Chapter 3
Lumican, a Small Leucine-Rich Proteoglycan, and Its Biological Function in Tumor Progression

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Abstract Lumican is a member of the small leucine-rich proteoglycan (SLRP) family that was originally discovered in the chick cornea and is found in many other tissues throughout the human body. The SLRP family includes decorin, lumican, biglycan, and fibromodulin and constitutes an abundant component of the extracellular matrix (ECM). Lumican plays a significant role in the ECM as an organizer of collagen, although recent studies demonstrate that lumican also modulates numerous cellular functions including proliferation, migration, and differentiation. The contribution of lumican to cancer progression has been noted in several cancers including breast, colorectal, and pancreatic; however, its precise biologic function is still being uncovered. In cancer, lumican appears to play a context-specific role, where high levels of lumican are associated with a poor prognosis in some cancers and a better prognosis in others. This chapter focuses on the function of lumican in cell biology and the ECM of solid tumors and is aimed at providing insights into molecular mechanisms surrounding lumican and tumor biology.

3.1 Structure, Function, and Regulation of Lumican

Lumican, also known as LDC or SLRR2D, is located at chromosome 12q21.33 (Chakravarti et al. 1995). It is a member of the small leucine-rich proteoglycan (SLRP) family that also includes decorin, biglycan, fibromodulin, keratocan, epiphycan, and osteoglycin. Lumican was originally characterized as one of the major keratan sulfate (KS)-containing proteoglycans and was initially purified by DEAE chromatography from the chick cornea; its distribution is now known to include interstitial collagenous matrices throughout the body (Blochberger et al. 1992a, b). Lumican contains an 18-amino acid signal peptide that facilitates secretion, followed by an N-terminal domain containing four cysteines, a ~40 kDa core

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R.A. Brekken, D. Stupack (eds.), *Extracellular Matrix in Tumor Biology*, Biology of Extracellular Matrix, DOI 10.1007/978-3-319-60907-2_3

protein with a central domain containing 6–10 characteristic leucine repeats (LLRs; Chakravarti et al. 1995), and a C-terminal domain with two cysteines and two LRRs. Lumican also contains four potential N-linked glycosylation sites distributed across the protein. When lumican assumes an arch-shaped tertiary structure (Kajava 1998), these glycosylation sites are presented on the convex surface, while the concave surface binds collagen and facilitates spacing between fibers (Kalamajski and Oldberg 2009; Weber et al. 1996).

Lumican was originally characterized for its role in collagen fibrillogenesis and structural organization (Chakravarti et al. 1998). Deficiencies in lumican result in abnormal collagen fibrillogenesis, which affects connective tissue structure and function (Nikitovic et al. 2008b). In the cornea, lumican not only organizes collagen (Chakravarti et al. 1998) but also influences corneal epithelial wound healing (Liu and Kao 2012). Healing of corneal epithelium of $Lum^{-/-}$ mice was significantly delayed compared to that of wild-type mice, and lumican was ectopically and transiently expressed in the corneal epithelium during the early stages of wound healing. In addition to controlling collagen fibril assembly, lumican participates in the regulation of key biological events including cell proliferation (Ishiwata et al. 2004; Pietraszek et al. 2013), migration (Nikitovic et al. 2008a; Lee et al. 2009; Fullwood et al. 1996), and adhesion (D'Onofrio et al. 2008; Brezillon et al. 2009; Cole and Mccabe 1991; Liu and Kao 2012). However, the opposite effects were noted in human embryonic kidney 293 (HEK293) cells, where cells stably expressing and secreting lumican showed decreased adhesion and growth compared to mock HEK293 cells, while migration and invasion were seemingly unaffected (Ishiwata et al. 2010). Lumican has also been implicated in the inhibition of matrix metalloproteases (MMPs). Specifically, the glycosylated form of lumican decreased MMP-14 activity in B16F1 melanoma cells. Lumican may protect collagen against MMP-14 proteolysis, thus influencing cell-matrix interaction in tumor progression. (Pietraszek et al. 2014; Niewiarowska et al. 2011; Pietraszek et al. 2013) and has also been implicated as an inhibitor of angiogenesis (Niewiarowska et al. 2011; Nikitovic et al. 2014; Sharma et al. 2013).

The complexity and diversity of its proteoglycan structure suggest that lumican may influence cell function through several mechanisms. Lumican can present itself in a variety of forms depending on glycosylation. A highly substituted form of lumican has been identified within aortic smooth muscle cells in rats (Qin et al. 2001), with serum analysis revealing proteoglycan, glycoprotein, and core protein forms. Recently, the importance in lumican glycosylation in aortic valve stenosis (AS) has begun to be studied (Suzuki et al. 2016). Insufficient glycosylation of lumican was associated with thickened and calcified regions of AS valves, potentially due to the impairment of collagen fibrils and induction of inflammation. In lung tissues, lumican was found in a large number of different glycosylation states. These studies demonstrated, however, that the glycosylation pattern of secreted lumican is much more uniform than intracellular forms, suggesting a requirement for a more uniform protein type when lumican is in the extracellular space. Lumican forms can also depend upon age. Within the ECM of articular cartilage (Grover et al. 1995), the highly substituted keratan sulfate proteoglycan form of

lumican is much more prevalent in juvenile tissues, whereas the keratan sulfate-lacking glycoprotein is correlated with adults. Interestingly, there is a higher abundance of lumican in adults, despite having the less substituted form. These differences suggest that lumican forms and function differ depending upon age and anatomic location.

3.2 Lumican Implications in Cancer

During the many steps of tumor metastasis, cancer cells must interact with their microenvironment to grow, invade locally, intravasate into blood and lymphatic vessels, migrate, and grow again at anatomically distant sites (Hanahan and Weinberg 2011). Throughout these events, cancer cells interact with the components of the extracellular matrix (ECM), growth factors, and cytokines associated with the ECM, as well as surrounding stromal cells (endothelial cells, fibroblasts, macrophages, mast cells, neutrophils, pericytes, and adipocytes; Bhowmick et al. 2004; Lu et al. 2012). Modifications of ECM components during tumor progression have been extensively reported, and the role of proteoglycans in particular has been emphasized recently. Early studies have evaluated the effect of lumican on the proliferation and metastasis of several cancers (Naito 2005; Fullwood et al. 1996; Wight et al. 1992), but further studies into the biological mechanism of its effect on cancer are still needed. The presence of lumican has been observed in breast, colorectal, lung, melanoma, prostate, and pancreas cancers (Leygue et al. 1998; Lu et al. 2002; Matsuda et al. 2008; Ping Lu et al. 2002; Pietraszek et al. 2013; Li et al. 2016; Yang et al. 2013; Suhovskih et al. 2013; Coulson-Thomas et al. 2013; Seya et al. 2006), among others. However, a consensus on whether lumican has a positive or negative impact on tumor dynamics has not been reached.

3.2.1 Breast Cancer

Lumican in breast cancer has been localized to the tumor stroma and fibroblasts surrounding the lesion, though not in the cancer cells themselves (Leygue et al. 1998). There is little to no expression of lumican in normal breast tissue, providing strong evidence that it plays a role in breast tumor formation. A high expression level of lumican in breast cancer is correlated to high tumor grade, low estrogen receptor levels, and younger patient age. The lumican observed in these tumors presents itself in an unsulfated state. The poorly sulfated form of this protein has been shown to induce macrophage attachment and spreading (Funderburgh et al. 1997), indicating that lumican may participate in macrophage recruitment in these tumors. Further studies are necessary to elucidate the influences and consequences of lumican in breast cancer.

3.2.2 Colorectal Cancer

Lumican in colorectal cancer, on the other hand, is strongly expressed in the cancer cells themselves (Lu et al. 2002). No evidence of lumican was detected in normal epithelial cells, but those within close proximity of a lesion were shown to have weak expression of lumican. This suggests that the cancer cells may influence the surrounding tissues to synthesize lumican in an effort to promote cancer cell growth. As in breast cancer studies, the lumican extracted from these cells was poorly sulfated, strengthening the notion that it contributes to cancer cell proliferation.

3.2.3 Lung Cancer

Lumican in lung cancer has been studied in squamous cell carcinoma (SqCC) and lung adenocarcinoma (ADC), with differing conclusions (Matsuda et al. 2008). Lumican is present in normal lung tissues, specifically peribronchial connective tissues and the bronchial epithelium (Dolhnikoff et al. 1998). However, enhanced expression is detected in stromal tissues and in cancer cells for SqCC and ADC. SqCC showed higher levels in the cancer cells than the stromal tissues, whereas ADC showed higher levels in stromal tissues than cancer cells. In either disease, secreted lumican was found to be variably and abnormally glycosylated, a feature which has been linked to malignant transformation (Kannagi et al. 2004). However, the glycosylation pattern was much more uniform within the cancer cells. This difference suggests different roles for lumican between cancer cells and stromal tissues. A particularly interesting finding was the increased vascular invasion in the presence of lumican in SqCC. While the effect of lumican on angiogenesis has been observed, most literature suggests lumican is an inhibitor of angiogenesis (Albig et al. 2007; Niewiarowska et al. 2011). A possible explanation for this apparent inconsistency is that the majority of lumican in SqCC is secreted by the cancer cells, while the studies that imply angiogenic inhibition focused on epithelial cell expression of the protein (Kannagi et al. 2004). These observations underscore the importance of the context within which lumican is studied. Additionally, these results highlight that lumican exerts its influence on cancer through microenvironmental cues that are still largely unknown (Sharma et al. 2013).

3.2.4 Pancreatic Cancer

More extensive research has been conducted on the role of lumican in pancreatic ductal adenocarcinoma (PDAC). Lumican is expressed in normal pancreas tissues, localized primarily in the alpha cells of islets (Ping Lu et al. 2002). Aberrant

expression of lumican has been observed in stromal cells and cancer cells of PDAC, with differing patient prognoses depending on location (Ishiwata et al. 2007). It was noted that patients with lumican-positive cancer cells had longer survival than those with lumican-negative cancer cells, while patients with lumican-positive stroma tended to survive for a shorter period than those that had stroma devoid of lumican. However, a separate study noted an association between stromal lumican and prolonged survival after surgery (Li et al. 2014). It should be noted that patient tumors studied in these two reports were at very different stages of disease, with the poor outcome identified in later-stage tumors versus the opposite trend identified in earlier-stage tumors. This observation adds tumor stage as an additional consideration to anatomic site when considering lumican in cancer. A study by Yang et al. focused on lumican expression in patients with PDAC and noted exactly this shift in effect and prognosis. Stromal expression of lumican was significantly higher in patients with later stages of disease and correlated with lower expression of Ki-67, vascular endothelial growth factor (VEGF), and mutated p53 (Yang et al. 2013).

Additional functional studies using PDAC cells identified that extracellular lumican stimulates epidermal growth receptor (EGFR) dimerization and internalization, resulting in decreased EGFR kinase activity and attenuation of its downstream activators Akt and HIF-1α. Reduced HIF-1α inhibits glycolytic metabolism and triggers apoptotic cell death (Li et al. 2014). More recently, we further demonstrated that extracellular lumican decreased AMP-activated kinase activity, inhibiting chemotherapy-induced autophagy in in vitro and in vivo PDAC models. Co-treatment of PDAC cells with lumican and gemcitabine increased mitochondrial damage, reactive oxygen species production, and cytochrome c release, indicating that lumican-induced disruption of mitochondrial function may be the mechanism of sensitization to gemcitabine (Li et al. 2016). Our data also identified pancreatic stellate cells (PSCs) as a significant source of extracellular lumican production through quantitative immunohistochemistry analysis of 27 PDAC patient specimens. We demonstrated that the cytokine, transforming growth factor-β (TGF-β), negatively regulates lumican gene transcription within human PSCs through its canonical signaling pathway and binding of SMAD4 to novel SMAD-binding elements identified within the promoter region. Extracellular lumican enhances stellate cell adhesion and mobility in a collagen-rich environment. Pan02 mouse cells have been injected into the lumican$^{-/-}$ pancreas of mice. Histologically, Pan02 cells grew a more moderately differentiated spherical growth pattern (Fig. 3.1a, b) in C57/BL6 wild-type mice, while Pan02 grew a more irregular finger-like or undifferentiated growth pattern in lumican$^{-/-}$ mice and showed local invasiveness (Fig. 3.1c, d; data not published). Figure 3.2 summarizes extracellular lumican regulation and biological functions in PDAC proliferation, apoptosis, adhesion, and migration.

In summary, it is clear that lumican plays an active role in many solid tumors. While its role in cell signaling is being elucidated, understanding how lumican functions as a cell matrix modulator with respect to drug delivery and tumor dynamics is of critical importance.

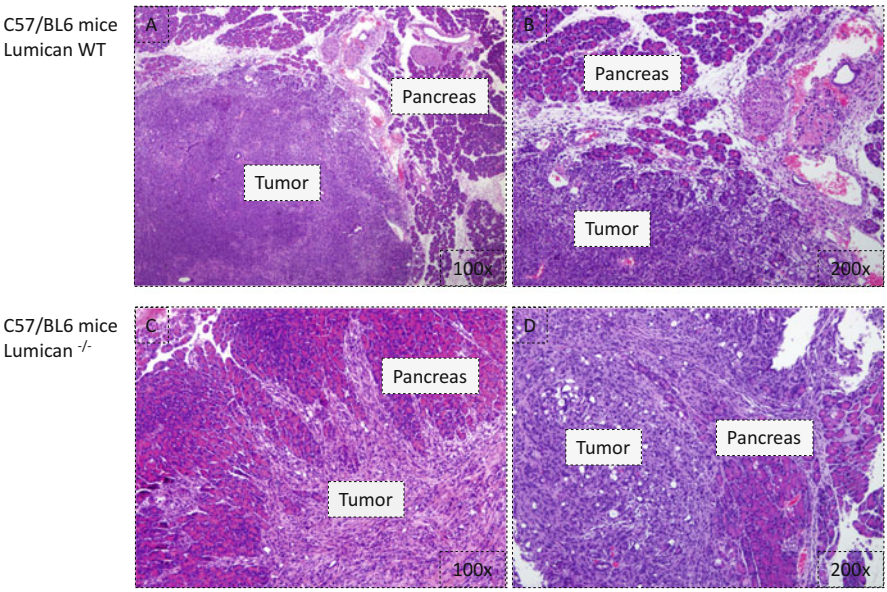

Fig. 3.1 H&E staining shows PanO2 tumor grown pattern in C57/BL6 wild-type (**a, b**) and lumican$^{-/-}$ (**c, d**) mice in orthotopic xenograft model

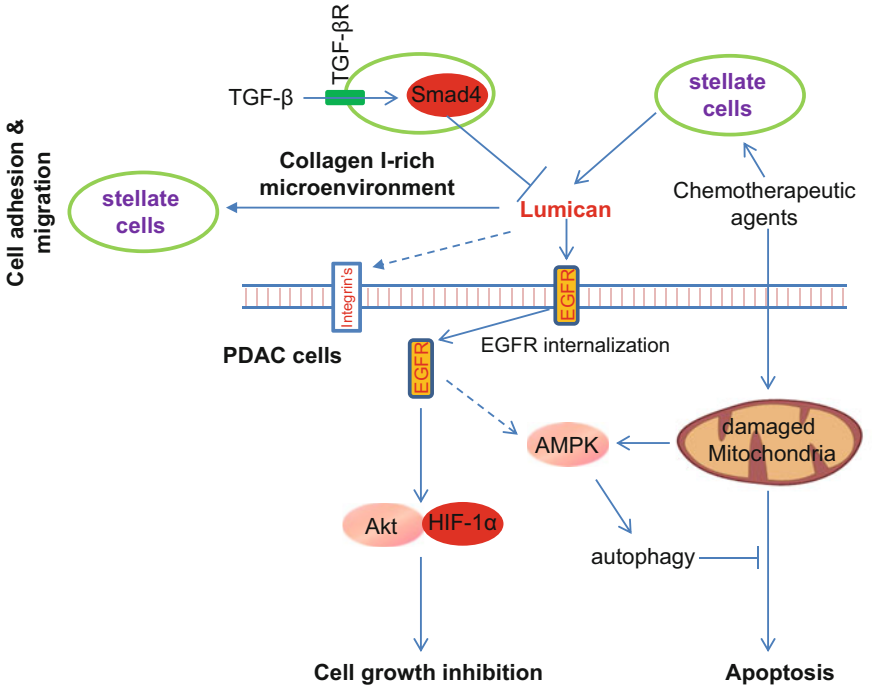

Fig. 3.2 A schematic of extracellular lumican function in pancreatic cancer. Figure adapted from Li et al. (2014, 2016)

3.3 Drug Delivery in Cancer and Its Association with Lumican Expression

A variety of barriers can prevent cancer drug delivery, not the least of which is the ECM in the tumor microenvironment (Sriraman et al. 2014). Achieving the necessary concentration of drugs within the tumor cells is particularly hindered by their inability to penetrate the tumor. This effect has been linked to the collagen content (Netti et al. 2000) and lack of proper vascularity (Folkman et al. 1989) in many of these tumors. Stromal lumican is typically identified within numerous human solid tumor malignancies (Naito 2005; Dolhnikoff et al. 1998; Qin et al. 2001; Baba et al. 2001; Onda et al. 2002; Ping Lu et al. 2002; Matsuda et al. 2008; Nikitovic et al. 2008a; Leygue et al. 1998; Ishiwata et al. 2007). While its expression has been observed in stromal and cancer tissue (Nikitovic et al. 2008b), this is not a consistent feature over all types of cancer. In addition, the differential expression of lumican based on tumor stage has also been noted (Panis et al. 2013). It is therefore important to consider lumican when considering the problem of solid tumor drug delivery.

Cancer has been described as an "over-healing" wound (Schafer and Werner 2008) in that there is a very often inflammatory response to the cancer cell growth that results in increased fibrosis. This desmoplastic reaction carries with it a number of side effects, which can build barriers to drug delivery. Of these obstacles, those most likely to have some connection with lumican are ECM density, inadequate vascularity, and increased tumor interstitial fluid pressure of many of these lesions.

3.3.1 Collagen Organization in Tumors

The ECM is a collection of extracellular molecules (including collagen, proteoglycans, etc.) that provide structural and biochemical support to the surrounding cells. It has been shown that a well-organized ECM impedes the progress of macromolecules through the tumor interstitium (Netti et al. 2000). Although as yet unproven, it is probable that lumican acts to organize and create an evenly spaced network of collagen fibrils within the TME. In so doing, this organized collagen could prevent distribution of therapy throughout the tissue. Investigations into drug distribution in lumican-negative tissues versus those with normal lumican are necessary to establish such a role in tumor dynamics. To counteract this obstacle, studies have discovered that collagenase pretreatment increases the penetration and distribution of therapy within solid tumors (Goodman et al. 2007). Matrix metalloproteases (MMPs) actually fulfill a similar role in terms of matrix degradation and proteolysis (Stetler-Stevenson and Yu 2001). Higher levels of MMP activity would result in increased drug delivery to tumors due to collagen matrix clearing. However, lumican has been shown to have MMP inhibitory activity (Pietraszek et al. 2014) and protects collagen from degradation (Geng et al. 2006), therefore theoretically

doubling its effectiveness in terms of creating a dense, organized ECM. However, it remains to be seen how the presence of lumican within a solid tumor ECM affects collagen organization, remodeling, and drug delivery.

3.3.2 VEGF and PDGF

Angiogenesis, and the associated increased levels of VEGF and platelet-derived growth factor (PDGF) in the TME (Kerbel 2008), is necessary for solid tumor progression beyond the earliest stages (Folkman et al. 1989). While VEGF and PDGF encourage new vessel growth and increase vessel permeability (Bates and Curry 1996; Harhaj et al. 2002), the delivery efficiency of tumor blood vessels is low. Additionally, the high interstitial pressure in the tumor forces the diffusion gradient into and not out of the vessels (Carmeliet and Jain 2000). Lumican inhibits angiogenesis (Sharma et al. 2013), specifically through the inhibition of VEGF (Albig et al. 2007). Another structurally similar SLRP, decorin, demonstrates PDGF-inhibiting activity (Baghy et al. 2013; Iozzo 1997). Both VEGF and PDGF have been reported to increase MMP and collagenase activity within the interstitium (Unemori et al. 1992; Sun et al. 2013), leading to rapid turnover and instability in ECM structures. One hypothesis about SLRPs is that they act to stabilize the vasculature and collagen matrix within the ECM of tumors. The normalization of tumor vasculature improves the delivery of cytotoxic therapy as seen in animal models (Carmeliet and Jain 2000), which opens the door for lumican as a therapeutic intervention to stabilize the TME.

3.4 Summary

Understanding all of the complex interactions between the tumor and its surrounding ECM is challenging; however, manipulating the ECM has proven to be an effective strategy to combat tumor progression and improve therapeutic delivery. Altogether, current evidence supports lumican as an antitumor molecule, although the importance of patient age, cancer site, and tumor stage should be taken into account when interpreting this data. In the proper context, however, lumican could represent a useful diagnostic and prognostic marker. Certainly, further studies are necessary to translate basic research on lumican into clinical application.

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