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Mini Review

Bone morphogenetic protein-7 and Gremlin: New emerging therapeutic targets for diabetic nephropathy

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ABSTRACT

Specific therapies of diabetic nephropathy (DN) are not available, and current treatment strategies are limited to management of blood glucose levels and control of hypertension. The re-activation of developmental programs in DN suggests new potential therapeutic targets. Bone morphogenetic protein-7 (BMP-7) and its antagonist, Gremlin is revealed to be involved in renal development and diabetic nephropathy. This article reviews the changes of BMP-7 and Gremlin in diabetic kidney, the protective effects on diabetic nephropathy when targeting BMP-7 and Gremlin, and the possible mechanism. The reorganization of the re-activation of Gremlin and BMP-7 in diabetic kidney had shed light on the identification of novel therapeutic targets for DN.

Introduction

It is estimated that there are now 150 million people with diabetes worldwide, expected to rise to 300 million by 2025 [1]. Diabetic nephropathy (DN) is the leading cause of end-stage renal diseases and about 20–40% of patients with diabetes ultimately develop diabetic nephropathy. Specific therapies to reverse or inhibit the progression of diabetic nephropathy to advanced stages are not available, and current treatment strategies are limited to management of blood glucose levels and control of hypertension [2]. Hyperglycemia is the major factor precipitating renal injury in the development of DN [3]. However, the downstream signaling pathways which influence this process are not fully defined. One known mediator in the development of both glomerulosclerosis and tubulointerstitial fibrosis is transforming growth factor-β1 (TGF-β1) [4]; however, because of its pleiotropic actions, TGF-β may not be an ideal therapeutic target. Recently, a role for the re-activation of developmental programs in DN has been recognized [5]. Increased expression of developmental genes including bone morphogenetic proteins (BMPs) and Gremlin, a BMP antagonist, supports the notion that the ontogenic processes are operative in the development of DN [4,6–8]. The re-activation of developmental programs in DN has shed light on novel pathways influencing the disease and suggests new potential therapeutic targets. Recent studies highlight the action of BMP-7 and its antagonist, Gremlin, thus, here we focus on these two molecules as putative therapeutic targets of DN.

Bone morphogenetic protein-7 (BMP-7) and Gremlin

Bone morphogenetic proteins (BMPs) which are originally identified by their ability to induce the endochondral bone formation are homodimeric members of the TGF-β superfamily of cysteine-knot cytokines [9]. In addition to their roles in kidney development, they also regulate growth, differentiation, chemotaxis, and apoptosis of various adult cell types, including epithelial, mesenchymal, hematopoietic, and neuronal cells [10]. Multiple BMPs are expressed in the kidney, among which BMP-7 is most abundant and reveals specific function [11]. In the adult life, BMP-7 is primarily expressed in kidney tubules, as well as glomeruli [12]. BMP-7 activity in the kidney is not only determined by availability of BMP-7 itself, but also by a balance of agonists, such as Kielin/chordin-like protein (KCP) and antagonists, such as Gremlin [10] (Fig. 1). Gremlin, one of the antagonists of BMP-7, was found important in renal diseases especially in diabetic nephropathy. It is reported that gremlin is the only one of the three BMP-7 antagonists (noggin, follistatin, gremlin) increased in diabetic rat kidneys [13]. Gremlin is a 184 amino acid protein and a member of the cysteine-knot superfamily. The protein is highly conserved during evolution and is present in soluble and cell-associated forms. It includes the headinducing factor Cerberus and the tumor suppressor DAN. Gremlin is important in limb development and neural crest cell differentiation and in the development of kidney as well. Gremlin gene knockout mice die shortly after birth because of the lack of kidney and lung defects [14]. Under basal conditions,

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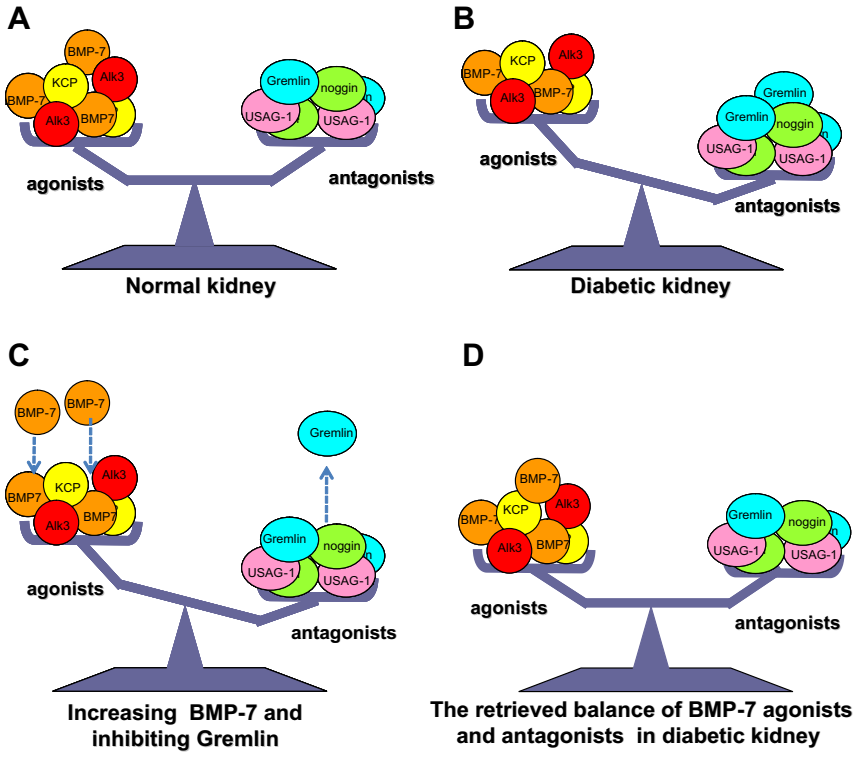

Fig. 1. Schematic illustration of the balance between BMP agonists and BMP antagonists in diabetic kidney.

Gremlin is present at relatively low levels in the adult kidney [15,16].

BMP-7 in diabetic kidney

Bone morphogenetic proteins, active in development, are homodimeric members of the TGF-β superfamily of cysteine-knot cytokines [17,18]. The TGF-β superfamily comprises over twenty BMPs, of which BMP-7 is the most prominent member involved in renal development and disease. BMP-7 is primarily expressed in kidney tubules and glomeruli [12,19,20]. Loss of endogenous BMP-7 expression occurs in diabetic rats and is associated with profibrotic activity [21,22]. In the streptozotocin diabetic model BMP-7 is reduced by 50% at 15 weeks and continues to decline further to 10% by 30 weeks [23]. In cultured tubular cells, TGF-β decreases BMP-7 expression, which suggests that a rise in tubular TGF-β levels during the evolution of diabetic nephropathy contributes causally to the loss of BMP-7 and BMP-7 type I and II receptors [21,22]. Morrissey and associates showed that exogenously administered recombinant human (rh) BMP-7 may even resolve, at least partially, glomerular and interstitial fibrosis in experimental diabetic nephropathy [21,22].

Gremlin in diabetic kidney

The expression of gremlin in adult kidney is almost undetectable in healthy status, but the expression increases in several kidney disease models [24], including streptozotocin induced diabetic rats model. Although Gremlin expression is low in normal adult kidney, it is highly expressed in biopsy specimens from patients with diabetic nephropathy, where it is predominantly observed in areas of tubulointerstitial fibrosis and where it co-localizes with TGF-β1 expression [15]. In addition, Gremlin mRNA levels directly correlate with elevated serum creatinine levels and tubulointerstitial fibrosis scores in patients with DN [3]. Further, Gremlin expression is enhanced in mesangial cells cultured under high glucose conditions and in those exposed to cyclic mechanical strain and TGF-β [17]. Collectively, these data suggest a role for Gremlin in the pathogenesis of tubulointerstitial fibrosis in DN.

BMP-7 and Gremlin as novel targets for DN: the mechanism

A number of studies showed that BMP-7 plays protective roles in cultured renal cells. De Petris et al. investigated the effect of rhBMP-7 on mouse podocytes [25]. They found that podocytes cultured under high glucose condition showed decreased synaptopodin, podocin and BMP-7 transcription and protein synthesis compared to those cultured under normal glucose condition. Treatment with rhBMP-7 restored the synaptopodin and podocin expression. They inferred that BMP-7 may delay high glucose induced podocyte injury via resistance of synaptopodin and podocin. In addition, the loss of podocytes contributes to glomerulosclerosis, which is a character of the pathological feature of advanced diabetic nephropathy. Mitu et al. also declared that BMP-7 is a podocyte survival factor and rescues podocytes from diabetic injury, especially apoptosis caused by the activation of capase-3 [26]. In addition, BMP-7 is also involved in ameliorating renal damage due to mesangial proliferation by suppression of mesangial cell mitosis via Smad-1, -5, -8 signaling [27]. BMP-7 is also able to prevent metanephric mesenchymal cells and renal epithelial cells from undergoing apoptosis, thereby preserving renal function [15].

Secondly, maintenance of BMP-7 activity may result in blockade of extracellular matrix (ECM) accumulation by maintaining the levels and activity of MMP2, partially through prevention of TGF-β dependent upregulation of PAI-1 [28]. Wang and Hirschberg reported that BMP-7 reduces the accumulation of extra cellular matrix (ECM) proteins, such as fibronectin, collagen type IV and thrombospondin, which are induced by TGF-β in mesangial cells [28]. Zeisberg et al. found that BMP-7 could reverse TGF-β1 induced epithelial to mesenchymal transition (EMT) by reinduction

of E-cadherin [29]. Systemic administration of recombinant human BMP-7 lead to repair of severely damaged renal tubular epithelial cells via restoration of E-cadherin expression [30].

Inhibition of Gremlin may induce therapeutic effects on the diabetic kidney by allowing the efficient binding of endogenous BMP-7 to receptors without inhibition. In addition, Gremlin can increase DNA synthesis and cell counts and accelerate cell cycle progression of vascular smooth muscle cells (VSMC) through mechanisms that include p27(kip1) down-regulation [18]. It is possible that Gremlin may regulate cell growth via a BMP-7-independent pathway. Thus Gremlin may be recognized as a novel therapeutic target in either a BMP-7 dependent or a BMP-7 independent way.

Concluding remarks and future perspectives

Emerging evidences have shown that the two developmental genes, BMP-7 and its antagonist Gremlin may serve as therapeutic targets for the treatment of DN, which, then, has important implications for the future development of therapeutic strategies targeting these two molecules.

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