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Review

Soluble biglycan as a biomarker of inflammatory renal diseases

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ABSTRACT

Chronic renal inflammation is often associated with a progressive accumulation of various extracellular matrix constituents, including several members of the small leucine-rich proteoglycan (SLRP) gene family. It is becoming increasingly evident that the matrix-unbound SLRPs strongly regulate the progression of inflammation and fibrosis. Soluble SLRPs are generated either via partial proteolytic processing of collagenous matrices or by *de novo* synthesis evoked by stress or injury. Liberated SLRPs can then bind to and activate Toll-like receptors, thus modulating downstream inflammatory signaling. Preclinical animal models and human studies have recently identified soluble biglycan as a key initiator and regulator of various inflammatory renal diseases. Biglycan, generated by activated macrophages, can enter the circulation and its elevated levels in plasma and renal parenchyma correlate with unfavorable renal function and outcome. In this review, we will focus on the critical role of soluble biglycan in inflammatory signaling in various renal disorders. Moreover, we will provide new data implicating proinflammatory effects of soluble decorin in unilateral ureteral obstruction. Finally, we will critically evaluate the potential application of soluble biglycan vis-à-vis other SLRPs (decorin, lumican and fibromodulin) as a promising target and novel biomarker of inflammatory renal diseases.

Contents

Abbreviations: 5/6-Nx, 5/6-nephrectomized Sprague-Dawley rats; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; ALK, activin like kinase; ATS, hymocyte serum; *BGN* (*Bgn*), biglycan; BDL, bile duct ligation; BMP, bone morphogenic protein; CCL, chemokine (C-C motif) ligand; CCR, chemokine (C-C motif) receptors; CD, cluster of differentiation; CS, chondroitin sulfate; CsA, chronic cyclosporine; CXCL, chemokine (C-X-C motif) ligand; DAMP, damage-associated molecular pattern; *DCN*, decorin; DS, dermatan sulfate; ECM, extracellular matrix; ELISA, enzyme-linked immunosorbent assay; Erk, extracellular signal-regulated kinase; *Fbn1*, fibrillin-1; GAG, glycosaminoglycan; GrB, Granzyme B; HPF, high-power fields; HSP90, heat shock protein 90; Ig, immunoglobulin; IL-1β, interleukin-1β; IL-6, interleukin-1-6; Irf-1, interferon regulating factor-1; IRI, ischemia-reperfusion injury; KS, keratan sulfate; LDL, low-density lipoprotein; LPS, lipopolysaccharide; LRP, low-density lipoprotein receptor-related protein; LRR, leucine-rich repeat; MMP, matrix metalloproteinase; MNS, Milan normotensive strain; Mpv17, mitochondrial inner membrane protein; MRL, Murphy Roths Large; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor-κB; NLR, Nod-like receptor; NLRP3, NLR pyrin domain containing 3; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; PDGF, platelet-derived growth factor; pLIVE, liver in vivo expression vector; RA, rheumatoid arthritis; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SLRP, small leucine-rich proteoglycan; SR-A, class A scavenger receptor; STZ, streptozotocin; TGF, transforming growth factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; TRIF, TIR-domain-containing adaptor-inducing interferon beta; UUO, unilateral ureteral obstruction; VEGF, vascular endothelial growth factor; WISP-1, Wnt-1-induced secreted protein-1.

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1. Introduction

Accumulation within the tissues or release into the circulation of the extracellular matrix (ECM) derived small leucine-rich proteoglycan (SLRP), biglycan is a common feature of a large number of renal pathologies. This has led to the proposal that this SLRP could directly contribute to the progression of renal diseases (Anders and Schaefer, 2014; Moreth et al., 2010; Moreth et al., 2014; Schaefer, 2011; Thompson et al., 2011; Yokoyama and Deckert, 1996).

A member of the class I family of SLRPs, biglycan consists of a 42 kDa protein core containing leucine-rich repeats (LRRs) and one or two covalently-linked glycosaminoglycan (GAG) chains at the N-terminus, consisting of either dermatan sulfate (DS) or chondroitin sulfate (CS) (Choi et al., 1989; Roughley and White, 1989). Notably, biglycan is also present in a non-proteoglycan form in extracts of human articular cartilage and intervertebral disc. The unglycanated form of biglycan is found only in a small proportion in newborn cartilage and has a wider abundance in adults. In contrast, the closely related decorin exists only in its proteoglycan form at all ages (Roughley et al., 1993).

Through either the protein core or GAGs, biglycan is able to interact with various ECM components such as collagen types I, II, III, and VI or elastin, contributing to the organization and stabilization of the matrix (Douglas et al., 2006; Reinboth et al., 2002; Schonherr et al., 1995; Wiberg et al., 2001; Wiberg et al., 2002; Wiberg et al., 2003). Consequently, biglycan was considered for long time only as a quiescent ECM derived-molecule. However, the last decade of research has brought biglycan to light as a bioactive molecule with key roles in signaling. In this capacity, biglycan interacts with bone morphogenic protein (BMP)-2, -4, -6 and chordin (Chen et al., 2004; Miguez et al., 2011; Moreno et al., 2005), transforming growth factor (TGF)-β (Hildebrand et al., 1994), tumor necrosis factor (TNF)-α (Tufvesson and Westergren-Thorsson, 2002), Wnt-1-induced secreted protein 1 (WISP1) (Desnoyers et al., 2001) and vascular endothelial growth factor A (VEGF) (Berendsen et al., 2014). Biglycan can also serve as a ligand for different receptors or complexes such as Toll-like receptors (TLRs) 2 and 4 (Schaefer et al., 2005), activin like kinase 6 (ALK6), purinergic receptors $P2X_7/P2X_4$ (Babelova et al., 2009), the class A scavenger receptor (SR-A) (Santiago-Garcia et al., 2003), low-density lipoprotein receptor-related protein 6 (LRP6) (Berendsen et al., 2011), MuSK (Amenta et al., 2012), and dystrophin-glycoprotein complex (Bowe et al., 2000; Rafii et al., 2006).

Given the magnitude of the biglycan interactome, it is not surprising that this SLRP leads to organ-specific effects encompassing renal diseases (Kuroda et al., 2004; Moreth et al., 2010; Moreth et al., 2014; Schaefer et al., 2004; Stokes et al., 2000), bone formation and healing (Berendsen et al., 2014; Chen et al., 2004; Desnoyers et al., 2001; Miguez et al., 2014), muscular dystrophy (Bowe et al., 2000; Rafii et al., 2006), control of neuromuscular synapses (Amenta et al., 2012) and autoimmune perimyocarditis (Popovic et al., 2011). In addition, biglycan has been recently linked to cancer cell proliferation (Hu et al., 2014; Niedworok et al., 2013). It is assumed that mainly the soluble form of biglycan, released from the matrix via partial proteolytic processing during tissue injury, binds and induces signaling through different receptors (Anders and Schaefer, 2014; Moreth et al., 2010; Moreth et al., 2014; Nastase et al., 2014; Zeng-Brouwers et al., 2014). Thus, selective targeting of soluble biglycan could be accomplished without disrupting tissue homeostasis in several pathological conditions. In this review we will focus on the role of circulating biglycan in the aggravation of different renal diseases, will address the possibility of using soluble biglycan as a biomarker in progressive renal pathologies, and critically assess the importance and the modalities of neutralizing matrix-unbound biglycan in therapeutics.

2. Biglycan expression and signaling in the kidney

Biglycan is expressed as a component of the ECM in all organs (Bianco et al., 1990; Ungefroren et al., 1998), a feature it shares with decorin (Iozzo, 1998). However, the expression patterns of these two SLRPs are not overlapping, suggesting different roles in pathology (Stokes et al., 2000).

2.1. Distribution and regulation of biglycan in the kidney

In normal adult rat kidneys, biglycan is found in collecting ducts, distal tubules and vessel walls as well as within the glomeruli, mainly associated with capillaries, but also within the mesangium and around podocytes (Schaefer et al., 1998). In contrast, decorin is expressed only in trace amounts in the mesangium (Merline et al., 2009a; Schaefer et al., 1998).

In human renal cortex, biglycan is expressed mainly in the tubulointerstitium, in the peritubular mesenchymal cells and distal tubules as well as in endothelial and weaker in mesangial and epithelial cells of the glomeruli (Schaefer et al., 2000). Notably, *in situ* hybridization studies have shown that endothelial cells are the main source of *BGN* (Schaefer et al., 2000). In the tubulointerstitium *BGN* mRNA is found in peritubular fibroblasts, distal tubules, and collecting ducts as well as in endothelial cells, smooth muscle cells, and the adventitia of blood vessels (Schaefer et al., 2000).

Biglycan overexpression is a common feature in the progression of several renal pathologies (see Table 1 and Section 4). Early studies demonstrated that the expression of biglycan in different types of cells in the kidney can be increased by growth factors or