—Review—

The Role of Small Leucine-rich Proteoglycan (SLRP) Family in Pathological Lesions and Cancer Cell Growth

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Abstract

The roles of lumican, a member of the small-leucine-rich-proteoglycan (SLRP) family, in pathological fibrosis, cancer tissues and tumor cell growth were reviewed.

Lumican is predominantly localized in the areas of pathological fibrosis including the thickened intima of human coronary arteries, ischemic and reperfused hearts, and acute pancreatitis and chronic pancreatitis (CP)-like lesions adjacent to pancreatic cancer nests. In these lesions, lumican mRNA and protein were transiently and ectopically overexpressed in most of the vascular smooth muscle cells (VSMCs) that migrated into the thickened intima, myocardial cells adjacent to an ischemic lesion, acinar cells, islet cells and fibroblasts of pathological pancreatic tissues. The low expression level of lumican in breast cancer is associated with rapid progression and poor survival. Lumican mRNA in breast cancer is overexpressed in fibroblasts adjacent to cancer cells but not in cancer cells. Furthermore, the high expression level of lumican is associated with a high pathological tumor grade, a low estrogen receptor level in the cancer tissues, and young age of patients. The suppression of lumican expression in culture cells induces their cell growth. Lumican-transfected tumor cells are characterized by a strong suppression of their anchorage-independent growth and capacity of invasion. Lumican significantly suppressed subcutaneous tumor formation in syngenic mice, with a concomitant decrease in cyclin D1 expression level, and induced and/or enhanced the apoptosis of these cells. The autocrine mechanism in cancer cells and the paracrine mechanism in cancer cells and fibroblasts via transforming growth factor (TGF)-beta and Smad signals may play important roles in the regulation of tumor growth by SLRPs.

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Key words: small-leucine rich proteoglycan, lumican, cancer, cell growth

Introduction

Proteoglycans are macromolecules consisting of a core protein and glycosaminoglycan side chains, and are widely distributed in stromal tissues in the human body. Proteoglycans are considered to regulate the water balance of the extracellular matrix; influence tissue biomechanics; facilitate cellular adhesion, proliferation, and migration; and modulate growth factors and cytokine activities[1–3]. The extracellular matrix of a cancer stroma is composed of different types of collagens, glycoproteins (including fibronectin, tenascin and thrombospondin), hyaluronan and proteoglycans. During the proliferation of a primary tumor or the

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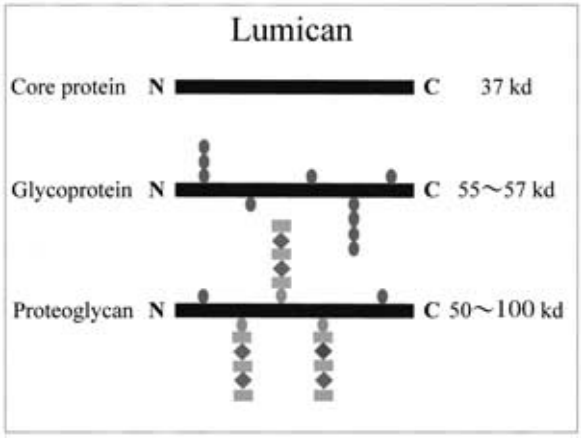

Fig. 1 The structures of Proteoglycan (Lumican)
Lumican contains three isoforms as its core protein, glycoprotein and proteoglycan. The glycoprotein form of lumican has mono or polysaccharides (blue ovals), and the proteoglycan form has glycosaminoglycan side chains (rectangles and lozenges).

establishment of metastatic foci, there is a continuous remodeling of the extracellular matrix characterized by various degrees of biosynthesis and degradation. In cancer cell growth, most cancer cell types exhibit various grades of fibrosis around cancer nests. These fibrous tissues mainly consist of collagen fibers and fibroblasts and are considered to affect cancer cell proliferation, migration and spread[2].

Proteoglycans belonging to the small-leucine-rich-proteoglycan (SLRP) family have relatively small molecular sizes with core proteins of approximately 40 kD, and possess 6～10 leucine-rich repeating units between the flanking cystein-rich disulfide-bonded domains at the N and C termini of the core protein[4–6] (**Fig. 1**). These SLRPs are composed of collagen fibrils in the extracellular matrix and may be involved in the maintenance of the tissue stromal structure. They have been reported to have an important role in cell migration, cell proliferation, tissue repair and tumor growth, in addition to their extracellular matrix functions in tissue hydration and collagen fibrillogenesis[7]. These SLRP members include keratocan, mimecan, decorin, biglycan, fibromodulin, epiphycan, osteoadherin and lumican[5,6,8–12]. The recent generation of knock-out mice has proven the role of these small proteoglycans in the regulation of the formation of collagen fibrillar network in the cornea and other tissues. The null mutations of SLRP family proteins, namely, decorin, biglycan, fibromodulin and lumican, are manifested by the malfunctions of connective tissues associated with an abnormal extracellular matrix, that is, fragile skin, cloudy cornea, and thick collagen fibrils[13]. Biglycan and decorin were reported to have one and two chondroitin/dermatan sulphate chains, respectively, attached to the core protein. Lumican was shown to be substituted by keratan sulphate in the cornea or by a nonsulfated polylactosamine chain in a tumor stroma. Data concerning skin lumican are few, although it was shown that, in the dermis, lumican is present in a glycoprotein form and may control fibrillogenesis. During tendon development, lumican and fibromodulin both influence the initial assembly of intermediates and the entry into collagen fibril growth, while fibromodulin facilitates the progression of the growth process leading to the formation of mature fibrils[14]. Cultured vascular endothelial cells start to express decorin after the formation of tube like structures and also up-regulate biglycan expression during the repair of injury. In the present report, I would like to focus on lumican. Lumican was reported to colocalize with fibrillar collagens in a corneal stroma and to regulate the assembly and diameter of collagen fibers and interfibrillar spacing[4]. The human lumican protein has 338 amino acids, including a putative 18-residue signal peptide; its gene is located on chromosome 12q21.3-q22 and the central region of the molecule possesses four asparagine residues capable of participating in N-linked glycosylation[15,16]. In the adult cornea, lumican exists as a proteoglycan; however, in the embryonic cornea, lumican was reported to be localized as a glycoprotein. The change from a glycoprotein to a proteoglycan may have an important role in corneal transparency[17].

The lumican gene does not contain a conventional TATA box; rather, a unique TATCA box is present upstream of the transcription initiation site[15]. However, transcription factors that induce lumican expression have not been elucidated to date. Lumican mRNA was reported to be expressed at high levels in the human cornea, skeletal muscle,

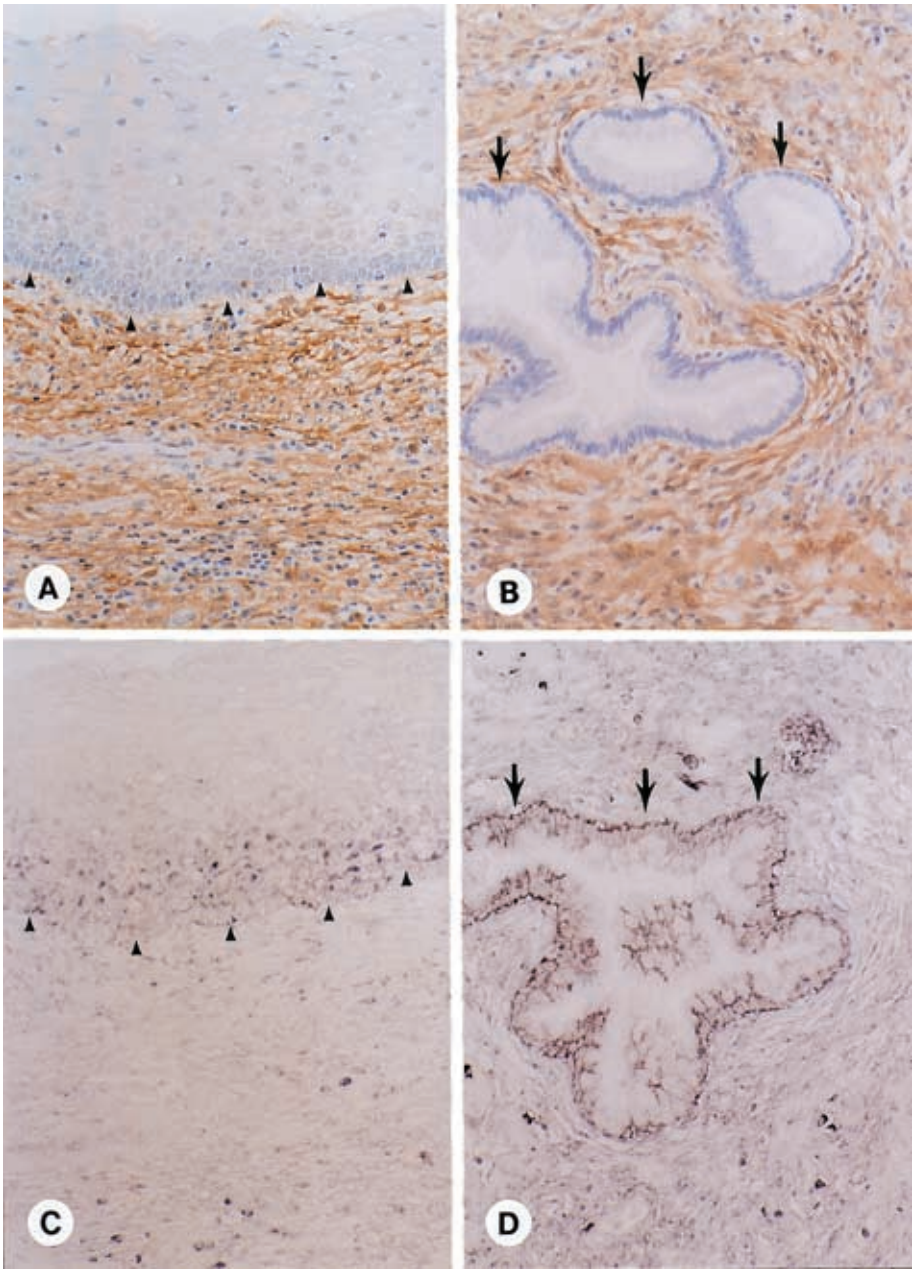

Fig. 2 Protein and mRNA of lumican expression in uterine cervical tissue close to cancer cells
In cervical tissues close to cancer cells, lumican protein was prominently localized in stromal tissues (A, B), but not in squamous (A, **arrowheads**) or ductal cells (B, **arrows**). In contrast, lumican mRNA was expressed in squamous (C, **arrowheads**) and ductal cells (D, **arrows**) close to cancer cells in serial sections. **A**, **B**; immunohistochemistry, **C**, **D**; in situ hybridization. (Ref. 21)

kidneys, placenta, heart, intervertebral discs, blood vessels, uterus and pancreas, but at low levels in the brain, lungs and liver[16,18–24]. Mice that are homozygous for a null mutation in lumican exhibit corneal opacification and skin laxity due to inhomogeneous collagen bundles[14,25–29]. Recently, lumican expression has been studied in several pathological conditions including tumor tissues. In corneal injury, the corneal epithelium ectopically and transiently expresses lumican during the early phase of wound healing, suggesting a potential function unrelated to collagen fibrillogenesis, for example, the modulation

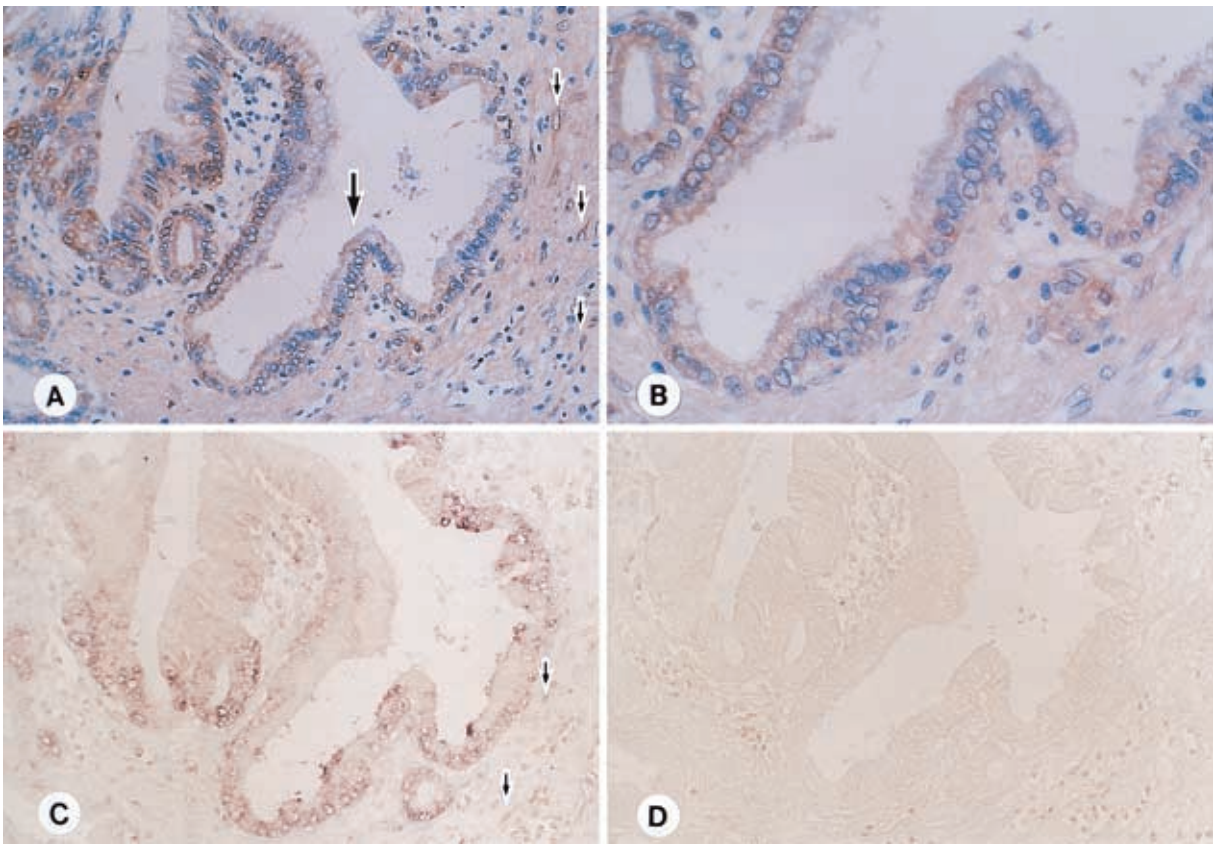

Fig. 3 Protein and mRNA expression of lumican in pancreatic cancer tissues
In pancreatic cancer tissues (A, B), lumican protein was prominently localized in cancer cells (**arrow**) and fibroblasts adjacent to cancer cells (**small arrows**). Strong lumican mRNA signals are expressed in cancer cells and fibroblasts (C; Antisense, D; Sense). **A**, **B**; immunohistochemistry, **C**,**D**; in situ hybridization. (Reproduced with permission of Copyright John Wiley and Sons, Ref. 34)

of epithelial cell adhesion or migration. Furthermore, the repair of corneal injury in lumican (−) / (−) mice is significantly delayed compared with lumican (+) / (−) mice[30]. In response to injury, mouse lens epithelial cells up-regulate lumican and α-smooth muscle actin (SMA)[31]. In different types of cancer, lumican is overexpressed in fibroblasts or fibroblast-like cells adjacent to infiltrating tumor cells.

Lumican in Pathological Fibrosis

We previously reported that lumican is predominantly localized in the areas of pathological fibrosis including the thickened intima of human coronary arteries, ischemic and reperfused hearts, and acute pancreatitis and chronic pancreatitis (CP)-like lesions close to pancreatic cancer nests[32–35]. The lumican protein exists in the core protein and proteoglycan forms in a normal rat heart. The expression level of lumican in the proteoglycan form increases, and that in the glycoprotein form is newly detected in an ischemic and reperfused rat heart. In a normal rat heart, lumican is expressed at low levels in the collagen fibers of the perivascular area, but it is at high levels in many capillary endothelial cells in ischemic lesions. A few myocardial cells close to an ischemic lesion express lumican mRNA. Lumican is considered to play an important role in the fibrillogenesis of the ischemic and reperfused rat heart. Moreover, the lumican protein and its mRNA were expressed in a small number of vascular smooth muscle cells (VSMCs) in a normal coronary artery. In atherosclerosis, the lumican was overexpressed in most of VSMCs that migrated into the thickened intima. In a normal human pancreas, a low expression level of lumican protein is observed

only in the alpha cells of islets. In contrast, lumican is transiently synthesized by acinar cells and fibroblasts in acute pancreatitis. The lumican protein synthesized by acinar cells, islet cells, and fibroblasts may contribute to an immature and a transient fibrosis in acute pancreatitis. In pancreatic cancer tissues, lumican mRNA is highly expressed in acinar cells, islet cells and proliferating fibroblasts in CP-like lesions which indicate a dense and progressive fibrosis adjacent to cancer nests. Lumican and decorin as abundant small leucine-rich proteoglycans in a breast stroma have been demonstrated to show an altered expression level after breast tumorigenesis[36]. Lumican is a major SLRP of breast carcinoma and up-regulated in the tumor zone in comparison with adjacent normal tissues. A decreased expression level of lumican is associated with a poor prognosis of invasive carcinoma[36,37]. A recent study has revealed that lumican is predominantly localized in the hyaline, chondroid and fibrous area of a pleomorphic adenoma in the salivary glands[38]. These findings suggest that newly synthesized lumican and SLRPs proteins may contribute to pathological fibrosis in various diseases.

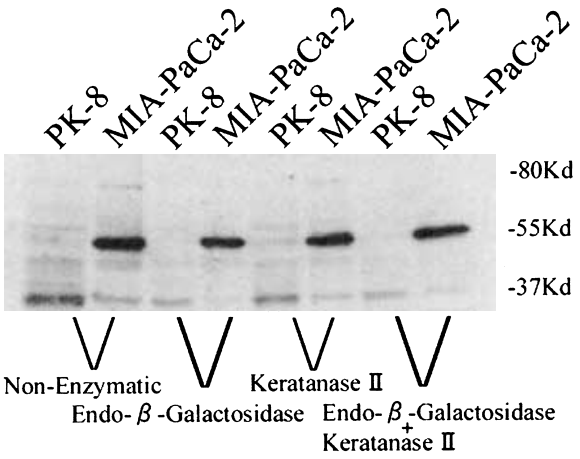

Fig. 4 Different glycosylated types of lumican in cancer cell lines detected by enzymatic digestion. The 80 kD lumican in MIA-PaCa-2 was digested by endo-β-galactosidase, indicating that lumican possesses no-sulphated or poorly sulphated polylactosamine chains. For both PK-8 and MIA-PaCa-2 cells, endo-β-galactosidase is more effective than keratanase II in digesting the variable sizes of lumican, except for the 37 kD lumican. (Reproduced with permission of Copyright John Wiley and Sons, Ref. 34)

Lumican Expression in Cancer Tissues

In breast cancer tissues, lumican mRNA is overexpressed in fibroblasts adjacent to cancer cells but not in cancer cells[36,37]. In contrast, the expression levels of other SLRPs including decorin, biglycan and fibromodulin do not increase in breast cancer tissues pathologically classified as adenocarcinoma. Furthermore, the high expression level of lumican is associated with a high pathological tumor grade, low estrogen receptor levels in the cancer tissue, and young age of patients. The low expression levels of lumican in breast cancer are associated with a rapid progression and a poor survival[39]. In contrast, in pancreatic adenocarcinoma, we previously reported that lumican is localized in human pancreatic cancer cells, and the cancer cells themselves synthesize lumican mRNA and different glycosylated types of its protein[34] (**Fig. 2, 3**). Furthermore, human colorectal cancer cells also synthesize lumican mRNA and its protein in eight of 12 colorectal cancer cases[40]. In cervical squamous cell carcinomas, lumican is synthesized by cancer cells and is predominantly localized in cancer cells at the periphery of the nests of cancer cells[21]. Lumican and its mRNA were not detected in squamous epithelial cells of a normal uterine cervix. In contrast, lumican mRNA was highly expressed in noncancerous squamous and ductal cells adjacent to cancer cells, but its protein was not detected in these cells (**Fig. 4**). It was reported that lumican is expressed ectopically and transiently in the corneal squamous epithelium during the early phase of corneal wound healing. In addition, the lumican protein changed its form from a proteoglycan to a glycoprotein in the embryonic cornea[17]. These findings indicate that lumican is not synthesized by normal squamous epithelial cells, but is ectopically synthesized by squamous and ductal epithelial cells close to cancer cells. Lumican mRNA is ectopically transcribed in squamous and ductal cells adjacent to cancer cells, but it may not be translated to its protein or efficiently excreted to stromal tissues. Some growth

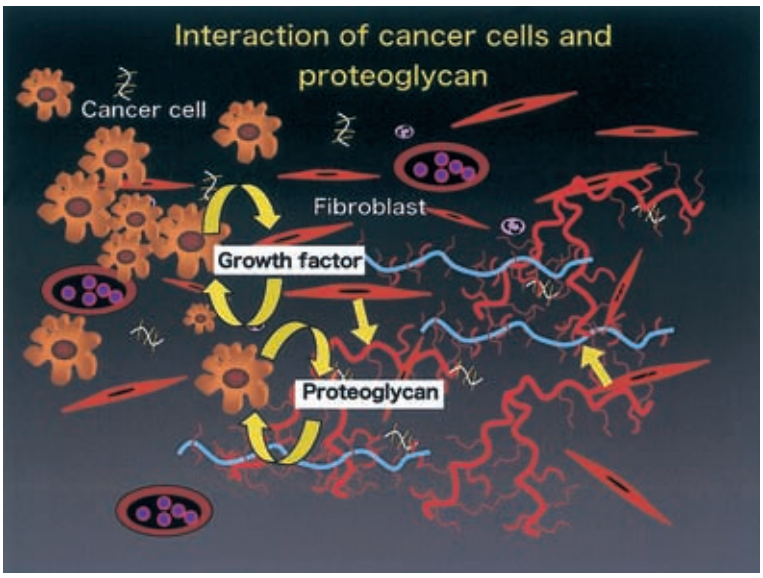

Fig. 5 Interaction of cancer cells and proteoglycan
The autocrine mechanism in cancer cells and the paracrine mechanism in cancer cells and stromal cells via growth factors and proteoglycans are considered to play very important roles in the regulation of tumor growth.

factors or cytokines produced by pancreatic and cervical cancer cells may stimulate the expression of the lumican protein in ductal or squamous epithelial cells adjacent to cancer cells. These observations in cancer and normal tissues suggest that lumican may contribute to the biological behavior and growth potential of certain cancer cells that are of epithelial origin (**Fig. 5**).

Role of Lumican in Tumor Cell Growth

Syndecan-1, a member of the heparan sulfate proteoglycans (HSPGs) family, is down-regulated in many epithelial cancers and in premalignant lesions of the oral mucosa and uterine cervix; its loss is an early genetic event contributing to tumor growth. The loss of syndecan-1 correlates with a short survival period in squamous cell carcinoma of the head and neck, laryngeal cancer and malignant mesothelioma. Decorin is a member of the SLRP family and its roles in cancer cell growth have been extensively examined[41,42]. Human colon cancer cells stably transfected with decorin cDNA exhibit a marked suppression of the transformed phenotype: the cells have a reduced growth rate in vitro, form small colonies in soft agar, and do not generate tumors in scid/scid mice[43]. Decorin interacts with the epidermal growth factor receptor (EGFR) triggering a signaling cascade that leads to an increase in endogenous p21 expression level and growth suppression. Decorin causes a sustained down-regulation of EGFR[42]. Decorin expressed in oral cancer cells may have lost its abilities to inhibit TGF-beta signaling and activate EGFR signaling pathways because of such an aberrant nuclear localization, resulting in a major dysfunction of an otherwise natural extracellular antagonist of TGF-beta and a putative tumor suppressor protein[44]. Lumican was reported to suppress the transformation induced by v-src and v-K-ras in primary rat embryonic fibroblasts, and tumorigenicity in nude mice induced by these oncogenes is also suppressed in these lumican-expressing clones[45]. Recently, we have reported that a decreased lumican expression level in HEK 293 cells induces the growth of these cells[46]. Lumican-transfected B16F1 mouse melanoma cells are characterized by a strong suppression of their anchorage-independent proliferation in agarose gel and capacity to invade the extracellular matrix gel. After subcutaneous injections of transfected B16F1 cells in syngenic mice, lumican expression

significantly suppresses subcutaneous tumor formation in vivo, with a concomitant decrease in cyclin D1 expression level. Furthermore, lumican induced and/or enhanced the apoptosis of B16F1 cells[47]. These lines of evidence suggest that lumican is involved in the control of cancer cell growth and invasion and may be considered, similar to decorin, as an anti-tumor factor. Decorin has been implicated in the negative regulation of tumor cell proliferation directly or via interactions with TGF-beta and its signal transduction mechanism. The isoforms of TGF-beta interact with other members of the SLRP family, such as biglycan and fibromodulin.

The mechanism underlying the tumor growth regulation of cancer cells by lumican is not well understood. A receptor for the lumican protein in macrophages was reported, but it has not been cloned yet. These cells bind the low-sulfated glycoprotein form of lumican, but not lumican modified with keratan sulfate chains, suggesting that non- or low-sulfated lumican may provide a scaffold for macrophage infiltration[48]. The autocrine mechanism in cancer cells and the paracrine mechanism in cancer cells and fibroblasts via TGF-beta and Smad signals may play important roles in the regulation of tumor growth such as in the case of decorin[44]. Moreover, it is also noteworthy that Tgfb2 (−/−) mice show an abnormal ocular morphogenesis and their corneal stroma shows a decreased expression level of ECM; for example, the expression levels of lumican, keratocan and collagen I are markedly decreased[49]. Further studies including the use of a recombinant lumican protein or a stable transfectant of the lumican gene may clarify the exact role of lumican in uterine cervical and other cancer cells. Proteoglycans and growth factor activities are considered to be closely related[50,51] (**Fig. 5**). Glypican-1, a HSPG is up-regulated in pancreatic cancer cells and surrounding fibroblasts, and the mitogenic response to pancreatic cancer cells to basic fibroblast growth factor (bFGF) and heparin binding epidermal growth factor is abrogated by the anti-sense attenuation of this HSPG[52]. Lumican may correlate to some growth factor or growth inhibitors.

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