Review

The Role of Y-Box Binding Protein 1 in Kidney Injury: Friend or Foe?

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Key Words

Y-box-binding protein 1 • Acute kidney injury • Chronic kidney disease • Translation

Abstract

Y-box-binding protein 1 (YB-1) is a multifunctional protein involved in various cellular processes via the transcriptional and translational regulation of target gene expression. YB-1 promotes acute or chronic kidney injury through multiple molecular pathways; however, accumulating evidence suggests that significantly increased YB-1 levels are of great importance in renoprotection. In addition, YB-1 may contribute to obesity-related kidney disease by promoting adipogenesis. Thus, the role of YB-1 in kidney injury is complicated, and no comprehensive review is currently available. In this review, we summarise recent progress in our understanding of the function of YB-1 in kidney injury and provide an overview of the dual role of YB-1 in kidney disease. Moreover, we propose that YB-1 is a potential therapeutic target to restrict kidney disease.

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Introduction

Y-box-binding protein 1 (YB-1), also known as nuclease-sensitive element-binding protein, is a DNA- and RNA-binding protein. YB-1 is an important transcription factor with an evolutionarily ancient and conserved cold-shock domain and participates in multiple cellular processes [1]. YB-1 is encoded by the *YBX1* gene and is a major component of protein complexes that mediate mRNA binding and transport [2]. In response to genotoxic stress, YB-1 translocates from the cytoplasm to the nucleus [3] where it acts as a transcriptional regulator to overcome DNA damage-dependent cell-cycle arrest and promote cell survival [2]. Moreover, YB-1 is a major component of messenger ribonucleoprotein particles in mammalian cells and regulates the stabilisation of mRNA and translation of mediators, such as profibrotic cytokine transforming growth factor (TGF)- β and pro-inflammatory cytokine C-C motif chemokine ligand 2 (CCL2)/monocyte chemoattractant protein 1 (MCP-1) [4, 5]. YB-1 has a prominent and distinct role in the regulation of the inflammation process [6]. YB-1 seems to fulfil a pacemaker role in diverse diseases, functioning in both inflammatory/pro-fibrogenic and tumourigenic pathways [7]. A more detailed description of YB-1 protein

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structure and function can be found in two outstanding reviews by Eliseeva et al. [2] and Lyabin et al. [1].

YB-1 acts as a central regulator of gene transcription and translation of several fibrosis-related genes [8, 9]. Recently, increasing evidence has shown that YB-1 plays a protective role in acute or chronic kidney injury [6, 10]. Furthermore, YB-1 may be involved in the pathogenesis of obesity-related kidney disease (ORKD) [11]. Unfortunately, no comprehensive review of the role of YB-1 in kidney injury is currently available. Here, we summarise recent progress in our understanding of the function of YB-1 in kidney injury and provide an overview of the dual role of YB-1 in kidney disease. Moreover, we propose that YB-1 is a potential therapeutic target for the treatment of kidney disease.

YB-1 and AKI

Acute kidney injury (AKI) is a common clinical syndrome that complicates up to 20% of hospital admissions and 30–50% of intensive care unit admissions [12, 13]. AKI is associated with up to an eight-fold increased risk in mortality due to limited therapy options [14, 15]. Ischaemia-reperfusion injury (IRI), the leading cause of AKI, accounts for 50% of all cases. The pathophysiology of AKI is complex and involves multiple processes, including inflammation, autophagy, cell-cycle progression, and coagulation activation [16–18]. Recent evidence has suggested that a single insult to the kidney significantly enhances the propensity to develop chronic kidney disease (CKD) [16]. Therefore, the development of effective therapies against AKI is urgently needed.

YB-1 plays an important role not only in the onset but also in the resolution of inflammation in AKI. Generally, YB-1 regulates the expression of pro-inflammatory mediators during the acute phase of inflammation [19]. At the onset of inflammation, YB-1 upregulates the expression of pro-inflammatory factors such as interleukin (IL)-6 [20] and C-C motif chemokine ligand 5 (CCL5) [19, 21]. CCL5, an important inducer of immune cell infiltration, is transcriptionally and translationally regulated by YB-1 in monocytes/macrophages [22] and human arterial smooth muscle cells [23]. Interestingly, half-maximal YB-1 expression results in the amelioration of AKI by inhibiting *CCL5* gene expression [19]. Moreover, increased tubular cell CCL5 expression was found in conditional *Ybx1* knockout animals with specific depletion in monocytes/macrophages (YB-1^{ΔLysM}) [6]. Regulatory T cell-derived IL-10 plays an important renoprotective role in murine models of ischaemia-reperfusion (I/R) [24]. However, Wang et al. [10] found that mice with half-maximal expression of YB-1 (Yb1^{+/-}) exhibited an ameliorated inflammatory response and kidney damage at the earlier stages (days 1 and 5) of I/R with aggravated kidney injury, inflammation, and less regeneration at later stages (day 21). Moreover, YB-1 was phosphorylated at serine 102 localised to the fourth intron, the IL10 gene locus, which was paralleled by enhanced IL-10 mRNA expression in mice following lipopolysaccharide (LPS) challenge and I/R. Furthermore, half-maximal expression of YB-1 led to diminished IL-10 expression upon LPS challenge, consistent with the results of a previous study [6]. However, higher YB-1 expression enhanced IL-10 mRNA expression [10]. Therefore, YB-1 exhibits both pro- and anti-inflammatory properties via IL10 gene regulation.

YB-1 alleviates AKI by mediating thrombomodulin (TM)-dependent activated protein C (aPC) signalling. Tissue factor-dependent coagulation and thrombin activation aggravate tubular injury through protease-activated receptor-1 (PAR-1)-dependent signalling [18]. Unlike thrombin, the anticoagulant serine protease aPC is nephroprotective and ameliorates acute renal injury [25, 26]. The therapeutic application of recombinant soluble TM ameliorated IRI in rats by aPC [27, 28]. Notably, YB-1 was required for the nephro- and cytoprotective effects of aPC *in vivo* and *in vitro* because aPC failed to provide renal protection in YB-1^{+/-} IRI mice [29]. Furthermore, the reduction in mature YB-1 and K48-linked ubiquitination of YB-1 was prevented by aPC after renal IRI, and aPC preserved the interaction of YB-1 with the deubiquitinating enzyme otubain-1 and maintained expression of otubain-1, which was

required to reduce K48-linked YB-1 ubiquitination and stabilise YB-1 after renal IRI (Fig. 1) [29]. Given that aPC plays a key role in attenuating inflammation [30], inflammatory factors such as CCL5, IL-6 and IL-10 should have been used as indicators in this study to clarify the relationship between YB-1 and inflammation.

YB-1 and CKD

CKD is defined as decreased kidney function demonstrated by a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m², markers of kidney damage, or both for at least 3 months regardless of the underlying cause. CKD is endangering the global health system. According to World Health Organization (WHO) global health estimates, 864, 226 deaths were attributed to this condition in 2012 alone [31]. CKD is currently ranked fourteenth in the list of leading causes of death, accounting for 12.2 deaths per 100, 000 people [31]. The final common pathological manifestation of CKD is renal fibrosis in which multiple serum cytokines are involved. Given the role of renal fibrosis, Lindquist J et al. proposed the novel idea that the risk for organ fibrosis should be quantifiable, similar to autoimmune disorders (autoantibody titres) or cancers (tumour markers), and that treatment options may be adjustable [32], which may decrease the mortality of CKD.

YB-1 alleviates renal fibrosis through multiple pathways. Excessive cellular infiltration and prolonged inflammatory responses may aggravate tissue damage and may therefore detrimentally impact kidney function [33]. YB-1 regulates proliferation, matrix protein synthesis, chemotaxis, and phenotypic alterations in monocytic cells; it is also crucially involved in the orchestration of inflammatory responses [1]. Bernhardt et al. [6] revealed increased inflammatory cell infiltration and tubular cell CCL5 expression in YB-1^{ΔLysM} mice following tubulointerstitial injury by unilateral ureteral obstruction. Furthermore, YB-1^{ΔLysM} mice exhibited enhanced tissue damage, myofibroblast activation, and fibrosis. Among bone marrow-derived macrophages, YB-1 deficient macrophages had defects in cell polarisation and function, including reduced proliferation and nitric oxide production, loss of phagocytic activity, and failure to upregulate IL-10 and CCL5 expression in response to inflammatory stimuli. Co-culture with primary tubular cells confirmed these findings. These findings indicate that YB-1 has prominent and distinct roles in the resolution of inflammatory processes [6]. Moreover, YB-1 acts as a cell type-specific activator of matrix metalloproteinase (MMP)-2 gene expression [34]. MMP-2 belongs to the family of zinc-dependent endopeptidases that control collagen degradation in the kidney and participate in fibrotic processes [34]. In addition, YB-1 serves as a potent negative transcriptional regulator of both the α -smooth muscle actin and collagen type 1 alpha 1 (Col1A1) genes, which are hallmarks of mesangial activation during fibrogenesis [35, 36]. Collectively, these results suggest that YB-1 plays a powerful role in inhibiting renal fibrosis by reducing inflammatory cell infiltration, enhancing the resolution of kidney inflammation and suppressing fibrotic genes and signalling.

Fig. 1. Schematic presentation of the signalling pathways by which aPC regulates YB-1 expression and stability in tubular cells.

However, YB-1 shows profibrotic effects through the regulation of Col1A1 translation and enhancement of inflammation [8, 19]. The immunosuppressive calcineurin inhibitor (CNI) cyclosporine A (CsA) can cause tubulointerstitial as well as mesangial fibrosis, with TGF- β believed to be a central inducer [37]. Hanssen et al. [8] found that intracellular levels of YB-1 increased several-fold in mesangial cells (MCs) following CNI treatment *in vitro* and *in vivo* in mice. CsA-induced YB-1 accumulation resulted in collagen mRNA stabilisation and the subsequent generation of collagen; this result conflicts with the role of YB-1 as a negative regulator of Col1A1 gene transcription [35]. Moreover, YB-1 can exacerbate

bacterial and sterile inflammation to promote renal fibrosis [19]. In proximal tubular cells, YB-1 controls TGF- β 1 expression by binding to a high-affinity site of TGF- β 1 mRNA to activate the translation of TGF- β 1, which is an important mediator of the pathogenesis of numerous fibrotic diseases [9] (Fig. 2). Furthermore, extracellular YB-1 promotes mesangioproliferative diseases through the activation of the Notch 3 receptor, which plays an active role in the pathogenesis of glomerular diseases [38, 39]; however, extracellular targeting of YB-1 also induces glomerular Notch-3 receptor expression and Notch signalling [40].

The phosphorylation and subcellular localisation of YB-1 may determine its effects on renal fibrosis [41] (Fig. 2). When localised to the nucleus, YB-1 acts as an anti-fibrotic protein via the repression of pro-fibrotic factors such as Col1A1 and α -smooth muscle actin [36]. YB-1 also activates anti-fibrotic factors such as MMP-2 and Smad 7, which interferes with TGF- β signalling and acts as an endogenous antagonist that restricts the fibrotic response [42, 43]. In line with this finding, a recent study reported that YB-1 localised to the cytoplasm could directly stabilise *Col1a1* mRNA, thus promoting fibrosis during ureteral obstruction. Conversely, the therapeutic forced nuclear compartmentalisation of phosphorylated YB-1 by small molecule HSc025 mediated the repression of the *Col1a1* promoter and attenuated fibrosis following ureteral obstruction. Moreover, HSc025 reduced tubulointerstitial damage even when applied at later time points during maximum renal damage [41]. Therefore, induced nuclear YB-1 shuttling may be a novel anti-fibrotic treatment strategy in renal diseases.

YB-1 may contribute to renal fibrosis via the induction of epithelial-to-mesenchymal transition (EMT). Although controversial, emerging evidence indicates that renal tubular EMT is an important event in the pathophysiology of renal fibrosis [44]. A number of studies have reported that YB-1 induces EMT in cancer [45, 46]. The mechanism by which YB-1 mediates EMT is probably related to YB-1-induced transcription and translation of vimentin and snail [46]. Vimentin is an intermediate filament protein and marker for myofibroblasts [47]. The expression of vimentin and snail correlated well with renal fibrosis [48]. This finding may explain how YB-1 regulates renal fibrosis.

YB-1 may contribute to ORKD by promoting adipogenesis. ORKD is essentially single-nephron hyperfiltration caused by a reduced ratio of nephrons to body mass. This disease is recognised as a distinct entity characterised by glomerulomegaly, progressive glomerulosclerosis and renal functional decline [49-51]. Bone morphogenic protein 7

Fig. 2. Schematic presentation of the signalling pathways by which YB-1 regulates the expression of TGF- β , collagen, MMP-2 and Bmp-7 and contributes to renal fibrosis and adipogenesis, leading to ORKD.

(BMP7) is critical for mesenchymal progenitor cells to commit to the brown fat lineage [52]. YB-1 binds and activates the *BMP7* promoter to promote its transcription. Moreover, YB-1 is essential for *Bmp7* expression during brown adipocyte differentiation *in vitro*. Furthermore, Ewing Sarcoma (EWS), a multifunctional protein that is essential in determining brown fat lineage during development, forms a complex with YB-1, and this complex directly activates *Bmp7* transcription to induce brown adipogenesis [11] (Fig. 2). Additionally, YB-1 showed the strongest induction (130-fold) in the white adipose tissue of cafeteria-diet fed animals [53]. YB-1 induces protein-tyrosine phosphatase 1B (PTP1B) expression by binding directly to its promoter, and the inactivation of PTP1B is related to obesity resistance [54].

Conclusion and Perspective

YB-1 plays a complicated and distinct role in acute and chronic kidney damage. During AKI, YB-1 plays a role in both the early and late phases, although the precise function of YB-1 in the different stages of AKI remains controversial. For example, YB-1 plays a renoprotective role in AKI as a downstream effector of aPC. This role may provide a novel strategy to mitigate AKI if a switch is developed to change the function of YB-1 in inflammation. In CKD, YB-1 has a dual role in the regulation of collagen synthesis, depending on its subcellular localisation. Moreover, YB-1 may accelerate renal fibrosis via TGF- β signalling as an upstream regulator with the ability to induce EMT. In addition, YB-1 may play an active role in ORKD by mediating adipogenesis, which offers a new direction to alleviate ORKD. Overall, although some advancements have been made in our understanding of the complicated role of YB-1 in kidney injury, further basic and preclinical studies are needed to validate YB-1 as a potential therapeutic target to restrict kidney disease.

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Disclosure Statement

All authors declare that there are no conflicts of interest.

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