Published in final edited form as:

Exp Eye Res. 2006 January ; 82(1): 3–4. doi:10.1016/j.exer.2005.08.012.

Focus on Molecules: Lumican

Winston W.-Y. Kao^{a,*}, James L. Funderburgh^b, Ying Xia^{a,c}, Chia-Yang Liu^a, and Gary W. Conrad^d

^a Department of Ophthalmology, University of Cincinnati, Cincinnati, OH, USA

^b Department of Ophthalmology, University of Pittsburgh, Pittsburgh, PA, USA

^c Department of Environmental Health, University of Cincinnati, Cincinnati, OH, USA

^d Division of Biology, Kansas State University, Manhattan, KS, USA

Keywords

lumican; matrikine; keratocan; SLRPs; gene expression; epithelium-mesenchyme transition; gene targeting; cornea

1. Structure

Lumican (NM_002345): A keratan sulfate proteoglycan in corneal stroma, lumican is a member of the family of small leucine rich proteoglycans (SLRPs), e.g. keratocan, mimecan, decorin, fibromodulin, biglycan, and PRELP.

Like other SLRPs, lumican has a molecular weight of ~40 kDa comprised of four major domains: (1) a signal peptide of 16 residues; (2) a negatively charged *N*-terminal domain containing sulfated tyrosine and disulfide bond(s); (3) tandem leucine-rich repeats (LXXLXLXXNXLSSL)₁₀ mediating binding to other extracellular components, e.g. collagen; (4) a carboxyl terminal domain of 50 amino acids containing two conserved cysteines 32 residues apart.

2. Function

Lumican plays an important role in regulating stromal collagen matrix assembly as exemplified by corneal opacity, skin fragility, abnormally large collagen fibril diameters, and disorganized interfibrillar spacing in lumican null mice. It has been suggested a key role for lumican in the posterior stroma in maintaining normal fibril architecture, most likely by regulating fibril assembly and maintaining optimal KS content required for transparency (Chakravarti et al., 2000). Increasing evidence suggests that lumican may also serve as a regulatory molecule of several cellular functions (Kao and Liu, 2002).

3. Disease involvement

Many ECM molecules have been shown to exhibit biological functions beyond that of their defined structural roles. These functions include regulations of cell proliferation, apoptosis, and differentiation. Such functions are often mediated by specific amino acid sequences (exposed surface epitopes or peptides released by after proteolysis) that bind cell surface receptors, e.g. integrins and/or growth factor receptors, inducing intracellular signalling. These

*Corresponding author. Tel.: +1 513 558 2802; fax: +1 513 558 3108. winston.kao@uc.edu (W.W.-Y. Kao).

bioactive sequences in matrix molecules have been termed matrikines. Ever increasing evidence indicates that members of SLRP family also have the characteristics of matrikines. For example, decorin is a SLRP protein which shares similar functions with lumican. Analogous to the lumican-null mice; decorin-null mice also exhibit skin fragility and impaired collagen fibrillogenesis. Decorin has also been shown to be involved in cell proliferation, migration and induction protein synthesis. Thereby, decorin has been suggested as a matrikine and shown capable of initiating signalling pathways, such as the ERK1/ERK2 pathways mediated via receptor tyrosine kinases.

More recently studies have shown lumican involvement in cell migration and proliferation during embryonic development, wound healing, and inflammatory responses. These observations suggest that lumican, like decorin, may have multiple functions in the maintenance of tissue homeostasis and function as a matrikine.

In normal unwounded corneas, lumican expression in cornea is limited to stromal keratocytes. These molecules are glycanated with keratan sulfate. In healing wounds, a non-glycan form of lumican is produced. Previous studies of epithelium wound healing demonstrated transient lumican expression by migrating corneal epithelial cells in Lum^{+/+} mice and delayed healing in Lum^{-/-} mice. These observations suggest lumican may have a role in modulating wound healing depending on its state of glycanation. This hypothesis was confirmed by showing that anti-lumican antibody retarded corneal epithelial wound closure in organ-cultured mouse eyes. Furthermore, the addition of human amniotic lumican to the medium promoted epithelial cell proliferation during the healing of epithelium debridement of organ cultured Lum^{+/+} and Lum^{-/-} mouse eyes. In addition, we recently observed that the infiltration of PMNs into the stroma of injured corneas is significantly retarded in Lum^{-/-} mice. Finally, we have shown that lumican is capable of facilitating keratocyte migration in an in vitro cell migration assay. These observations support the notion that lumican modulates cell adhesion, migration and proliferation, thus contributing to corneal epithelial wound healing.

Modulation of cell behaviour by lumican is further supported by the observation that following cataract surgery, opaque scar tissues containing fibrous collagen types and lumican, are formed by lens epithelial cells undergoing proliferation and epithelium-mesenchyme transition (EMT). This transition is characterized by expression of α -smooth muscle actin (α -SMA) by transformed lens epithelial cells. Interestingly, expression of lumican by injured lens epithelial cells precedes the expression of type I collagen and α -SMA. Lumican-null mouse lens epithelial cells showed decreased and delayed α -smooth muscle actin expression and delayed EMT induction by TGF β -2 in vitro. These observations lend support to the hypothesis that lumican modulates EMT of mouse lens cells.

A role for lumican has been suggested in growth and metastasis of cancers, e.g. breast, colorectal and pancreatic tumor, and benign prostatic hyperplasia. The expression of lumican by cervical carcinoma squamous epithelial cells has also been reported. However, the role of lumican in tumorigenesis remains elusive, because it has recently been demonstrated that over-expression of lumican suppresses transformation induced by v-src and v-K-ras. These contradictory observations may be explained by the possibility that lumican receptor(s) mediate different signalling transduction pathways in a cell type-specific manner. A cell surface receptor for non-glycanated lumican was identified in macrophages, which did not recognize the proteoglycan form of the molecule (Funderburgh et al., 1997).

We recently found that lumican matrikine activity may be responsible for differences in the corneal phenotypes of Lum^{-/-} and Kera^{-/-} mice. The former have thin and cloudy corneas with a disarrayed stromal matrix, whereas the latter have thin but transparent corneas with little perturbation in stromal organization. We showed decreased keratocan expression in the

Lum^{+/-} and a further decrease in the Lum^{-/-} mice compared to wild-type Lum^{+/+} littermates. This suggests the corneal phenotypes (opacity, perturbed fibrillogenesis and thin corneal stroma) in the lumican knockout animals are not solely the result of an absence of lumican expression, but also a result of concomitant decrease in keratocan expression in the stroma of Lum^{-/-} mice. This suggests direct regulation of keratocan expression in response to lumican abundance. To examine this possibility, we performed intrastromal injection of lumican cDNA into lumican-null animals, finding an increase in expression of both lumican and keratocan. The mechanism by which lumican can regulate keratocan expression was explored using an in vivo promoter assay where the presence of lumican was able to significantly increase keratocan promoter activity in Lum^{-/-} mice. Furthermore, incubation with lumican siRNA caused decreases in lumican, keratocan, and aldehyde dehydrogenase synthesis by cultured bovine keratocytes in vitro. These observations demonstrate lumican indeed regulates keratocan expression by keratocytes in vivo and in vitro (Carlson et al., 2005).

4. Future studies

To elucidate the structure/function relationship of lumican, it is imperative to identify and characterize the lumican regulatory domain capable of modulating keratocan expression and other cellular functions (the matrikine domain). Identification of such a domain may be useful for designing therapeutic reagents in treatment of diseases involving lumican, e.g. wound healing, cancer. The signaling mechanism behind these novel functions of lumican is very likely via a cell surface receptors. Access of the lumican matrikine domain to such receptors, however, may be mediated by the state of glycosylation of this protein. Identification and characterization of cell surface lumican receptors is an important next step in elucidating the molecular mechanisms of lumican matrikine function. (Fig. 1)

Acknowledgments

Support in part by grants NIH EY 11845 (WWYK), EY 09368 (JLF), EY 12486 (C-YL), EY 015227 (YX), EY 00952 (GWC), Research to Prevent Blindness, Inc., and Ohio Lions Eye Research Foundation.

References

- Carlson EC, Liu CY, Chikama T, Hayashi Y, Kao CW, Birk DE, Funderburgh JL, Jester JV, Kao WW. Keratocan, a cornea-specific keratan sulfate proteoglycan, is regulated by lumican. *J Biol Chem* 2005;280:25541–25547. [PubMed: 15849191]
- Chakravarti S, Petroll WM, Hassell JR, Jester JV, Lass JH, Paul J, Birk DE. Corneal opacity in lumican-null mice: defects in collagen fibril structure and packing in the posterior stroma. *Invest Ophthalmol Vis Sci* 2000;41:3365–3373. [PubMed: 11006226]
- Funderburgh JL, Mitschler RR, Funderburgh ML, Roth MR, Chapes SK, Conrad GW. Macrophage receptors for lumican. A corneal keratan sulfate proteoglycan. *Invest Ophthalmol Vis Sci* 1997;38:1159–1167. [PubMed: 9152235]
- Kao WW, Liu CY. Roles of lumican and keratocan on corneal transparency. *Glycoconj J* 2002;19:275–285. [PubMed: 12975606]

Fig. 1.

Molecular model of lumican 3D structure and lumican functions mediated via cell surface receptor Lumican 3D model was created using Deep View software (<http://swissmodel.expasy.org/spdbv>) based on homology with decorin crystal structure. Model shows bovine lumican from Cys41 to C-terminus. Cys residues are yellow. Beta-sheet structures are red. Asn proposed to be modified with *N*-linked oligosaccharides (J. Biol. Chem. 272:28089) are green. Top view imposes hybrid-type *N*-linked oligosaccharide at modified Asn moieties. Lumican binds to its receptor and transduces signals leading to expression of genes involved in cell proliferation, migration, differentiation and epithelium-mesenchyme transition (EMT).