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ADAM Proteases as Novel Therapeutic Targets in Chronic Kidney Disease

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1. Introduction

More than 20 million Americans suffer, and ultimately die, from chronic kidney disease (CKD). Based on data from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the yearly cost of dialysis treatment of patients with end stage renal disease (ESRD) is currently \$35 billion [1], and this number is predicted to rise as the US population ages and more people develop obesity, metabolic syndrome, and diabetes. CKD is associated with progressive renal fibrosis and inflammation, and currently there is no cure for the disease.

The most common primary illnesses which result in end stage renal disease (ESRD) are diabetes (~37%), hypertension (~24%), glomerulonephritis (~15%), cystic kidney diseases (~4.7%) and urologic diseases (2.5%) [1]. There were 111,000 new ESRD patients diagnosed in 2007 and out of a total of ~500,000 ESRD patients 368,500 people received dialysis treatment in the same year. Dialysis patients have poor quality of life due to high hospitalization rate (458/1000 patients in 2008), high morbidity and mortality (~20%) [1]. Presently, kidney transplant is the only option for these patients to have a close to normal life. According to the US Renal Data System 2010 [1] however, out of the ~85,000 patients awaiting transplant about 18,000 will receive kidney since the amount of available organs did not increase significantly above this number for several years.

Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are widely used to attenuate the development of cardiovascular diseases and support renal function in CKD patients. However, novel therapeutic targets are desperately needed to effectively treat CKD and slow down disease progression.

Currently, there are about 2,000 clinical trials worldwide addressing some aspects and/or co-morbidities of CKD [2]. These include treatment of anemia, hypertension, secondary hyperparathyroidism, depression and inflammation among others. So far increasing frequency and quality of dialysis did not show advantages in survival rate [2]. Similarly, treatments targeting hypercholesterolemia [3] and hyperhomocysteinemia [4] or the usage of statins [5] failed to increase significantly the survival of ESRD patients.

In recent years, we and others obtained exciting new data on the pathophysiological role of the disintegrin and metalloenzyme ADAMs in renal fibrosis and CKD. This chapter is dedicated to summarize these discoveries and discuss their significance and potential role in the future treatment of patients with renal diseases.

2. Physiology of ADAMs and ADAMTS

ADAMs (a disintegrin and metalloenzymes) and ADAMTS (ADAMs with thrombospondin-1-like domains) are membrane-bound multidomain proteins similar to snake venom metalloenzymes and disintegrins. Both groups have pro-, metalloenzyme-like, disintegrin-like and cysteine-rich domains, but compared to ADAMs ADAMTS do not possess cytoplasmic or transmembrane regions. Catalytically active ADAMs are Zn^{2+} -dependent endopeptidases and are best known for their sheddase activity. They cleave epidermal growth factor ligands, cytokines and their receptors, adhesion molecules and the infamous amyloid precursor protein among others [6]. ADAMs participate in interreceptor crosstalk between G protein coupled receptors (like angiotensin receptors [7], bradykinin receptors [8] and serotonin receptors [9]) and members of the tyrosine kinase receptors (epidermal growth factors receptor, tumor necrosis factor receptor) by shedding membrane-bound pro-forms of tyrosine kinase ligands (Figure 1). ADAMs are indispensable for normal development, cell proliferation and growth however, at the same time, they can drive pathological cell division and inflammation and have major role in the development of several proliferative and inflammatory diseases [8]. Some of the ADAMs have mutation in their so-called hemopexin-domain (HEXXHXXGXXH) which is responsible for the Zn^{2+} -binding of the protein. These ADAMs are catalytically inactive and may have a role in cell-matrix and cell-cell interactions rather than in proteolytic processes [11].

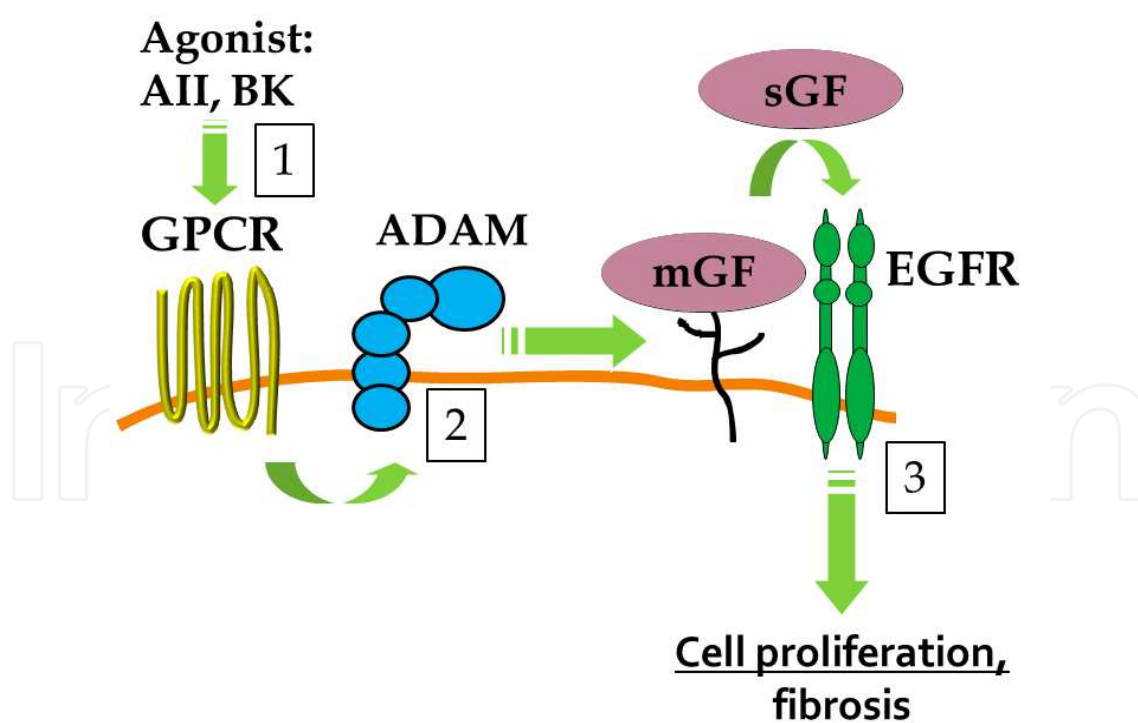


Fig. 1. ADAMs participate in inter-receptor crosstalk: triple membrane spanning signalling. AII: angiotensin-II, BK: bradykinin; GPCR: G protein-coupled receptor; mGF: membrane-bound growth factor, sGF: soluble growth factor; EGFR: epidermal growth factor receptor.

ADAMTSs are secreted proteins which anchor to extracellular matrix molecules through their thrombospondin-1 domain [12] and are involved in proteolytic cleavage of proteoglycans [13], and of the von Willebrand factor [14]. Both protein families can have significant contribution to CKD progression.

2.1 Expression of ADAM enzymes in the normal kidney

There are several ADAM and ADAMTS proteins which expression was shown in the human or murine kidney by various techniques. Histochemical analysis showed that ADAM9 was expressed in the nephron: both in the glomerulus and in tubular epithelial cells [15]. Expression of a short form of the enzyme lacking the cytoplasmic region was also reported in the kidney [16]. ADAM10 expression was first shown in chick kidney [17], in mouse kidney of mesenchymal origin [18] and later in humans in the distal tubule, in the connecting tubule, in the principal cells of the collecting duct and in the thick ascending limb of Henle [19]. ADAM11, which is known as a disintegrin metalloenzyme primarily expressed in the central and peripheral nervous system, was also expressed in the epithelial cells of the collecting duct at a low level [20]. Since ADAM11 is differentially expressed during development, it may have an important role in normal kidney morphogenesis. There is also data on the expression of ADAM13 mRNA in the developing mouse kidney [21]. ADAM17 is a disintegrin metalloenzyme which is ubiquitously expressed in almost all mammalian cells. It is present in the kidney [22] and its expression is upregulated in various renal diseases in humans [23]. The mRNA of ADAM19 was present in developing human kidney, and in the endothelial cells and in cell of the distal tubules of the adult kidney [23]. Expression of ADAM31, another proteolytically active disintegrin metalloenzyme was also identified in the epithelium of the convoluted tubuli [24]. High mRNA level of mouse ADAM33 was also shown in the kidney [25]. Since this protein is catalytically inactive, it may have a role in cell-cell interaction and communication.

Of the ADAMTS proteins ADAMTS-1 is expressed at high levels in the adult mice kidney [26], and in situ hybridization showed high level of ADAMTS-1 in the epithelia of the developing kidney [27]. In the rat higher level of ADAMTS-1 was observed in the adult animals compared to newborns, and expression pattern of the protease was restricted to the renal medulla and the principal cells of the collecting ducts in the kidney [28]. ADAMTS-5 was observed in glomerular mesangial cells [29]. ADAMTS-9 [30] and ADAMTS-10 [18] are highly expressed in the developing and adult kidney, respectively, similarly to human ADAMTS-14, -15, -16 [31] with no known function at the present. ADAMTS-13 was shown in healthy human kidney samples and in kidneys of patients with thrombotic thrombocytopenic purpura by real-time PCR and immunohistochemistry. ADAMTS-13 was present in the glomeruli as well as in the tubuli [32]. Also, various transcripts of ADAM16 were shown in the developing human and rat kidneys [33, 34].

2.1.1 ADAM and ADAMTS in kidney development - what we learned from knockout studies

There is very few data available on the role of ADAMs and ADAMTS enzymes in kidney development. There is evidence that expression pattern of ADAMTS-1 [27] and ADAM10 [35] and ADAM13 [21] changes in the kidney during development and that ADAMTS-9 is

highly expressed in the mesenchyme of the developing kidney [30]. However, as of present, there is no detail about how knocking down ADAMs influence kidney development.

Targeted knockout of Adamts-1 in mice showed that the enzyme has an important role in kidney development. Deletion of exon 2 (encoding part of the metalloenzyme domain) resulted in lack of ADAMTS-1 protein in mice and high perinatal lethality of the animals due to kidney malfunction [36]. In these animals both the cortical and medullary areas were reduced with concomitant increase in the caliceal space. Another group found that lack of the whole metalloenzyme domain (deletion of exon 2-4) rendered ADAMTS-1 catalytically inactive which resulted in enlarged renal calices and fibrosis of the uteropelvic junction [37]. These animals also developed bilateral hydronephrosis and papillary atrophy shortly after birth [38]. Since normally there is a high level of ADAMTS-1 expressed in the epithelium of the collecting ducts and of the uteropelvic junction, and because the phenotype greatly resembles to symptoms of the human uteropelvic obstruction, these animals can be good models for this genetic disease.

These data also show that targeting strategies can greatly influence the evolving phenotypes.

3. ADAMs and ADAMTSs in chronic kidney diseases

3.1 ADAMs in diabetic nephropathy

There is increasing evidence on the pathophysiological role of ADAM17 (TACE), ADAM19, ADAMTS-13 in CKD.

ADAM17 is a most well-studied sheddase enzyme. It was originally identified as the tumor necrosis factor (TNF)-α converting (or activating) enzyme [22] or TACE. It cleaves cell surface molecules, most importantly cytokines and growth factors [39]. By activating EGFR ligands and TNF-α ADAM17 has a central role in inflammatory and proliferative processes both of which have crucial role in the development of CKD (Figure 2).

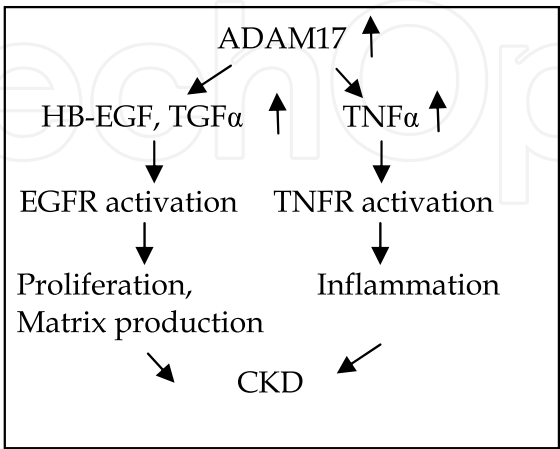


Fig. 2. Role of ADAM17 in CKD.

Besides initiating inflammation, $\text{TNF}\alpha$ has important pathophysiological role in insulin resistance (reviewed in [40]). After activation by ADAM17, the soluble homotrimer of $\text{TNF}\alpha$ activates the TNF receptor and downstream signaling molecules. Activation of the MAP kinase pathway initiates serine phosphorylation of the insulin receptor substrate (IRS) intracellularly. Being phosphorylated on serine inhibits tyrosine phosphorylation of the IRS which results in insensitivity of the insulin receptor to extracellular insulin and contributes the development of diabetes (Figure 3).

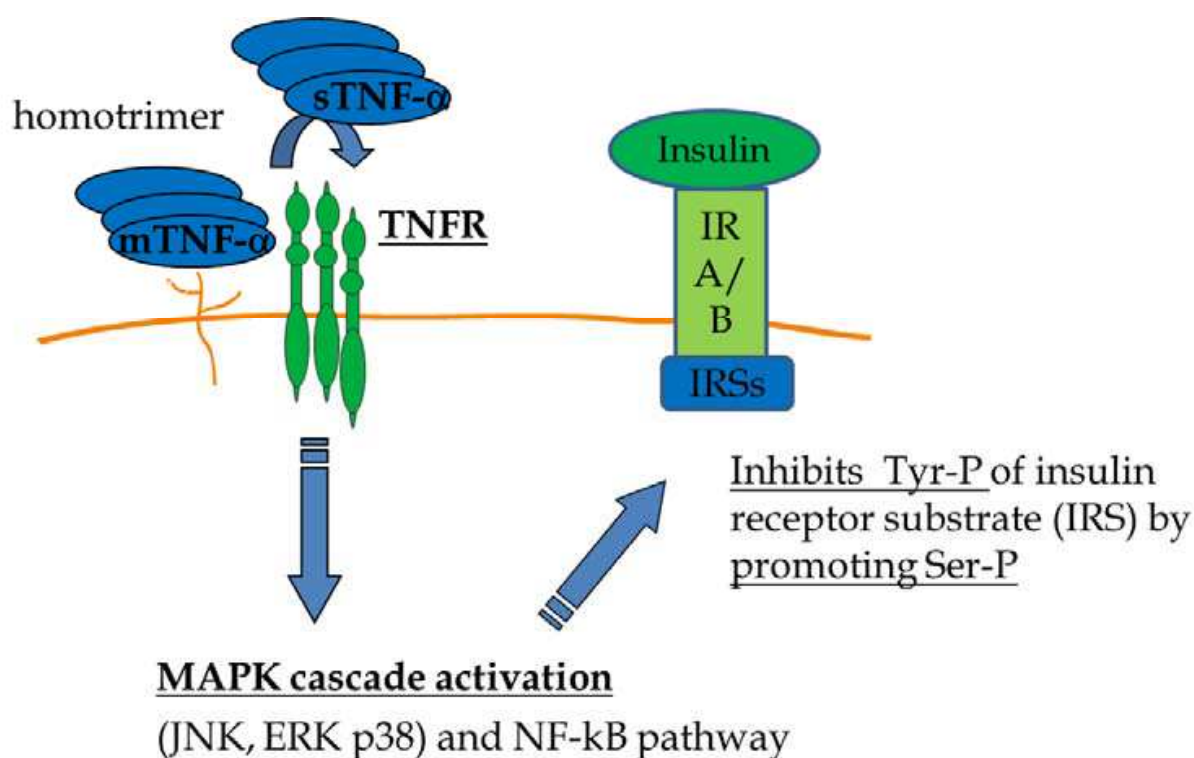


Fig. 3. Mechanism of $\text{TNF}\alpha$ -induced insulin resistance

High glucose was also shown to promote heparin-binding growth factor (HB-EGF) shedding through ADAM17 activation, however the exact mechanism is unknown [41].

Since ADAM17 activates secretion of $\text{TNF}\alpha$, pharmacological inhibitors of the enzyme were tested on blood glucose regulation in animal model of non-obesity-related insulin resistance (fructose-fed rats). ADAM17 inhibitor restored the animals' insulin resistance [42]. In another study, animals heterozygous for ADAM17 (+/-) proved to be relatively protected from high-fat diet-induced obesity and diabetes [43].

A close structural relative of ADAM17, ADAM10 is involved in shedding of RAGE: receptor for advanced glycation end products [44]. Since soluble RAGE can block pathophysiological processes initiated by RAGE, ADAM10 activation may slow down development of diabetes.

As of today, we do not have data on the pathophysiological role of ADAMTS enzymes in diabetes mellitus.

3.2 ADAMs in renal transplant dysfunction and ischemia reperfusion injury

In vitro studies modelling mechanisms of transplant rejection showed that the mRNA expression of ADAM17 was upregulated in the kidney and that the protein expression of the enzyme was localized next to TNF receptor II. This suggested that ADAM17 may antagonize the effect of $\text{TNF}\alpha$ by shedding of its receptor during transplant rejection and therefore higher ADAM17 activity might be beneficial [45]. On the other hand, ADAM17 also co-localized with HB-EGF in experimental ischemia-reperfusion injury which suggested that increased shedding of the growth factor may have contributed to the observed fibrotic injury [46]. Pharmacological inhibitors targeting ADAM17 activity reduced renal tissue injury associated with reperfusion. This confirmed that the increased enzyme activity was a cause rather than the consequence of the tissue injury [47].

Another ADAM enzyme, ADAM19 was also implicated in allograft nephropathy however, we do not know any mechanistic details of its actions [48].

3.3 ADAMs in renal fibrosis

Renal fibrosis is a manifestation of several pathological processes. Glomerular fibrosis can be induced by over-activation of the renin-angiotensin system, and the developing fibrosis and inflammation can be successfully attenuated by ADAM17 inhibitors in animal models of the injury [7]. We showed previously that serotonin-induced mesangial cell proliferation, which is an important component of glomerular fibrosis, can be inhibited by knocking down ADAM17 expression and inhibiting the enzyme activity [9]. On the other hand, we also found that ADAM17 can protect glomerular function by decreasing podocyte permeability through inducing re-arrangement of the zonula occludens protein ZO-1 [8]. These data suggest that depending on the cellular context the enzyme can have different effect on the renal function. Nonetheless, inhibitors of ADAM17 decreased infiltration of macrophages both in the glomeruli and in the interstitium in models of kidney fibrosis [7, 46] proving that targeting ADAM17 can be beneficial for preserving renal function.

There is very few data available on ADAMTS enzymes and renal fibrosis. Unilateral ureteral obstruction in rat induced upregulation of ADAMTS-1 in the tubular epithelial cells. Further,

secreted ADAMTS-1 of cultured epithelial cells decreased proliferation of a tubular fibroblast cell line which suggested that ADAMTS-1 may have anti-fibrotic effect [49].

3.4 ADAMs in polycystic kidney disease (PKD)

Autosomal-recessive polycystic kidney disease (AR-PKD) is one of the most common genetic disorders of the kidney results in end-stage renal disease. This disease leads to rapid enlargement of the kidney through massive cysts formation. The main pathogenic process in cyst development is the overactivation of the mislocalized EGFR in the cystic apical epithelia (for review see [50]). Excessive shedding of the pro-proliferative growth factor, transforming growth factor (TGF) α was also observed. Since secretion of TGF α is regulated by ADAM17, therapeutic potential of ADAM17 inhibitors were explored and established in the *bpk* murine model of AR-PKD [51]. In a later study, the role of TGF α was not confirmed even if ADAM17 inhibitors were beneficial for attenuating cyst development in AR-PKD [52].

3.5 Thrombotic thrombocytopenic purpura (TTP)/ haemolytic-uremic syndrome (HUS)

Thrombotic thrombocytopenic purpura/haemolytic uremic syndrome are often considered variants of a disease characterized by microangiopathic haemolytic anaemia [53]. Platelets are consumed by spontaneously developing microscopic thrombosis. ADAMTS-13, the enzyme which normally processes the very large von Willebrand factor (vWF) is missing [54] or disabled [55, 56] in this disease. Therefore, the very large vWF “capture” circulating platelets and initiates microthrombi formation. The red blood cells passing through the damaged arteries experience excessive shear stress which leads to haemodialysis. Besides purpura and anaemia there are often fever and neurologic symptoms present and the disease can lead to both acute kidney failure and CKD [57, 58]. Interestingly, a recent study which investigated plasma level of vWF in patients with chronic kidney disease of different origin found decreased level of vWF-cleaving protease [59]. Level of vWF was higher in stage IV patients compared to stages II and III, but whether the increased vWF contributed to the worsening of CKD is currently not known.

4. ADAMs in kidney cancer

Several ADAM enzymes were upregulated at the message level in human renal cell carcinomas. Compared to normal tissue mRNA levels of ADAM8, -17, -19, -28 as well as ADAMTS-2 were upregulated. Interestingly, mRNA level of ADAMTS-1 did not change [60]. In other studies, ADAM10 [61] and ADAM9 expression was increased in renal cancer cells and associated with tumor progression [62] suggesting that expression of these enzyme may be used as tumor markers. ADAM15 and -17 contributed to the migratory potential of kidney cancer cells through activation of the EGFR [63] and ADAM17 silencing disabled the capability of renal carcinoma cells to form in vivo tumors [64]. Therefore these enzymes seem to have direct role in renal cancer pathophysiology.

5. Conclusion

ADAM and ADAMTS families include growing number of metalloenzymes which have important role in kidney development and are indispensable to normal kidney function.

Lack or overactivation of certain ADAM enzymes (especially ADAM17 and ADAMTS-13) can have major pathophysiological role in development of various type of CKD. Therefore, targeting these enzymes can be an exciting novel therapeutic approach in the future and a new hope for CKD patients.

6. Acknowledgment

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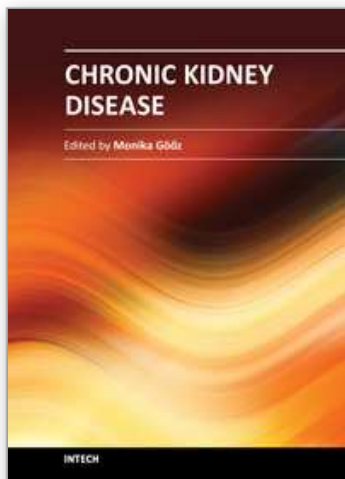
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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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