Section A-Research paper

Brief Overview about Lupus Nephritis and Urinary Matrix Metalloproteinase 7 (MMP7)

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Abstract

Background: Lupus nephritis (LN) is clinically evident in 50-60% of patients with SLE, and it is histologically evident in most SLE patients, even those without clinical manifestations of renal disease. Lupus nephritis is diagnosed by clinical and laboratory manifestations that meet ACR criteria (persistent proteinuria > 0.5 g per day or greater than 3+ by dipstick, and/or cellular casts including red cell, hemoglobin, granular, tubular or mixed). a review of the ACR criteria has recommended that a spot urine creatinine/protein ratio >0.5 can be substituted for the 24 hours protein measurement, and "active urinary sediment" (>5 RBC/hpf, >5 WBC/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts an additional, perhaps optimal, criterion is a renal biopsy demonstrating immune complex-mediated glomerulonephritis compatible with lupus nephritis. Matrix metalloproteinases (MMPs) are a group of Zn2+-dependent proteins that are found in the extracellular milieu (ECM) of various tissues. Based on sequence homology and substrate specificities, the MMPs can be classified into several subgroups including collagenases, gelatinases, stromelysins, matrilysins and the membrane-type metalloproteinases. There is considerable overlap in substrate specificities, and the MMPs appear to be involved in degradation of abundant ECM components, including laminins, collagens and fibronectin, but also in the release and turnover of cytokines and cell surface receptors of adjacent cells. MMP-7 is commonly expressed in epithelial cells, including the liver, the ductal epithelium of exocrine glands in the skin, salivary glands, and pancreas, and the glandular epithelium of the intestine and reproductive organ and breast. Under normal physiologic conditions, adult kidney exhibits little MMP-7 expression. Early identification and diagnosis are important for slowing the progression of kidney affection in SLE and preventing its complications. Serum creatinine and blood urea nitrogen (BUN), two widely used markers for the diagnosis of kidney deterioration, increase only in the advanced stage of nephropathy. So, kidney affection are usually diagnosed at a later stage, and the implementation of therapeutic interventions is usually delayed. Therefore, there is an urgent need to develop biomarkers for early detection and prognostic assessment of renal flares in LN.

Keywords: Lupus Nephritis, Urinary Matrix Metalloproteinase 7 (MMP7).

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Introduction

Systemic lupus erythematosus (SLE) is a complex multisystemic autoimmune disorder characterized by a chronic and excessive inflammatory response. It results from a breakdown in the innate and adaptive immune responses that lead to the production of pathogenic autoantibodies and inflammatory cell infiltration in target organs. **(1)**

Involvement of all aspects of the patient's life, physical, psychological, and social well-being, SLE represents a significant impact on the quality of life with higher mortality rates versus the general population **(2)**

SLE has a striking female predominance, with almost 10 women patients for every man affected by the disease. Incidence ranges between 0.3–31.5 cases per 100000 individuals per year and has increased in the last 40 years, probably due to recognition of milder cases. Adjusted prevalence rates worldwide are approaching or even exceeding 50–100 per 100000 adults **(3*).***

SLE is a chronic, systemic autoimmune disease with a relapsing–remitting course and characterized by the production of a wide range of autoantibodies. Although people of any age and gender can be involved, SLE can have a wide range of manifestations and its severity can vary from very mild disease without major organ involvement, to severe life-threatening conditions. Lupus nephritis (LN) is clinically evident in 50-60% of patients with SLE, and it is histologically evident in most SLE patients, even those without clinical manifestations of renal disease. **(4)**

Lupus nephritis is defined as clinical and laboratory manifestations that meet ACR criteria (persistent proteinuria > 0.5 g per day or greater than 3+ by dipstick, and/or cellular casts including red cell, hemoglobin, granular, tubular or mixed). a review of the ACR criteria has recommended that a spot urine creatinine/protein ratio >0.5 can be substituted for the 24 hour protein measurement, and "active urinary sediment" (>5 RBC/hpf, >5 WBC/hpf in the absence of infection, or cellular casts limited to RBC or WBC casts) can be substituted for cellular casts an additional, perhaps optimal, criterion is a renal biopsy demonstrating immune complex-mediated glomerulonephritis compatible with lupus nephritis (**5).**

LN is the most common cause of morbidity and mortality in patients with SLE, it has a flaring–remitting course, with patients often experiencing episodic active renal lesions (flares) that lead to cumulative renal damage. LN is a common complication of SLE. The involvement may range from mild subnephrotic proteinuria to diffuse progressive glomerulonephritis leading to chronic kidney damage. It is usually occurs early in the course of SLE. New-onset hypertension, hematuria, proteinuria, lower extremity edema, and elevation in creatinine shall raise suspicion for LN **(6).**

Pathophysiology:

LN is a type-3 hypersensitivity reaction. This occurs when immune complexes are formed autoimmunity plays a significant role in the development of lupus nephritis leading to the production of autoantibodies that are directed against
nuclear elements. The characteristics of these autoantibodies in relevance to
lupus nephritis are :

- Anti-dsDNA antibodies may cross-react with the glomerular basement membrane.
- Higher-affinity autoantibodies may result in intravascular immune

complexes that get deposited in glomeruli.

- Cationic autoantibodies have a greater affinity for the anionic basement Membrane.
- Activation of complements by autoantibodies of certain isotypes.

These autoantibodies make immune complexes within the vessels that are deposited in glomeruli. immune complexes induce an inflammatory response by the activation of the complement system and recruitment of inflammatory cells glomerular thrombosis is another phenomenon that plays a part in the pathogenesis of lupus nephritis particularly in patients with antiphospholipid syndrome and is believed to be the result of an interaction between antibodies and negatively charged phospholipid-proteins **(7).**

Histopathology:

The histologic type of lupus nephritis that develops depends on numerous
factors such as :

- The antigen specificity.
- Properties of the autoantibodies.
- The type of inflammatory response that is determined by other host factors.

The commonest alteration is the presence of mesangial and/or capillary immune deposits. Other changes include: increase of the matrix and/or mesangial cellularity, endocapillary proliferation, thickening of capillary walls, glomerular tuft necrosis, extracapillary proliferation (crescents), karyorrhexis, hyaline thrombi (micronodular intracapillary aggregation of immune complexes), and glomerular sclerosis (segmental or global). Some features are suggestive of lupus nephritis: hyaline thrombi and "wire loop"

lesions (homogenous and "rigid" thickening of peripheral capillary loops due to subendothelial immune deposits), nevertheless, the only alteration considered by many authors as *pathognomonic* of lupus nephritis are the *hematoxylin bodies***,** it is very unusual to find them at the present, reason why its utility is very limited (sensitivity near 2%) **(8).**

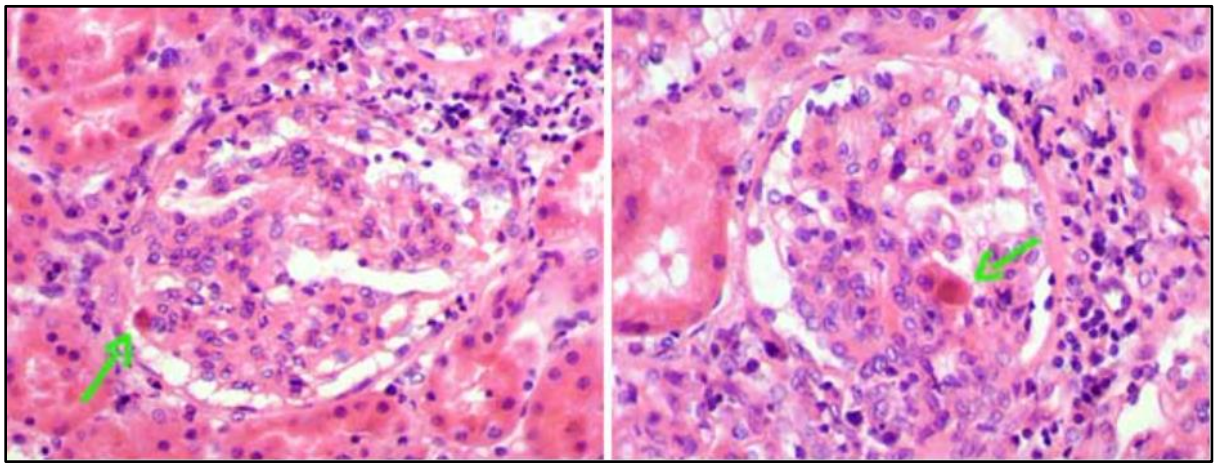

Figure (1): Hematoxylin bodies (arrows) are the histologic representation of the LE cells, they are extremely uncommon (approximately found in 2% of biopsies with lupus nephritis) and they are considered as pathognomonic of lupus. **(9)**In more severe forms of lupus nephritis, the proliferation of endothelial, mesangial, and epithelial cells and the production of matrix proteins lead to fibrosis.

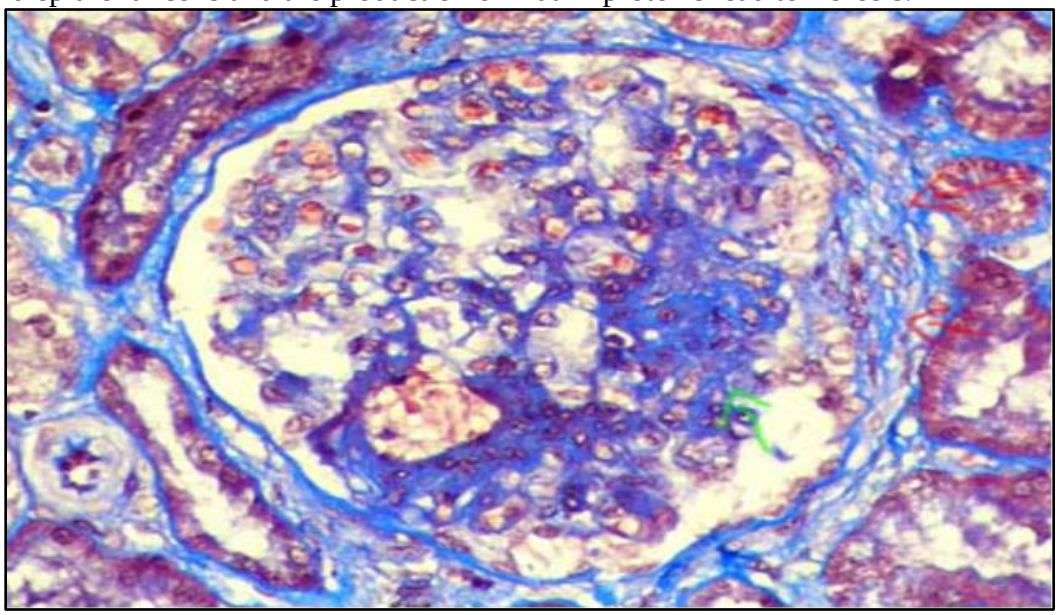

Figure (2) : In this case we found a segmental chronic lesion (green arrow) that indicates sequels of previous active lesions. Also we can see a zone of fibrosis that arises from the Bowman's capsule (red arrows) and that suggests a fibrous crescent; this finding also must be classified as chronic lesion, indicating class III or IV lupus nephritis (according to the percentage of involved glomeruli) **(9)**

The current standardized classification system for lupus nephritis is derived from the World Health Organization (WHO) and the International Society of Nephrology/Renal Pathology Society's recommendations. The classification system is based on glomerular morphologic changes seen on light microscopy (LM), immune deposits seen on immunofluorescence (IF), and also electronic microscopy (EM).
The International Society of Nephrology/Renal Pathology Society's classification: **(9)**
Class I - Minimal Mesangial Lupus Nephritis

- (LM) - Normal
- (IF/EM) - Mesangial immune deposits

Class II - Mesangial Proliferative Lupus Nephritis

- (LM) - Mesangial hypercellularity purely or expansion of mesangial matrix with mesangial immune deposits
- (IF/EM) - Mesangial immune deposits with few immune deposits in subepithelial or subendothelial spaces possible

Class III - Focal Lupus Nephritis

- (LM) - Active or inactive with focal, segmental, or global involvement affecting fewer than 50% of all glomeruli
- (IF/EM) - Mesangial and subendothelial immune deposits

Class IV - Diffuse Lupus Nephritis

- (LM) - Active or inactive with diffuse, segmental, or global involvement affecting approximately 50% of all glomeruli. It is subdivided into:

Diffuse segmental **(class IV-S)** when around 50% of involved glomeruli manifest segmental lesions (meaning less than half of glomerular tuft is affected) and

Diffuse global **(class IV-G)** when approximately 50% of affected glomeruli have global lesions. It shows wire-looping.

- (IF/EM) - Subendothelial immune deposits

Class V - Membranous Lupus Nephritis

- (LM)- Diffusely thickened glomerular basement membrane with no inflammatory infiltrate. It can possibly show subepithelial deposits and basement membrane spikes on specific stains, such as silver and trichrome. It may occur in combination with class II or IV and may reveal advanced sclerosis.
- (IF/EM) - Subepithelial and intramembranous immune deposits.

Class VI - Advanced Sclerosis Lupus Nephritis

- (LM) - Advanced glomerular sclerosis affecting almost 90% of glomeruli, tubular atrophy, and interstitial fibrosis, all manifestations of irreversible renal injury

Table (1): World health organization (WHO) classification of LN ***:*** **(9)**.

			CLINICAL CLUES[a]					
CLASS	PATTERN	SITE OF IMMUNE COMPLEX DEPOSITION	Sediment	Proteinuria (24 h)	Serum creatinine	Blood pressure	Anti-dsDNA	C3/C4
I	Normal	None	Bland	<200 mg	Normal	Normal	Absent	Normal
II	Mesangial	Mesangial only	RBC or bland	200–500 mg	Normal	Normal	Absent	Normal
III	Focal and segmental proliferative	Mesangial, subendothelial, ± subepithelial	RBC, WBC	500–3500 mg	Normal to mild elevation	Normal to elevated	Positive	Decreased
IV	Diffuse proliferative	Mesangial, subendothelial, ± subepithelial	RBC, WBC, RBC casts	1000–>3500 mg	Normal to dialysis-dependent	High	Positive to high titer	Decreased
V	Membranous	Mesangial, subepithelial	Bland	>3000 mg	Normal to mild elevation	Normal	Absent to modest titer	Normal

A kidney biopsy is indicated when the patient develops nephrotic range proteinuria. It may also be useful in patients with repeated episodes of nephritis. With the help of renal biopsy, the histologic form and stage of disease (activity and chronicity) can be established which is, in turn, helpful in determining prognosis and treatment.

Table (2): Modified NIH lupus nephritis activity and chronicity scoring system: **(9)**

2018 Modified NIH lupus nephritis activity & chronicity scoring system	
Modified Activity Index Score (0 to 24):	**<25% (1), 25%–50% (2), or >50% (3)**
1. Endocapillary hypercellularity in of glomeruli	score: 0-3
2. Neutrophils and/or karyorrhexis in of glomeruli	score: 0-3
3. Fibrinoid necrosis in of glomeruli	score 0–3 **x 2**
4. Wire loop lesions and/or hyaline thrombi in of glomeruli	score: 0-3
5. Cellular and/or fibrocellular crescents in glomeruli	score 0-3 **x 2**
6. Interstitial leukocytes in the cortex	score: 0-3
Modified Chronicity Index Score (0 to 12):	**<25% (1), 25%–50% (2), or >50% (3)**
1. Total glomerulosclerosis score, global and/or segmental sclerosis of glomeruli	score: 0-3
2. Fibrous crescents of glomeruli	score: 0-3
3. Tubular atrophy of the cortical tubules	score: 0-3
4. Interstitial fibrosis in the cortex	score: 0-3

Prognosis of Lupus Nephritis : **(10)**

- Excellent prognosis: Minimal mesangial lupus nephritis and mesangial proliferative lupus nephritis (classes I and II).
- Good prognosis: Focal lupus nephritis (class III), with only a minority of patients developing progressive renal failure.

- Fair prognosis:

✓ Diffuse lupus nephritis (class IV) with a significant number of patients developing progressive renal failure.

✓ Membranous lupus nephritis (class V) with a significant number of patients developing progressive renal deterioration gradually over time.

- Poor prognosis: Advanced sclerosis lupus nephritis (class VI).

Poor prognostic indicators of LN: **(11)**

1. Delay in treatment of more than 5 months from onset of nephritis
2. Young age at onset of nephritis -- Male sex -- Black racial background
3. Hypertension
4. Nephrotic syndrome
5. Elevated creatinine level (>3 mg/dL) at presentation
6. Persistently elevated anti-dsDNA and low C3 and C4 levels
7. Renal biopsy findings showing diffuse lupus nephritis or high chronicity index.

Matrix metalloproteinases (MMPs) are a group of Zn2+-dependent proteins that are found in the extracellular milieu (ECM) of various tissues. Based on sequence homology and substrate specificities, the MMPs can be classified into several subgroups including collagenases, gelatinases, stromelysins, matrilysins and the membrane-type metalloproteinases. There is considerable overlap in substrate specificities, and the MMPs

appear to be involved in degradation of abundant ECM components, including laminins, collagens and fibronectin, but also in the release and turnover of cytokines and cell surface receptors of adjacent cells **(12).** MMP-7 is one of the smallest secreted members of the MMP family. also known as (matrilysin 1). It is notable for its affinity for collagen IV. Produced in both the tubular and glomerular compartment of the kidney, it was recently described to be involved in several types of renal diseases with glomerular involvement, including diabetic nephropathy and X-linked Alport syndrome. **(13)**

MMP-7 is a major factor in the turnover of tenascin (an oligomeric glycoprotein that is important for the functioning of the glomerular filtration barrier) and other basement membrane components, such as laminin, entactin and proteoglycans, as well as in activation of several proinflammatory mediators, including MMP-2 and MMP-9. **(14)**

The relevance of MMP-7 in SLE has not yet been evaluated, but it remains an interesting candidate mediator of changes in membrane composition in lupus nephritis.

Structure

MMP-7 was first discovered in the rat uterus. **(15)**

The human MMP-7 gene is located on chromosome 11 q22.3. The cDNA of MMP-7 encodes a protein containing 267 amino acids. Structurally, MMP-7 only consists of a pro-peptide domain and a catalytic domain, which separates it from most other MMPs that contain an additional hinge region and a hemopexin-like domain. **(16)**

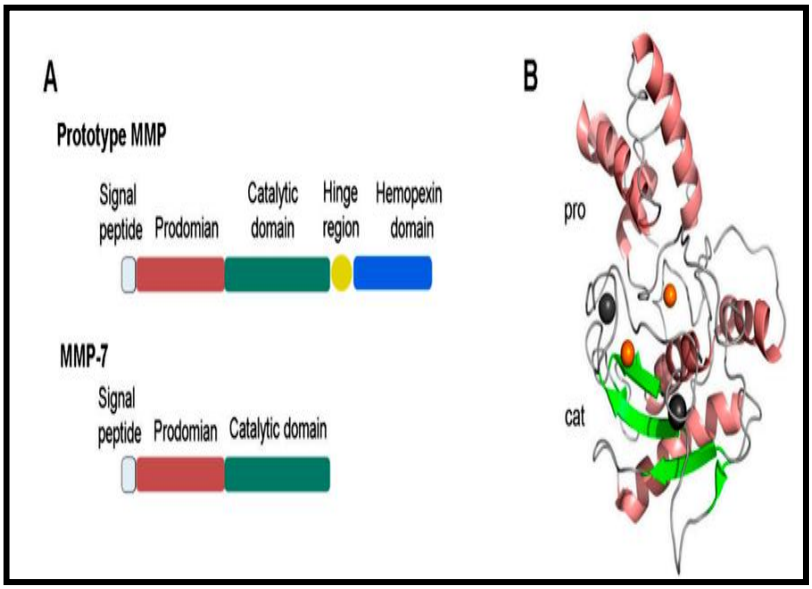

Figure (3): Structure of proMMP-7. **(A)** Full-length proMMP7 only consists of two domains: a pro peptide domain (pro) and a catalytic domain (cat), which separates it from the prototype of MMPs. **(B)** The pro-peptide domain consists of three α-chains and connecting loops. The catalytic domain contains two zinc ions, two copper ions, and a ball-like structure consisting of three α-helices, five β sheets, and multiple loops**. (16)**

Activation

MMP-7 protein is produced and secreted as an inactive zymogen, which is maintained by a conserved cysteine residue that interacts with the zinc in the active site, making the protease inactive. **(17)**

Disruption of this called (cysteine switch) is required for activation and can occur via proteolytic cleavage by many proteases, including trypsin, plasmin, or even other MMPs. generate a functional MMP-7 from the zymogen, the pro-peptide domain is proteolytically degraded in a stepwise manner. The latent form of MMP-7 is a 28 kDa protein. After removing an approximately 9 kDa sequence from the pro-peptide domain, the resultant 19 kDa peptide represents the active and functional endopeptidase. MMP-7 is also bound by two calcium ions, which plays an important role in stabilizing the secondary structure of the protein. **(8)**

Regulation

The proteolytic activity of MMP-7 is regulated by a family of naturally occurring endogenous inhibitors known as tissue inhibitors of metalloproteinases (TIMPs)., α2-macroglobulin, netrins, tissue factor inhibitor 2, type I collagen C-proteinase enhancer protein, cell surface inhibitor, and the reversion-inducing cysteine-rich protein with Kazal motifs (RECK). In general, all MMPs are inhibited by TIMPs. The mechanism of TIMP inhibition is binding of N-terminal domain to the catalytic site of the MMPs, where a cysteine chelating group inactivates the catalytic zinc site with an N-terminal amino and carbonyl group. TIMPs specifically inhibit MMPs and regulate ECM turnover and tissue remodeling by forming tight-binding inhibitory complexes with MMPs, binding the zinc atom on the MMP active site. Thus, the role of TIMPs involves the maintenance of the balance between ECM formation and ECM breakdown. There are four known TIMPs; however, it remains elusive which TIMP has the greatest specificity for MMP-7. **(18)**

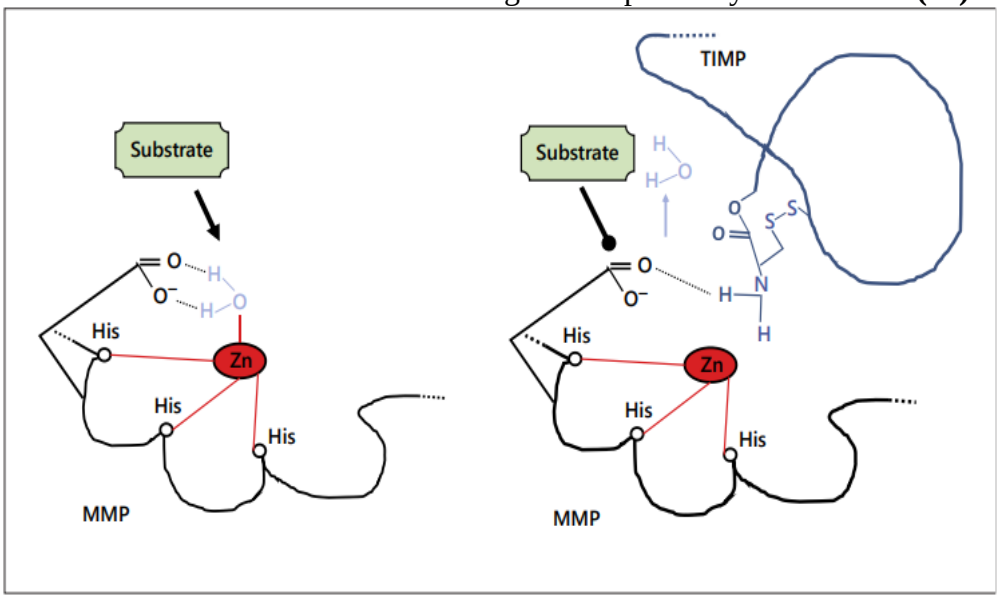

Figure (4): Schematic structure of the MMP-TIMP interaction. **(18)**

Expression in tissues

MMP-7 is commonly expressed in epithelial cells, including the liver, the ductal epithelium of exocrine glands in the skin, salivary glands, and pancreas, and the glandular epithelium of the intestine and reproductive organ and breast. Under normal physiologic conditions, adult kidney exhibits little MMP-7 expression **(19).**

Also, the expression of MMP-7 is transcriptionally regulated by different cues, particularly the Wnt/β-catenin and transforming growth factor-β (TGF-β). The promoter of the human MMP-7 gene contains a TATA box, an activator protein 1 (AP-1) site, and T cell factor (TCF)-binding elements. The AP-1 binding site is essential for mediating MMP-7 expression in response to growth factors, oncogenes, and phorbol ester, while the TCF-binding elements are responsible for mediating MMP-7 induction by Wnt/β-catenin. ATGF-β is known to activate β-catenin signaling, it remains elusive whether TGF-β controls MMP-7 expression directly or via β-catenin indirectly. **(14)**

Role of MMP7 in kidney diseases

The actions of MMP-7 in kidney diseases are mediated by its ability to cleave different substrates. As the primary role of activated MMP-7 is to break down ECM components, MMP-7 is well known to degrade macromolecules, including casein, type I, II, IV, and V gelatins, fibronectin, and proteoglycan. Recent

findings reveal, however, that MMP-7 is also capable of degrading a number of non-ECM substrates, such as FasL, E-cadherin, nephrin, and proMMP-2 and -9. These actions of MMP-7 play a crucial role in mediating its functions in the pathogenesis of kidney disorders as diabetic nephropathy, hydronephrosis, glomerulonephritis, fibrosis, tubulointerstitial fibrosis and renal cell carcinoma. **(20)**

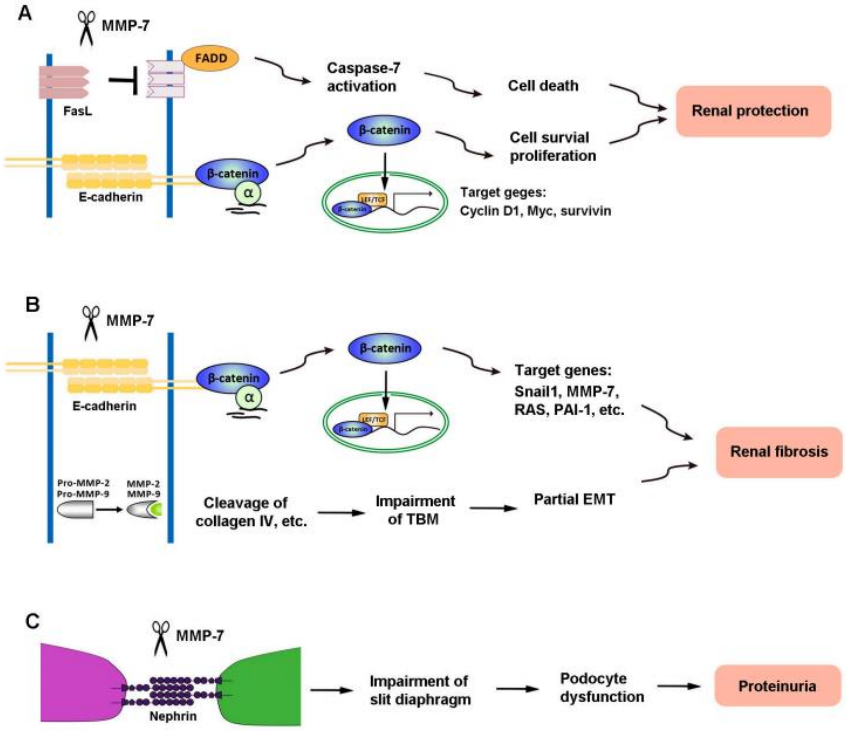

Figure (5) The mechanisms of MMP-7 action in kidney disease. **(A)** In renal tubular epithelial cells, MMP-7 promotes cell proliferation and reduces cell death by degrading E-cadherin and FasL, respectively, and finally plays a role in protecting the kidney during acute kidney injury (AKI). **(B)** However, MMP-7 also degrades E-cadherin and activates proMMP-2 and -9, leading to renal fibrosis. **(C)** In podocytes, MMP-7-mediated degradation of nephrin impairs the integrity of the slit diaphragm, which subsequently causes an increase in proteinuria and eventually leads to renal fibrosis **(8)**

MMP7 as a biomarker

Early identification and diagnosis are important for slowing the progression of kidney affection in SLE and preventing its complications. Serum creatinine and blood urea nitrogen (BUN), two widely used markers for the diagnosis of kidney deterioration, increase only in the advanced stage of nephropathy. So, kidney diseases are usually diagnosed at a later stage, and the implementation of therapeutic interventions is usually delayed. Therefore, there is an urgent need to develop biomarkers for early detection and prognostic assessment of renal flares in LN. **(21)**

MMP-7 is upregulated in various kidney diseases, and its protein is predominantly distributed in the apical region of tubular epithelial cells and is detected in the fluids present in the tubular lumen suggesting that this protein could be secreted to the urine,so it can be a useful non invasive marker for renal flares in LN. **(8)**

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