Proto-Oncogene Ets-1 and the Kidney

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Introduction

Most forms of advanced glomerular diseases, if not all, are characterized by abnormal turnover of extracellular matrix (ECM) proteins in glomeruli, resulting in structural alterations of glomerular basement membrane and mesangial matrix, usually leading to proteinuria. It is, therefore, important to elucidate the regulatory mechanisms of ECM metabolism in glomerular diseases. Various types of collagens, laminin, fibronectin, and sulfated proteoglycans are the normal components of glomerular matrix [1–5]. In vivo and in vitro studies have shown that these matrix components are produced by mesangial and visceral epithelial cells [6, 7]. It has also been demonstrated that in glomerular diseases, phenotypically altered activated renal cells are mainly responsible for the increased production of these matrix components as well as disease-specific matrix components that are not expressed in the normal kidney [8–11]. Several lines of evidence now suggest that an imbalance between synthesis and degradation of these matrix components is closely associated with accumulation of ECM and subsequent progression of renal diseases [12]. Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) have been reported to play an important role in ECM remodeling in various renal diseases [13, 14].

Recent studies have also shown that the proto-oncogene Ets-1 plays a role in the transcriptional regulation of matrix proteinases such as MMP-3 and u-PA [15–19]. We summarize herein the existing information about possible roles of Ets-1 in matrix remodeling as well as other functions in renal diseases.

Ets-1 Proto-Oncogene

The c-ets-1 gene has been identified as the cellular progenitor of viral oncogene v-ets which is associated with v-myb in the genome of the avian leukemia retrovirus E26 [20]. The c-ets-1 gene product Ets-1 is composed of 450 amino acids and contains DNA-binding ETS domain, transactivation domain, and pointed domain. The ETS domain binds to the ETS-binding motif GGAA/T in the cis-acting element of target genes and cooperates with the c-Fos/c-Jun complex at AP-1 site to activate the expression of certain promoters [21]. This motif has been found in the promoter region of numerous genes including MMP-1, MMP-3, MMP-9, u-PA, and TIMP-1 [15–18, 22].

The expression of Ets-1 proto-oncogene has been detected in various cells, and the role of ets-1 gene expressed in mesodermal lineage cells such as fibroblasts and endothelial cells has drawn a wide attention in the fields of embryogenesis and angiogenesis [23–26]. Ets-1 has been shown to be transiently expressed in the endothelial cells during vascular development in the embryo and during...
angiogenesis in the adult [24, 27, 28]. Elimination of the expression of Ets-1 resulted in inhibition of cell migration and invasion and angiogenic activity of endothelial cells [29]. Ets-1 proto-oncogene plays an important role in T cell activation [30]. High levels of ets-1 gene expression have been demonstrated in T lymphocytes and that such expression is essential for the maintenance of the normal pool of resting T cells [31, 32] and that the Ets-1-binding site is contained in T cell receptor gene enhancer and CD4 gene core promoter [33, 34]. Moreover, recent studies have also shown that Ets-1 protein exhibits multifunctional activities in the transcriptional regulation of numerous genes including MMP-3 and u-PA [15–18].

### Ets-1 and MMPs

It has been demonstrated that Ets-1 protein interacts with the promoter genes coding for proteinases including MMP-1, MMP-3, and u-PA and could enhance the promoter activity of these genes.

MMPs are generally classified into five categories based on their properties: collagenses (MMPs 1, 8, 13, and 18), gelatinases (MMPs 2 and 9), stromelysins (MMPs 3 and 10), membrane-type MMPs (MMPs 14–17), and others (MMPs 7, 11, 12, and 19) [35]; these zinc-dependent proteases play a vital role in the turnover of ECM components including collagens, elastin, laminin, proteoglycans, fibronectin, and other glycoproteins.

The progression of renal diseases due to structural remodeling has been shown to be associated not only with excessive synthesis of matrix proteins [36–38], but also with an imbalance between synthesis and degradation of MMPs and TIMPs in various types of glomerular diseases [13, 14]. Earlier studies have shown that glomerular resident cells express and secrete several types of MMPs, including gelatinase A (MMP-2), stromelysin-1 (MMP-3), and gelatinase B (MMP-9) in both animal and human kidneys [39–43]. Altered expression of MMP-3 and TIMP-1 has been detected in renal biopsy sections in various renal diseases including IgA nephropathy [39, 40]. In the passive Heymann nephritis model, McMillan et al. [41] demonstrated a marked increase in MMP-9, commonly known as type I collagenase synthesis within glomerular epithelial cells. Moreover, in vitro studies have shown the expression of a variety of MMPs by cultured mesangial and/or glomerular epithelial cells [42, 43]. It is generally accepted that matrix-degrading proteinases play an important role in various renal diseases, and it seems that Ets-1 protein regulates the transcriptional activity of several proteinases; therefore, to elucidate the role of Ets-1 in human and experimental renal diseases ought to widen our knowledge about the pathomechanism of disease process.

### Ets-1 and the Kidney

Numerous studies have shown that ets-1 gene is essential for the normal development of mammalian kidneys and the maintenance of glomerular integrity and that Ets-1 protein may act as an upstream regulator for the expression of FREAC-4, a winged helix transcriptional factor detected during nephrogenesis [44, 45]. Ets-1 has been shown to be expressed during early kidney development in the tubular structures of mesonephros day E10.5 p.c. [46]. Moreover, the ets-1 knockout mouse kidney showed various glomerular abnormalities including sclerosis, atrophy, and markedly fewer and immature glomeruli [44]. These results denote an essential role for Ets-1 for a normal structural development of the kidney.

The renin-angiotensin system plays an important role in the regulation of blood pressure and electrolyte metabolism in the kidney. Renin, which is synthesized by renal juxtaglomerular cells, catalyzes the conversion of angiotensinogen to angiotensin I. Ets-1 has been shown to bind the human renin gene promoter, and potential exists for a role of Ets-1 in the renin-angiotensin system, possibly by regulating the expression of renin in the kidney [47].

Angiogenic factors like basic fibroblast growth factor, vascular endothelial growth factor, and epidermal growth factor have been shown to induce the expression of Ets-1 in human endothelial cells. Moreover, Ets-1 plays an important role in angiogenesis by regulating the expression of u-PA and MMP-1 and migration of endothelial cells [19, 23, 29]. As a pathogenic role of basic fibroblast growth factor, vascular endothelial growth factor, and epidermal growth factor has been reported in various renal diseases [48], it will be interesting to explore whether these growth factor induced renal injuries are partly regulated by Ets-1 proto-oncogene.

Recently, we found a coordinated upregulation of MMP-3 and Ets-1 in experimentally induced crescentic glomerulonephritis. The expression pattern and cellular distribution of MMP-3 and Ets-1 protein were similar, and MMP-3-positive renal cells often expressed Ets-1 protein in the diseased kidney, revealing a close association between Ets-1 and MMP-3 expression [49]. From the results of this in vivo study, it has been concluded that upregulation of the expression of MMP-3 possibly by the
transcriptional activation of Ets-1 might participate in the matrix remodeling in renal diseases. Further studies using human renal tissue are necessary to determine the possible role of Ets-1 proto-oncogene in various renal diseases.

**Conclusions**

Although comprehensive studies are required to clarify the precise role of Ets-1 in renal injury, however, existing information seems to indicate its broad biological functions in the kidney, ranging from embryonic development to disease process. Over the past several years, remarkable progress has been made in understanding the molecular mechanisms of tissue remodeling in normal and diseased kidneys [1, 8, 12, 13, 43, 50]. However, very little is known about possible involvement of Ets-1 and other transcriptional factors in the initiation of disease processes. An advance in molecular biology techniques has allowed us to identify most of the factors and even predict their roles (to some extent) in routine biopsy sections. Applying all these molecular biological techniques, identifying regulating factors like Ets-1, those that might actively participate in initiating the immuno-inflammatory cascade in various renal diseases and establishing an effective therapeutic strategy by targeting those early factors to treat and/or control the progression of disease process will be an enormous clinical challenge.

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