal tissues performing proteolytic action [9]. The main cell types excreting MMPs are macrophages, fibroblasts, osteoblasts, endothelial cells, neutrophils and lymphocytes [8].

MMPs have been studied in many conditions. It has been found that they have an impact on tumor cell behavior as a result of their ability to make alterations on cell surface receptors, growth factors, cell adhesion molecules and cytokines. Furthermore, MMPs are able to produce apoptosis-resistant cells, which leads to generation of an aggressive phenotype. MMPs may also regulate angiogenesis positively or negatively in cancer depending on activation of proangiogenic factors or generation of angiogenesis inhibitors, respectively [10].

In bladder cancer, it has been shown that there is a correlation with the levels of MMP-2 and MMP-9 and tumor grade and invasiveness [11]. MMP-2 levels were also found to be strongly associated with tumor stage and prognosis [12]. In a study, serum level of MMP-7 was also found to be associated with the prognosis of the patient. It is reported that in bladder cancer patients treated with radical surgery high MMP-7 plasma levels were significantly associated with poor overall- and disease-specific survival [13].

5. Role of ECM molecules on urinary system

5.1. Upper urinary system

In the renal cortex, the ECM is present in anatomically distinct areas with different functions depending on its molecular components. Glomerular basal membrane, which is thicker, compared to most other basal membranes in the body mainly contains laminin, collagen type IV, nidogen and heparan sulfate proteoglycans [14].

Laminins in glomerular basal membrane form a network required to maintain the basement membrane integrity. A genetic defect in laminin β2 chain will result in Pierson syndrome, which is characterized by congenital nephrotic syndrome and diffuse mesangial sclerosis, muscular hypotonia, distinct ocular abnormalities like microcoria (small pupils) and impairment of vision and neurodevelopment [15]. Leading cause of death, which occurs within first days, or weeks of life in Pierson syndrome is renal failure.

Nidogens bind to collagen type IV and laminin separately. Nidogens have a role in the basement membrane formation but experimental evidence on animal studies showed that they are not essentially required for GBM formation [16]. The most common type of heparan sulfate found in healthy basal membrane is agrin [4].

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In normal physiologic conditions, ECM of glomerular mesangium consists of fibronectin, collagen type IV, collagen type V, laminin, chondroitin sulfate, heparan sulfate and nidogen [7, 17]. Mesangial ECM allows larger molecules to pass to the mesangium in contrast to glomerular basal membrane. The small proteoglycans like decorin, biglycan, fibromodulin and lumican are most commonly localized in the tubular interstitium and they are also weakly expressed in mesangium [7].

Normally, the renal tubulointerstitial matrix is composed of collagen types I, III, V, VI, VII and XV, both sulfated and nonsulfated GAGs, glycoproteins and polysaccharides. During fibrosis, decreased degradation and increased synthesis of ECM components result in accumulation of these components leading to the formation of scar tissue in the interstitial space [14, 18].

Increasing evidence suggest that MMPs have a complex role in renal fibrosis [19]. For example, MMP-9 mediates collagen degradation. As a result, collagen fragments were formed, and these fragments mediate neutrophil chemotaxis. Including their action on ECM components, it is also shown that MMPs have functional effect on the modulation of growth factors, their receptors and adhesion molecules [19].

In diabetic nephropathy, glomerular hypertension and hyperfiltration lead to mechanical stress on glomerular cells, resulting increased transcription of transforming growth factor (TGF)-β1 and decreased MMP activity. As a result, in diabetic nephropathy, changes seen on glomerular basal membrane increase in the concentration of laminin, fibronectin, collagen IV and VI; increase in glycation of collagen IV, increase in crosslinking of collagen IV and decrease in the concentration of agrin, perlecan and collagen XVIII [18]. Stokes et al. showed an increase in decorin, collagen type 1 and biglycan levels on mesengial matrix in renal fibrosing disease [20]. Collagen type 4 reported to increase both type 1 and type 2 DM associated with the degree of decline in renal function [14].

There are some conditions in which defects on ECM components affect upper urinary tract. Mutations on the α5 chain of collagen type IV result in Alport's syndrome. Genetic defects on the α3 and α4 chains of collagen type 4 can cause autosomal dominant or recessive Alport's syndrome and thin basement membrane nephropathy. Goodpasture syndrome and Alport posttransplantation disease are two autoimmune conditions in which autoantibodies attacking glomerular basal membrane cause rapidly progressive glomerulonephritis.

Thrombospondin-1 (TSP-1) is a glycoprotein, which has adhesive properties, and it is involved in fibroblast proliferation and migration. TSP-1 is correlated with the degree of tubulointerstitial fibrosis. It is also shown that TSP-1 is transiently expressed at early stages of fibrosis. It is suggested that by the activation of TGF-β, TSP-1 could have a possible role as a mediator of interstitial fibrosis [14].

Matrix molecules such as heparan sulfate, proteoglycans, laminins, integrins and MMPs along with a group of growth factors (e.g., TGF-β) are involved in stimulation or inhibition of growth and branching of the ureteral bud [21]. The important role of ECM components and MMPs on the development of ureters puts these molecules on the scope of most recent studies investigating pathophysiology of congenital ureter-related abnormalities. It is suggested that an increase in ECM components such as collagen 1 may result in ureter-related disorders such as

ureteropelvic junction (UPJ) obstruction and ureterovesical junction (UVJ) obstruction [9, 22–24].

5.2. Bladder and lower urinary system

The bladder ECM consists of proteins, proteoglycans and GAGs. ECM in bladder provides support and signaling to the cells of the bladder [25]. ECM components have an important role in the protection of urothelium and the storage of urine. The protective layer of GAGs (predominantly chondroitin and heparan sulfates) that cover urothelial cells forms a barrier against various toxic components [25].

Bladder lamina propria forms a highly effective barrier between epithelial and mesenchymal layers. It consists of mainly connective tissue and it also contains myofibroblasts, nerve fibers, lymphatics and blood vessels [26, 27].

Detrusor muscle is associated with laminin, osteopontin and collagen fibrils (I and III) During physiologic bladder filling and emptying, keratoepithelin is organized in complex folds and facilitates expansion and compaction of the bladder. Further, the ECM composition of the bladder wall, and in particular the type of collagen (type I favored in normally compliant bladders), as well as the collagen-to-elastin ratio, are critical to the maintenance of a low-pressure state in the bladder during normal filling [21].

Studies on bladder cancer show that changes in ECM play a crucial role in the course of the disease. It has been shown that bladder cancer cells cultured in a normal ECM lose their invasiveness or ability to form papillary structures. Instead, they align in either multi- or single-layered formation resembling normal urothelium [28].

Altered distribution of laminin-5 γ2-chain is found to be associated with worse overall survival, higher risk of recurrence and progression; and it is regarded as independent prognostic factor in bladder cancer treated with TUR-B. Studies demonstrated that loss of collagen IV was associated with invasive behavior and worse overall survival [29].

Fibronectin is found at increased levels in lamina propria and in urine in urothelial carcinoma. Increased expression of it is also found to be associated with stage of the cancer but has no prognostic value. Increased value of fibronectin in urine suggested to be used for early detection of the tumor whereas decreased fibronectin level in the urine can be used to assess response to Bacillus Calmette Guérin (BCG) therapy [29].

Increased stromal expression of tenascin C is found to be associated with worse overall survival in bladder cancer; on the contrary tumor cell expression of tenascin C is associated with improved overall survival [29]. It is also found that in patients with decreased expression levels of TSP-1, high rate of recurrence and worse overall survival is seen [29].

In the function and diseases of prostate the noncellular stroma and ECM of the organ play an important role. Prostate basement membrane contains type IV and V collagen meshwork that is laminin rich and supports basal cells, stem cells, transit-amplifying cells and secretory epithelium.

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6. ECM on UPJ obstruction

Total or partial blockage at the level where renal pelvis and the ureter are joined is defined as UPJ obstruction. Obstruction can be congenital or acquired. In this case, the passage of urine from the kidney to the ureter was damaged partially or completely, depending on the grade of the obstruction. As a result, deterioration in renal function due to hydronephrosis may occur in untreated cases in the future.

In a normal kidney, the UPJ does not differ histologically from the renal pelvis. However, in an obstructed kidney, the longitudinal muscle fibers are significantly increased with more collagen deposits around the muscle fibers in addition to attenuation of muscle bundles [21].

The role of ECM in the pathogenesis of UPJ obstruction is still unclear. Major pathologic component of obstructive renal injury is tubulointerstitial fibrosis, which results in obstruction-induced renal dysfunction. Tubulointerstitial fibrosis is regarded as the final common pathway for all kidney diseases that lead to chronic renal failure [30]. One of the earliest histologic changes in the obstructed kidney is an increase in inflammatory cell infiltration into the interstitial compartment of the kidney. This results in the secretion of growth factors and cytokines. As a response to increased cytokine and growth factor levels, matrix-producing fibroblasts accumulate in renal interstitium. In response to stimulation from cytokines and growth factors, fibroblasts will secrete collagen, elastin, proteoglycans and fibronectin into the interstitial space. MMPs strictly regulate ECM secretion process in healthy individuals. Tissue inhibitors of MMPs (TIMPs) are produced by both tubular cells and interstitial cells in the kidney, and they function to inhibit the activity of MMPs [21]. An increase in TIMPs expression has been shown as a result of urinary obstruction. Although it is thought that this mechanism could be the result of ECM accumulation the role of MMPs on renal fibrosis is still not clear. Some studies show that inhibition of MMPs results in increased renal fibrosis [31] whereas there is evidence that MMP-9-deficient mice have a dramatic reduction on interstitial fibrosis in response to urinary obstruction [32].

Kaya et al. show that there seems to be increased expression of ECM components in the patients with congenital UPJ obstruction. In their study, surgical specimens of 21 patients who underwent a pyeloplasty surgery were examined immunohistochemically. Their study showed that collagen III and tenascin C expression was significantly higher in patients with UPJ obstruction. Their study also reveals that in UPJ obstruction MMP-2 expression was significantly elevated compared with healthy controls, which represents increased matrix turnover. This study also showed decreased S100 protein expression emphasizing decreased neural structure which helps us to better understand pathophysiology of this condition [9].

Another study performed by Kim et al. [33] in 65 patients demonstrated that the more collagen compared to smooth muscle the worse renal function recovery after surgery. Although this study showed that increased collagen levels are associated with poor prognosis it lacks to investigate relations with collagen subgroups.

Supporting these findings, in 2009, Özel et al. performed a controlled study with 36 patients performing immunohistochemistry and found that fibronectin, type 4 collagen and laminin

levels were significantly higher in patients with UPJ obstruction. They also expressed that apoptosis was higher in UPJ obstruction group [34].

Although it is a highly investigated area, role of ECM proteins in the development of UPJ obstruction and their impact on treatment success is still controversial. Current literature lacks a study that compares child and adult patient populations, which could give us a clearer picture for the progression of UPJ obstruction thought the life. Such information could help the physician to decide the timing of the surgery with more objective data.

7. ECM on UVJ

Similar to UPJ studies, UVJ shows decreased muscle density and increased ECM components in diseased patients. In a study published in 2004, 36 UVJ segments were evaluated and MMP1 production was found significantly higher in the group with an obstructed junction. This study also found that an increased level of CD68+ macrophages was found in obstructed junctions and as a result there was an increase in cytokines and growth factors and ECM is secreted at elevated levels [23].

Oswald et al. have shown that markers of smooth muscle structure decrease in UVJ pathologies whereas collagen concentration increases significantly by examining tissue specimens of 29 patients with a refluxing ureter and comparing them with nonrefluxing tissues.

Studies showing changes in ECM composition in UVJ-related disease gives us a picture of what happens after pathological process starts. In most conditions, our knowledge lacks the information of what really starts these changes on subcellular level. There is a need for more detailed and larger studies to get a clear picture of the conditions and develop better treatment strategies.

8. Conclusion

With advancement in the technology and increased data on ECM components, it was realized that many diseases have a close relation with the composition of ECM in the affected tissue.

ECM composition, in some conditions, gives us a view about the prognosis and progression of disease whereas in others it can give information about the cause and pathophysiology of the disease. With better understanding of ECM one can develop new treatment and follow-up models. Also better knowledge of ECM is essential for tissue engineering. Although there is a lot of data on ECM subject there are still needs for well-planned clinical trials, which can change our perspective on this subject.

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