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Tolloid-like Proteinases
Orchestrate Extracellular Matrix Formation

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Purification of osteogenic activity initially isolated bone morphogenetic proteins (BMPs) 1 through 7 from bone extracts.1 BMPs 2 through 7 are members of the TGF-β superfamily, and on the basis of sequence homology, more than 30 TGF-β-like BMPs have been identified.2 In contrast, despite its name, BMP1 has pro-collagen C-proteinase (PCP) activity responsible for removing C-propeptides from procollagen types I through III.3 Consequently, BMP1 is the prototype of a group of proteinases, referred to as Tolloid (TLD)-like proteinases, that are conserved in species ranging from Drosophila to humans.4

Four mammalian TLD-like proteinases have been identified so far, which include BMP1, mammalian TLD (mTLD; also called BMP1-3) that is encoded by alternatively spliced mRNA produced by the BMP1 gene, and mammalian TLD-like 1 and 2. BMP1 null mice, which lack BMP1 and mTLD, show a mild dorsal-ventral patterning defect and abnormal collagen fibrillogenesis and bone formation,4 possibly as a result of failure to cleave a BMP antagonist, Chordin, and deficient extracellular matrix (ECM) formation, respectively.

Collagen types I through III are synthesized as procollagens with N- and C-terminal propeptides. Removal of these pro-peptides by the PCP activity of TLD-like proteinases is essential for their maturation through self-assembly into fibrillar collagens.5 In addition, TLD-like proteinases process noncollagenous ECM components such as perlecan and small leucine-rich proteoglycans (SLRPs). Perlecan is a large proteoglycan that is a major component of basement membranes. The C-terminal motif of Perlecan promotes apoptosis resistance in fibroblasts through interactions with α2β1 integrins when removed from perlecan by TLD-like proteinases.6 SLRPs such as biglycan and decorin are synthesized as precursors,7 and biglycan and decorin are processed by TLD-like proteinases into the mature proteoglycans.8,9

Although biglycan and decorin modulate collagen fibrillogenesis as well as the bioactivity of various members of the TGF-β superfamily,6 their processing is thought to be another mechanism by which TLD-like proteinases regulate ECM formation. Because biglycan is located in the pericellular ECM, whereas decorin is more abundant in the interstitial ECM, biglycan may be responsible for the sequestration of TGF-β to cell-surface receptors, promoting ECM formation. In contrast, decorin may sequester TGF-β away from the cell surface to inhibit its receptor binding, suppressing ECM formation.6

TGF-β induces a net increase in ECM formation in development, tissue repair, and fibrosis by inhibiting expression of ECM-degrading proteinases. TGF-β also increases expression of ECM components, lysyl oxidase, and proteinases such as TLD-like proteinases that process ECM components and lysyl oxidase into their mature forms.2 Most TGF-β is secreted as a large latent complex (LLC), composed of latent TGF-β-bonding protein (LTBP), and small latent complex (SLC), formed by TGF-β and latency associated peptide (LAP).9 SLC is disulfide-bonded to LTBP through LAP, and LLC is covalently bound to the ECM by LTBP. TGF-β can be activated through removing LAP by metalloproteinases (MMPs) or through interactions with thrombospondin or integrins. Although TLD-like proteinases do not remove LAP, they cleave LTBP to liberate LLCs from the ECM,9 rendering LAP susceptible to cleavage by MMPS with subsequent TGF-β activation. TGF-β activation by TLD-like proteinases and MMPS can also be upregulated by TGF-β. In addition, TGF-β can induce expression of probiglycan, which is then activated by TLD-like proteinases and promotes TGF-β’s binding to their receptors. Therefore, TLD-like proteinases complete a positive feedback loop in ECM formation.

JASN, Grgurevic et al.10 report that BMP1-3/mTLD is detectable in plasma of patients with chronic kidney disease (CKD), which suggests for the first time a profibrotic role for BMP1-3/mTLD in CKD. The authors found that administration of recombinant BMP1-3/mTLD increased whereas its neutralizing antibody reduced renal fibrosis in rats with subtotal renal ablation.
This supports their hypothesis that BMP1-3/mTLD plays a pivotal role in renal fibrosis. In addition, in both cultured kidney cells and remnant kidneys, BMP1-3/mTLD administration increases the transcription of profibrotic genes encoding procollagen type I, TGF-β1, and β-catenin and decreases the transcription of an antifibrotic gene encoding BMP7.

The authors attributed these molecular events to a decrease in decorin expression by BMP1-3/mTLD’s signaling through integrin β1. However, mechanistic interactions between BMP1-3/mTLD and integrin β1 remain to be clarified. As stated already, prodecorin is processed by TLD-like proteinases into the mature form that sequesters TGF-β in the interstitial ECM to suppress ECM formation.6 However, in this study, BMP1-3/mTLD decreases prodecorin expression in the kidney so that BMP1-3/mTLD facilitates the expression of renal fibrosis.

The integrins are a large family of adhesion molecules that are essential for the regulation of cell growth and function and play key roles in a diverse range of diseases, including organ fibrosis.11,12 So far, pharmacologic inhibitors of only a small number of integrins have received approval because of insufficient, vague effects on target cells and nonnegligible adverse effects.11 Therefore, the alternative of targeting BMP1-3/mTLD, one of the ligands to integrin β1, seems a better candidate for antifibrotic strategy. Although the authors used neutralizing anti–BMP1-3 antibody to block this interaction directly,10 some modulators of TLD-like proteinase activity that also may be applicable as therapeutic tools have been reported. The glycoprotein procollagen C-proteinase enhancer 1 and secreted Frizzle-related protein 2 (sFRP2) increase the PCP activity of TLD-like proteinases.13,14 In fact, the level of cardiac fibrosis is markedly reduced in Sfrp2 null mice subjected to myocardial infarction.14 Cellular fibronectin also positively regulates BMP1-processing activity against procollagen type I, Chor-din, and probiglycan.15 In contrast, α2-microglobulin entrap and irreversibly inhibits proteinases, including TLD-like proteinases, which cleave bait regions within α2-microglobulin to cause a conformational change.16

Recombinant α2-microglobulin with modified bait regions proved to be an efficient TLD-like proteinase inhibitor16 that may be further optimized for specifically inhibiting BMP1-3/mTLD. Because α2-microglobulin circulates at high levels in the blood, TLD-like proteinases once activated in tissues and leaked into the blood seem to be immediately entrapped and inactivated. Although the authors presume a profibrotic action of circulating BMP1-3/mTLD as a humoral factor in this study,10 the role of BMP1-3/mTLD produced as a local factor needs to be validated because the authors identified this protein in normal and diseased kidney tissues.

A number of research achievements that support the notion that TLD-like proteinases can conduct a variety of components to orchestrate ECM formation have been reported. Although further studies are necessary before its clinical application, Grgurevic et al.10 introduce the BMP1-3/mTLD-integrin β1 interaction as a brand new factor promoting renal fibrosis and reveal its potential as a promising therapeutic target for CKD.

DISCLOSURES

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