Chapter 4
Versican: Role in Cancer Tumorigenesis

Paul A. Keire, Inkyung Kang, and Thomas N. Wight

Abstract Versican is an extracellular matrix proteoglycan that is expressed in a wide variety of cancers. Several cellular sources for versican have been identified in a multitude of cancers including tumor cells, stromal cells, myeloid cells, and lymphoid cells. Versican plays a role in five of the six hallmarks of cancer including proliferative signaling, evasion of growth suppressor signaling, promotion of tissue invasion and metastasis, angiogenesis, and resistance to cell death. Versican also interacts with growth factors and cytokines to modify their activity and involvement in the cancer response. The synthesis and accumulation of versican is regulated by similar pathways that regulate cancer progression, such as the canonical Wnt/β-catenin pathway and receptor tyrosine kinases. The expression and accumulation of versican are associated with poor prognosis, disease progression, metastasis, and chemoresistance. A detailed analysis of the role of versican in the disease course of leiomyosarcoma is provided here as an example of the importance of this extracellular matrix component in cancer pathogenesis. Collectively, our results and those from other groups suggest that versican could serve as a point of control in the management and treatment of many cancers.

Abbreviations

ADAMTS	*A d*isintegrin *a*nd *m*etalloproteinase with a *t*hrombo*s*pondin family
CAF	Cancer-associated fibroblast
CTLs	Cytotoxic T lymphocytes
DAMP	Danger-associated molecular pattern
ECM	Extracellular matrix
EGF	Epidermal growth factor
FAK	Focal adhesion kinase
α-GAG	α-Glycosaminoglycan
β-GAG	β-Glycosaminoglycan

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HAS	Hyaluronan synthase
HYAL1	Hyaluronidase-1
LEFs	Lymphoid-enhancing factors
LMS	Leiomyosarcoma
LOX	Lysyl oxidase
MMP	Matrix metalloproteinase
PSCs	Pancreatic stellate cells
PSGL-1	P-selectin glycoprotein ligand-1
RHAMM	Hyaluronan-mediated motility receptor
αSMA^{+}	Alpha smooth muscle actin positive
TAMs	Tumor-associated macrophages
TCFs	T-cell factors
TGFβ	Transforming growth factor beta
TLR2	Toll-like receptor 2
TNFα	Tumor necrosis factor α
TSP1	Thrombospondin-1

4.1 Introduction

Versican is a large extracellular matrix (ECM) proteoglycan, named in recognition of its versatile modular structure (Fig. 4.1). Versican belongs to the hyaluronan-binding family of proteoglycans (hyalectins) whose other members include aggrecan (abundant in cartilage), brevican, and neurocan (nervous system proteoglycans). Versican expression is normally low in adult tissues but dramatically increases during development (Dutt et al. 2006; Perris et al. 1996), inflammatory disease (Cattaruzza et al. 2002; Wight 2002; Wight et al. 2014), and in a number of cancers (reviewed by Du et al. 2013; Ricciardelli et al. 2009; Theocharis et al. 2010). Furthermore, as will be discussed, versican is central to many of the hallmarks of cancer (Hanahan and Weinberg 2000) such as proliferative signaling, the evasion of growth suppressors, the promotion of tissue invasion and metastasis, angiogenesis, and resistance to cell death (Fig. 4.2). Versican also appears to be central to the more recently described hallmarks of cancer, which include immune surveillance evasion, immunomodulation, and tumor-promoting inflammation (Hanahan and Weinberg 2011). In this chapter, we will address (1) the sources of versican in cancer, (2) the structure and binding partners of versican and their expected function in cancer progression, (3) known regulators of versican expression implicated in cancer, and (4) proposed mechanisms of how versican regulates cell behaviors critical for tumor progression.

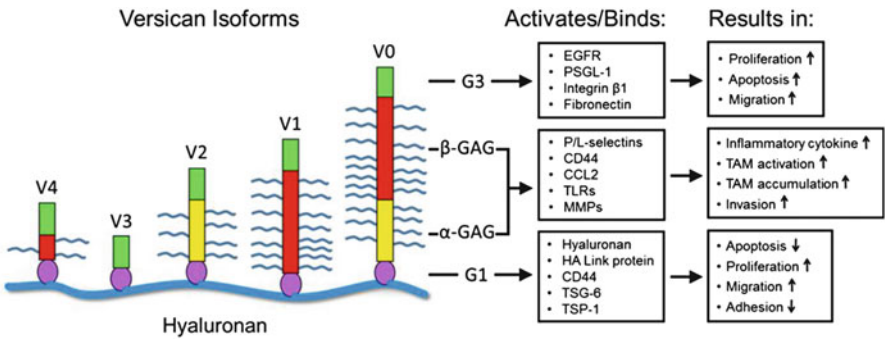

Fig. 4.1 Domain structures of versican isoforms and the importance of these interactions with various cell surface receptors and other ECM molecules. As a result of binding, charge-charge attraction and/or repulsion, bridging, or complex stabilization, versican, depending on its form, facilitates cancer progression

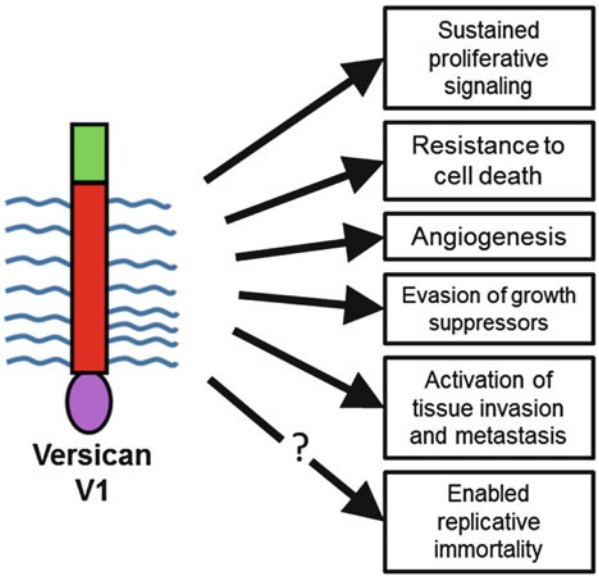

Fig. 4.2 Versican participates in at least five of the six hallmarks of cancer described originally by Hanahan and Weinberg (2000)

4.2 Source of Versican in Cancer

There are at least four major sources of versican in cancer: the tumor cells, tumor-associated stroma, tumor-associated myeloid cells, and tumor-infiltrating lymphoid cells. For example, tumor cells show an elevated expression of versican in lung carcinoma (Kim et al. 2009), ovarian cancer (Li et al. 2013), leiomyosarcoma

(LMS; Keire et al. 2014), hepatocellular carcinoma (Xia et al. 2014), colon carcinoma (Bogels et al. 2012), glioma (Hu et al. 2015), myeloma (Hope et al. 2014), and bladder cancer (Said and Theodorescu 2012). Amplified expression of versican in cancer cells is also observed in primary malignant and metastatic melanomas (Touab et al. 2002). This upregulation of versican by cancer cells themselves is significant for several reasons. In the case of Lewis lung and breast carcinomas, the presence of versican leads to an accumulation and activation of tumor-associated macrophages (TAMs) via toll-like receptor 2 (TLR2) and its co-receptors TLR6 and CD14 (Du et al. 2013; Grivennikov et al. 2010; Kim et al. 2009; Tang et al. 2015; Hope et al. 2016). Similarly, versican expressed by glioma cells promotes tumor expansion via TLR2 receptors on resident microglia/macrophages in the brain (Hu et al. 2015). There are multiple ramifications of versican-TLR2 engagement on myeloid cells. For example, the activation of microglial cells via TLR2 ligation with versican leads to the expression of MT1-MMPs and a cascade of proteases that characterize the spread and growth of glioma (Hu et al. 2015; Liu et al. 2015; Busek et al. 2016). Versican engagement of the TLR2 receptor complex also induces tissue necrosis factor α (TNFα) secretion by myeloid cells and thus strongly enhances tumor proliferation and metastatic growth. By another mechanism, in bladder cancer, elevated versican expression by cancer cells inhibits protective metastatic suppressor G-protein signaling genes, thus facilitating an aggressive cancer phenotype (Said and Theodorescu 2012). Moreover, versican release into the tumor microenvironment by the tumor cells may affect the ability of the immune system to mount an appropriate response. Versican binding of TLR2 on the surface of dendritic cells, which are a key link between innate and adaptive immunity (Steinman 2012), leads to a suppression of immune surveillance. Dendritic cells typically prime CD8+ T cells which results in the generation of cytotoxic T lymphocytes (CTLs); however, when versican binds to dendritic cells, IL-6 and IL-10 are released, leading to dysfunctional CTL activity, tumor growth, and metastatic progression (Tang et al. 2015). Collectively, these studies find a direct correlation between tumor versican expression and tumor grade. In addition, our experience with LMS indicates that the level of versican expression by tumor cells is directly associated with the aggressiveness and progression of the cancer (Keire et al. 2014).

In other cancers and their subtypes, stromal cells serve as a major source of versican, such as in cancers of the breast (de Lima et al. 2012; Kischel et al. 2010; Nara et al. 1997; Ricciardelli et al. 2002; Takahashi et al. 2012), colon (Iozzo 1995; Iozzo et al. 1982), ovaries (Yeung et al. 2013), and prostate (Ricciardelli et al. 1998; Sakko et al. 2001, 2003, 2007; True et al. 2009). Versican is typically not expressed in normal breast tissue, but with the onset of cancer, it is observed at low levels in ductal epithelial cells and at even higher levels in periductal lobular stroma (de Lima et al. 2012). In the case of breast cancer, it is likely that the overexpression of transforming growth factor beta (TGFβ) by ductal epithelial cells contributes to this pattern of strong stromal versican induction and cancer progression (Derynck et al. 1987; Van Bockstal et al. 2014) as versican expression is upregulated in response to TGFβ in a variety of cell types (Onken et al. 2014; Nikitovic et al. 2006; Schönherr et al. 1991; Kähäri et al. 1991). In a similar manner, versican was

identified as a key TGFβ-induced gene in cancer-associated fibroblasts (CAFs) associated with ovarian cancer progression (Yeung et al. 2013).

In some cancers, such as endometrial and cervical cancers, tumor and stromal cells display increased levels of versican (Kodama et al. 2007a, b). The combination of tumor and stromal expression of versican correlates with shortened disease-free survival and overall survival (Kodama et al. 2007b). Moreover, in cervical cancer, disease progression is marked by increased levels of versican in tumors, lymph node metastases, and in the lymph-vascular space (Kodama et al. 2007a). As has been identified in other cancers, elevated levels of versican expressed by cancer and stromal cells appear to enhance the activation of TAMs, which likely promotes cervical cancer progression, but the role of versican in this cancer has not been studied in great detail. Paradoxically, system-wide ($Vcan^{flox/flox}$) ablation of versican expression leads to a decrease in the number and density of CAFs in stroma as seen in a fibrosarcoma tumor model (Fanhchaksai et al. 2016). Notably, decreases in CAFs through alpha smooth muscle actin-positive (αSMA^{+}) myofibroblast ablation have been associated with immunosuppression, more aggressive tumor behavior, and a poorer prognosis in pancreatic cancer (Ozdemir et al. 2014). The problem with such experiments is the unintentional depletion of the fraction of αSMA^{+} cells which are homeostatic and the consequent loss of the natural compartmentalization of the organ matrix imparted by the tissue stroma. Other cells in the tissue stroma, such as the pancreatic stellate cells (PSCs), are in low abundance in the normal homeostatic pancreas (Omary et al. 2007); however, when activated, PSCs comprise a large portion of the desmoplastic pancreatic cancer matrix associated with pancreatic ductal adenocarcinoma progression and metastasis (Neesse et al. 2011). If it is determined that versican is produced by PSCs, this is another mechanism whereby versican accumulation in the stroma could lead to cancer progression. Versican, for example, is implicated in interfering with T cell-mediated tumor destruction by displacing T cells from the appropriate tumor target (Joyce and Fearon 2015). Whether versican has dual functions in regulating the behavior of tumor cells and stromal cells to impact tumor progression and immunosuppression is not yet clear and requires further study.

Myeloid cells are also a major source of versican under inflammatory (Gao et al. 2012a; Chang et al. 2012, 2014) and hypoxic conditions (Asplund et al. 2010, 2011; Sotoodehnejadnematalahi et al. 2015; Wang et al. 2015; Zhang et al. 2012). Consistently, in breast cancer, versican derived from myeloid cells is critical in promoting tumor metastasis (Gao et al. 2012b). Using a murine model of spontaneous breast cancer, Gao and colleagues found that versican expressed by CD11b+ $Ly6C^{high}$ myeloid cells promotes lung metastasis in a TGFβ-dependent manner (Gao et al. 2012a). Intriguingly, co-culture of myeloid cells with bladder carcinoma cells results in an upregulation of versican in the myeloid cells, suggesting that the source of versican in cancerous tumors includes myeloid cells associated with the tumor (Said and Theodorescu 2012). Such co-sourcing of versican from both the myeloid cells (e.g., TAMs and myeloid-derived suppressor cells) and from the cancer cells serves to exacerbate the spread of the cancer and is thought to facilitate cancer progression (Gutmann 2015; Senda et al. 2016; Said et al. 2012). Such studies highlight potential crosstalk created by versican among different cell types

that may provide key links to cancer initiation, promotion, immunosuppression, and metastatic progression.

4.3 The Role of Versican in Cancer

There are at least five naturally occurring versican isoforms that have been identified and characterized. The isoforms, designated V0, V1, V2, and V3, are generated by alternatively splicing the central α-glycosaminoglycan (α-GAG) and β-glycosaminoglycan (β-GAG) domains. Versican isoforms V0 and V1 are the predominant isoforms produced by adult mesenchymal cells with V1 as the most abundant form (Kischel et al. 2010; Wight et al. 2014) and the most highly expressed in late-stage or metastatic cancer. V2 is primarily expressed in neural tissue and not typically by other tissues, and V3 is variably expressed in a number of tissues but at comparably lower levels than the other isoforms (Lemire et al. 1999). Moreover, it was discovered that at least in breast cancer, a unique fifth versican splice variant termed V4 is expressed (Kischel et al. 2010). Versican V4 arises from a splice variation of exon 8, resulting in a truncated or shortened β-GAG domain (Fig. 4.1).

Common to these splice variants are the N- and C-terminal ends or G1 and G3 domains, respectively. The G1 domain of versican, which contains a hyaluronan-binding region, mediates cell proliferation, adhesion, and migration (Yang et al. 1999), while the G3 domain is involved in cell phenotype control through its association with integrins (Wu et al. 2004, 2005), microfibrilar fibulins (Miosge et al. 1998), and epidermal growth factor (EGF) receptors (Xiang et al. 2006). Sakko et al. have shown that an increase in versican expression in the ECM facilitates local tumor invasion and metastasis by decreasing cell-ECM adhesion (Sakko et al. 2003). One of the mechanisms by which versican affects ovarian tumors is through binding to cell surface CD44 (Ween et al. 2011). This in turn activates signaling pathways such as JNK and NF-κB and thus enhances cell migration and tumor progression through the production of tumorigenic proteins, such as hyaluronan-mediated motility receptor (RHAMM) and matrix metalloproteinase (MMP)-9 (Yeung et al. 2013). The G1 domain of versican also binds to thrombospondin-1 (TSP1; Kuznetsova et al. 2006). The concurrent upregulation of TSP1 and versican is reported in stromal cells of human breast carcinomas (Brown et al. 1999). Thus, the interaction of versican with various ECM components via the G1 or G3 domains is likely to regulate the stromal responses that are critical to modulating cancer progression (Bhowmick et al. 2004). In general, the G1 domain of versican is thought to stimulate proliferation by destabilizing cell adhesion (Yang et al. 1999), while the G3 domain mediates proliferation through EGF-like domain interaction with EGF receptors (Ang et al. 1999; Du et al. 2010; Zhang et al. 1998, 1999). In support of this, a corresponding relationship of high versican expression to tumor growth is observed in gliomas, breast, prostate, gastric, pancreatic carcinomas, and uterine sarcomas (Cai et al.

2013; Keire et al. 2014; Nara et al. 1997; Onken et al. 2014; Shen et al. 2015; Skandalis et al. 2006a; Wade et al. 2013).

Between the terminal G1 and G3 domains of versican are alternatively spliced α-GAG and β-GAG attachment domains important to versican biology (Wu et al. 2005; Wight 2002). The GAG chains are known to interact with inflammatory mediators and are key to versican's role in the progression of the cancer phenotype described by Hanahan and Weinberg (2000, 2011; Fig. 4.2). Versican interacts with inflammatory mediators via its chondroitin sulfate chains, including CCL2/MCP1, CD44, P-selectin glycoprotein ligand-1 (PSGL-1), TLR2, and MMPs (Hirose et al. 2001; Malla et al. 2013; Wang et al. 2009; Wu et al. 2005). In addition, the interaction of versican with hyaluronan via its G1 domain plays a significant role in the ability of cancer cells to migrate, adhere, proliferate, and interact with the surrounding ECM and immune system (Evanko et al. 2012; Frey et al. 2013; Keire et al. 2014; Toole et al. 2002; Wight et al. 2014). Hyaluronan is made entirely of repeating disaccharide (D-glucuronic acid β-1,3-*N*-acetylglucosamine-β-1,4) units and is synthesized by three related hyaluronan synthases (HAS1, HAS2, and HAS3; Toole et al. 2002).

Significantly, versican and hyaluronan interact to form large multimolecular weight aggregates around cells, which accumulate in various types of tumors and are associated with tumor progression, including tumors of the prostate (Bharadwaj et al. 2007; Ricciardelli et al. 2007), breast (Koyama et al. 2007; Suwiwat et al. 2004), bone (Nikitovic et al. 2006), lung (Pirinen et al. 2005), cartilage (Romeo et al. 2007), skin (Karvinen et al. 2003; Papakonstantinou et al. 2003; Touab et al. 2003), brain (LaPierre et al. 2007), pancreas (Skandalis et al. 2006a), cervix (Kodama et al. 2007a), uvea (Folberg et al. 2006), larynx (Skandalis et al. 2006b; Skandalis et al. 2004), mouth (Pukkila et al. 2007), testis (Labropoulou et al. 2006), and ovaries (Ricciardelli and Rodgers 2006; Ween et al. 2011). The expression of hyaluronan and versican in such a wide variety of cancers suggests an active role for these molecules in tumor development.

Versican and hyaluronan are ECM components that are at the center of angiogenesis (Du et al. 2013; Feinberg and Beebe 1983; Fu et al. 2011; Montesano et al. 1996; Rivera et al. 2011; Rooney et al. 1993, 1995; Slevin et al. 2007, 2009; West et al. 1985; West and Kumar 1989; Zheng et al. 2004b). Angiogenesis is a normal and vital process in development, wound healing, and cancer and, in part, occurs in matrices enriched in versican and hyaluronan. Versican levels in the tumor microenvironment have been shown to positively correlate with the number of microvessels in the tumor stroma of ovarian and testicular germ cell tumors (Ghosh et al. 2010; Labropoulou et al. 2006). We found that human stromal stem cells can regulate the angiogenic phenotype of endothelial cells by modulating the formation of provisional matrices enriched in versican and hyaluronan (Kreutziger et al. 2011). In addition, we found that different clonal stromal stem cell types support endothelial network formation in vitro with varying degrees of effectiveness. Stromal stem cells that produce elevated levels of versican formed a more extensive vascular network when co-cultured with vascular endothelial cells. Furthermore, patches containing these pro-angiogenic cells, when transplanted onto

uninjured athymic rat hearts, developed 50-fold more vessels than stromal cells with low versican expression (Kreutziger et al. 2011). Versican is actively processed during the early stages of VEGF-A-induced pathological angiogenesis (Fu et al. 2011). These observations plus the fact that the tumor stroma contains provisional matrix components such as fibrin, fibronectin, and hyaluronan (Dvorak 1986, 2002, 2015) highlight the importance of this specialized ECM in the pathogenesis of cancer. Dvorak first postulated that "tumors are wounds that do not heal" (Dvorak 1986) due to their high content of provisional ECM components such as versican. In angiogenic models, the increased expression of versican is often accompanied by an increased expression of hyaluronan (Koyama et al. 2007; Nara et al. 1997). Hyaluronan and fragments of hyaluronan play a key role in new blood vessel formation, affecting the behavior of endothelial cells (Feinberg and Beebe 1983; Montesano et al. 1996; Rooney et al. 1993, 1995; Slevin et al. 2007, 2009; West et al. 1985; West and Kumar 1989).

An ECM enriched in hyaluronan and versican has also been shown to promote myeloid cell adhesion and retention (de la Motte et al. 2003; Potter-Perigo et al. 2010; Wilkinson et al. 2006), which was recently acknowledged as an important aspect of tumor progression by its recruiting myeloid-derived suppressor cells and TAMs (see reviews by Kitamura et al. 2015; Marvel and Gabrilovich 2015; Shalapour and Karin 2015). The interaction between versican and myeloid cell surface receptors such as PSGL-1 and TLR2 further induces macrophage aggregation (Zheng et al. 2004a) and the expression of cytokines and MMPs (Bogels et al. 2012; Hu et al. 2015; Kim et al. 2009; Wang et al. 2009; Zhang et al. 2012). These findings indicate that chondroitin sulfate-bearing isoforms of versican promote leukocyte accumulation and activation. Our studies demonstrated that blocking versican accumulation by a blocking antibody or regulating versican synthesis inhibits the adhesion of monocytes/macrophages to the ECM (Kang et al. 2014; Potter-Perigo et al. 2010). The mechanism of versican-dependent monocyte/macrophage adhesion is achieved by attenuating the activation of NF-κB p65 as well as a number of NF-κB-responsive pro-inflammatory molecules, which promote leukocyte adhesion and accumulation including VCAM1, ICAM1, CCL2 (MCP1), and CXCL1 (Kang et al. 2014, 2015). These molecules have also been shown to be critical in promoting metastasis (Kitamura et al. 2015). Recent studies have established that versican is a danger-associated molecular pattern (DAMP) molecule that activates TLR2 on macrophages leading to the production of inflammatory cytokines such as TNFα and IL-6, which significantly increase invasion and metastatic growth in many cancers including ovarian and bladder cancer, Lewis lung carcinoma, myeloma, and glioma (Bogels et al. 2012; Hope et al. 2014; Hu et al. 2015; Kim et al. 2009; Said et al. 2012; Wang et al. 2009).

Numerous studies have shown that increased levels of versican and hyaluronan correlate with elevated metastatic potential and poor disease prognosis (Kim et al. 2009; Labropoulou et al. 2006; Nikitovic et al. 2006). Versican stimulates inflammatory cytokine production by bone marrow mononuclear cells, thus facilitating metastasis (Kim et al. 2009). Versican, through its binding to TLR2 and adhesion molecules expressed by inflammatory cells, leads to the activation of those cells and

the expression of inflammatory modulating cytokines such as TNFα, IL-1β, and IL-6 (Kim et al. 2009). These cytokines contribute to the establishment of an inflammatory cancer cell microenvironment favoring proliferation, tissue invasion, and metastasis. Furthermore, in prostate cancer, versican's binding partner hyaluronan and its fragments bind to TLR2, synergizing the activation of monocytes to macrophages and the production of inflammatory cytokines (Hu et al. 2015; Lokeshwar et al. 2005).

The inhibition of hyaluronan and versican production has been associated with decreased cancer progression. For example, antisense inhibition of HAS2 in osteosarcoma cells inhibits hyaluronan retention and tumorigenicity (Nishida et al. 2005). Moreover, silencing the gene for HAS2 using RNA interference (RNAi)-mediated suppression leads to a less aggressive phenotype of breast tumor cells (Li et al. 2007). Versican also appears to synergize with hyaluronan to drive cell proliferation (Keire et al. 2014).

4.4 The Regulation of Versican Expression in Cancer

A number of key signal transduction pathways critical for tumorigenesis have been identified as regulators of versican expression. Enhanced versican levels in ovarian cancer leads to the subsequent activation of both the JAK/STAT and PI3-kinase/AKT pathways (Carvalho et al. 2003; Ricciardelli and Rodgers 2006; Ween et al. 2011). In the process of ovulation, an increase in luteinizing hormone leads to a dramatic increase in versican and other ECM components in the cumulus-oocyte complex (Russell et al. 2003). Both G protein-coupled receptors and tyrosine kinase proteins are activated with the induction of ovulation by luteinizing hormone (Carvalho et al. 2003). Expression of versican rises and falls during the ovarian cycle; however, in ovarian carcinoma, versican is constitutively and continuously expressed at relatively high levels. This dysregulation involves specific signaling pathways such as JAK/STAT and PI3-kinase/AKT. It is known that the activation of AKT leads to increases in β-catenin signaling. Importantly, the canonical Wnt/β-catenin pathway, which is critical in early embryogenesis, cell differentiation, and neoplasms (Huang and He 2008; Korswagen and Clevers 1999; Taipale and Beachy 2001), is a primary driver of versican expression (Rahmani et al. 2006). The accumulation of β-catenin and subsequent formation of a complex with T-cell factors (TCFs) or lymphoid-enhancing factors (LEFs) on the versican promoter leads to increased versican expression. Interestingly, the tumor suppressor gene, p53, promotes versican expression, especially postradiation (Yoon et al. 2002). Often p53 is mutated in cancer, so as the cell attempts to control rampant cell cycling, even more p53 is produced in advanced or high-grade tumors (Mattioni et al. 2015). Other factors such as promotor methylation and microRNA expression may also control versican expression levels. For example, key microRNA sequences have been recently shown to impact versican expression and play a role in benign versus metastatic tumor states (Li et al. 2014). In addition,

versicanases, such as *a d*isintegrin *a*nd *m*etalloproteinase with *t*hrombo*s*pondin motifs (ADAMTS-5), expressed by T cells, degrade versican thus controlling versican levels (McMahon et al. 2016) and the tumor-directed CTL response described earlier.

4.5 Versican as a Diagnostic and Prognostic Marker in Cancer

Versican expression is diagnostically associated with a poor prognosis, disease progression, metastasis, and chemoresistance in cancers. Elevated levels of versican, hyaluronan, and CD44 are all associated with the poor prognosis of ovarian cancers (Ricciardelli and Rodgers 2006). Furthermore, high stromal versican staining is associated with reduced 5-year survival rates of ovarian cancer patients (44 versus 32%; Voutilainen et al. 2003). Versican is significantly upregulated in chemoresistant ovarian cancer when compared to chemosensitive ovarian cancer (Pan et al. 2009). For example, in primary oral squamous cell carcinoma, increases in stromal versican correlate with both an increased risk for disease recurrence and shortened patient survival (Pukkila et al. 2007). In colon cancer, versican, biglycan, collagen1A1, and sulfatase1/sulfatase2 expression are identified as potential tumor microenvironment biomarkers and/or targets for diagnostics and treatment (Suhovskih et al. 2015). In addition, versican is identified as significantly upregulated along with β-catenin, β1 integrin, and focal adhesion kinase (FAK) in the disease course of multiple myeloma, which is a malignancy of B cells characterized by the proliferation and dissemination of malignant plasma cells from the bone marrow (Gupta et al. 2015). However, the prognostic role of versican is tissue specific. For example, in pharyngeal squamous cell carcinoma, versican expression in the primary tumor is not an independent prognostic factor, although a signature of significantly higher versican staining in the draining lymph nodes of the tumor is observed (Pukkila et al. 2004). Versican has been identified in a number of other cancers as having some diagnostic and prognostic value as well (Sluiter et al. 2016; Kobayashi et al. 2015; Driessen et al. 2016; Ju et al. 2010).

4.6 Versican in LMS: Our Experience

Significantly greater amounts of versican are expressed and accumulate in LMS compared to benign leiomyomas and normal healthy tissue (Keire et al. 2014; Fig. 4.3, panels a–e). Supporting microarray analyses of 80 LMS tumors and 24 leiomyomas showed a significant increase in versican mRNA in LMS versus benign leiomyomas. Such findings indicate that versican may play a role in mediating the aggressiveness of LMS tumors compared to leiomyomas. We also

demonstrated that inhibiting versican synthesis in LMS cells using versican-directed siRNA reduced their proliferation and migration in vitro (Fig. 4.3, panels f and g). LMS cells form extensive pericellular matrices enriched in versican and hyaluronan when grown in tissue culture, and inhibiting versican synthesis in these cells dramatically reduced the thickness of their pericellular matrices (Fig. 4.3, panels h and i). Adding versican back to these cells restored both the thickness of their pericellular coats (Fig. 4.3j) and heightened their proliferative rate (Fig. 4.3k). Nude mice injected with LMS cells stably expressing versican shRNA developed tumors with lower volumes and mitotic indices compared to mice injected with control LMS cells (Fig. 4.4, panels a and b). The manner in which versican and hyaluronan are thought to influence cell phenotype is shown diagrammatically in Fig. 4.5. Collectively, these results provide a potential strategy to control versican expression in LMS. Constitutive siRNA knockdown of versican in LMS cells resulted in increased expression of tropoelastin in vitro as assessed by qRT-PCR, immunohistochemistry, and Western blot analyses (Keire et al. 2016). Desmosine analysis, a marker for elastin synthesis and maturation, confirmed a 70% increase in elastin over LMS controls. Microarray analysis identified significant changes in 270 genes expressed in versican knockdown cells, a subset of which were selected for later validation by TaqMan low-density microarray. Within the set of 96 genes analyzed by TaqMan low-density array, tropoelastin was significantly upregulated as were elastin-associated genes that included fibulin-1, fibulin-5, and lysyl oxidase (LOX). LOX is an enzyme that initiates the cross-linking of collagen and elastin. In addition to cross-linking ECM proteins, LOX appears to play a role in tumor suppression (Bouez et al. 2006). Fibulin-5 is an elastin-associated protein expressed by endothelial cells and fibroblasts. The overexpression of fibulin-5 in endothelial cells results in reduced proliferation (Preis et al. 2006), while fibulin-5-expressing hepatocellular carcinoma cells exhibit decreased migration and invasion by downregulating the expression of the elastin-degrading enzyme, MMP-7 (Tu et al. 2014). Gene array and cell culture studies are further supported by in vivo studies, where versican siRNA LMS tumor cells injected into nude mice deposit significantly more elastic fibers than do control LMS cells (Keire et al. 2016). Collectively, in vitro and in vivo results suggest an important role for versican in regulating tumorigenesis and tissue homeostasis through the regulation of homeostatic molecules such as elastin.

In addition, we have found that the downregulation of versican leads to significant changes in the expression of a number of ECM proteolytic genes in LMS cells (Keire et al. 2016). For example, with the downregulation of versican, significant increases in MMP-12, ADAMTS-9, ADAMTS-20, and hyaluronidase-1 (HYAL1) levels are accompanied by substantial decreases in HYAL2, ADAMTS-4, and MMP-7. These changes are consistent with a less aggressive or benign cancer phenotype. For example, antisense-mediated suppression of HYAL2 inhibits breast cancer tumorigenesis and progression (Udabage et al. 2005). The overexpression of MMP-7 and MMP-9 is implicated in the invasion and metastasis of colorectal cancer (Woo et al. 2007) as well as in breast cancer (Vizoso et al. 2007), while MMP-12 overexpression is associated with increased survival and decreased

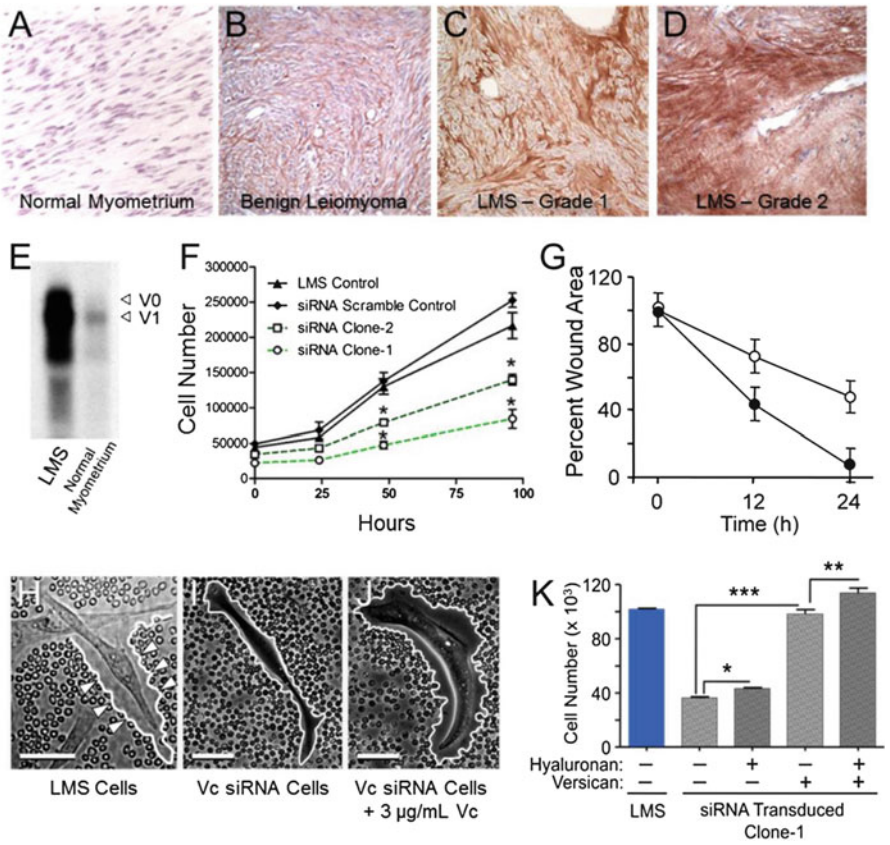

Fig. 4.3 Versican is highly expressed in clinical samples of leiomyosarcoma compared to normal tissue and benign tumors, and downregulation of versican dramatically changes cell phenotype. Normal human myometrium (**a**) stained for versican shows no staining, compared to a representative, benign leiomyoma tumor (**b**), which shows a greater amount of versican (*brown*) staining, but less than grades 1 (**c**) and 2 (**d**) LMS, which have extensive immunostaining. Northern blot analyses show increased versican in the LMS tumor compared to control (**e**). Cell proliferation assays indicate that the LMS/WT (*filled triangles*) and LMS/siRNA Scramble (*filled circles*) control cells divide and proliferate at a significantly higher rate than the two different versican siRNA LMS cell clones (*open squares* and *open circles*) (**f**). In a scratch wound cell migration assay (**g**), the migration of LMS cells (*filled up-pointing triangles*) was significantly greater (*single asterisks*, $p < 0.05$) at 12 and 24 h than that of LMS cells transduced with versican siRNA (*open circles*) ($n = 4$). LMS smooth muscle cells in culture treated with fixed red blood cells to image the pericellular matrix (**h–j**). The LMS cells exhibit extensive pericellular coats (**h**), while the LMS cells in which versican expression has been inhibited lack extensive cellular coats (**i**). LMS pericellular coat 24 h after adding back versican display extensive cell coats (**j**). *Arrowheads* (*white triangles*) and *solid white lines* mark the pericellular boundaries. *Scale bars* 50 µm. Large molecular weight hyaluronan by itself does not restore the proliferative profile of LMS/siRNA Vc cells to LMS/WT levels but does with the addition of purified versican (**k**). Although there is a significant increase in cell proliferation with the addition of hyaluronan (30 µg/ml; *single asterisks*, $p < 0.015$), the increase due to the addition of versican at nanogram levels is significantly greater (*triple asterisks*, $p < 0.0001$), and near complete restoration (96.6%) of the native LMS cell proliferative rate is achieved at 100 µg/ml versican. The difference between versican alone and versican *plus sign* large hyaluronan is significant (*double asterisks*, $p < 0.004$), suggesting an

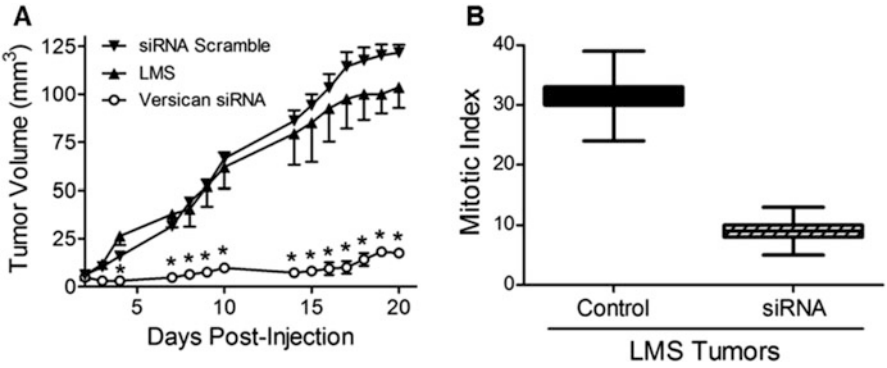

Fig. 4.4 Tumor growth in a mouse model of LMS using LMS cells treated or not treated with siRNA to versican. This figure shows (**a**) reduced tumor growth in the animals receiving siRNA versican LMS cells and (**b**) the mitotic index (MI) of LMS control versus LMS/siRNA Vc tumors. The *box graph* in (**b**) depicts median MI ± SD, and *error bars* show the minimum and maximum range of mitotic figures per 10 400× fields ($n = 15$). This figure was originally published in the *Journal of Biological Chemistry*. Keire PA, Bressler SL, Lemire JM, Edris B, Rubin BP, Rahmani M, McManus BM, van de Rijn M, Wight TN. A role for versican in the development of leiomyosarcoma. *J Biol Chem*. 2014; 289:34089–34103. © the American Society for Biochemistry and Molecular Biology

metastasis of colorectal cancers (Zucker and Vacirca 2004). Versican is a substrate of ADAMTS-1, ADAMTS-4, ADAMTS-5, ADAMTS-9, and ADAMTS-20 (Stanton et al. 2011), and when versican is degraded, it is associated with vascular smooth muscle cell death in vivo (Kenagy et al. 2009). Interestingly, the gene for ADAMTS-9 is localized to chromosome 3p14.3-p14.2, an area known to be lost in hereditary renal tumors and esophageal cancer development (Lo et al. 2007). Furthermore, ADAMTS-9 and ADAMTS-20 expression suppresses esophageal and nasopharyngeal carcinoma tumor formation (Lo et al. 2010). This suggests that protease-specific versican degradation products may react differently in different tissues. For example, our research shows that the downregulation of versican leads to a decrease in the ECM-degrading proteases ADAMTS-4 and ADAMTS-5 which are highly expressed in human glioblastomas (Held-Feindt et al. 2006), whereas ADAMTS-9 and ADAMTS-20 are upregulated and may be homeostatic (Keire et al. 2016). Thus, versican may influence the phenotype of every cell directly and indirectly through the modulation of its ECM interactive partners and matrix modulatory enzymes.

Fig. 4.3 (continued) additive or synergistic effect between hyaluronan and versican on cell proliferation. This figure is adapted from research originally published in the *Journal of Biological Chemistry*. Keire PA, Bressler SL, Lemire JM, Edris B, Rubin BP, Rahmani M, McManus BM, van de Rijn M, Wight TN. A role for versican in the development of leiomyosarcoma. J Biol Chem. 2014; 289:34089–34103. © the American Society for Biochemistry and Molecular Biology

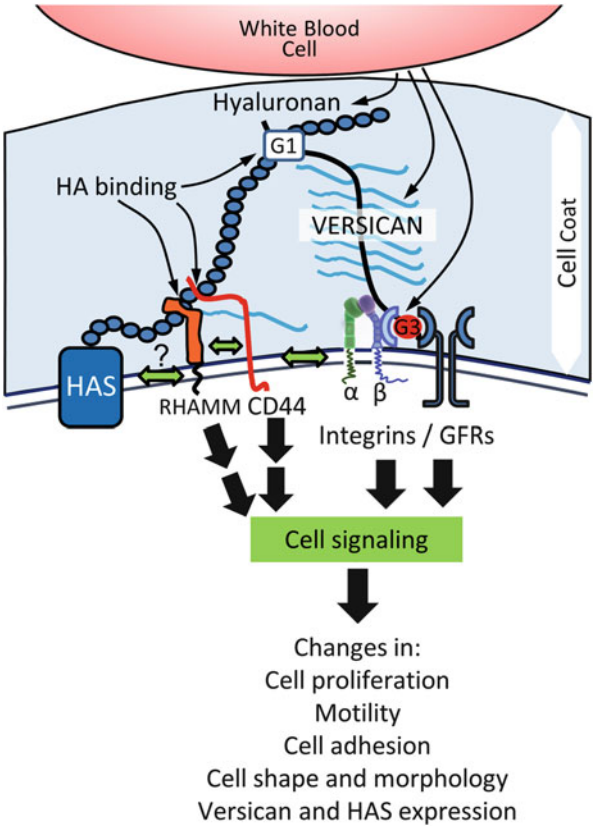

Fig. 4.5 Schematic diagram details the described interplay between versican and hyaluronan and how this interaction transduces changes in cell phenotype observed in cancer. Through its G3 domain, versican binds to and activates growth factor receptors and integrins leading to downstream cell signaling. The G3 and α- and β-GAG domains of versican bind white blood cells (neutrophils, eosinophils, basophils, T cells, B cells, NK cells, and monocytes) through their PSGL-1 cell surface receptors leading to downstream signaling and phenotypic changes in those cells. The HAS enzyme embedded in the plasma membrane synthesizes hyaluronan. The G1 domain of versican then interacts strongly with the emerging hyaluronan chains leading to cell surface localization. This in turn leads to interaction and activation of CD44, RHAMM, TLRs, MMPs, and other cell surface proteins. *RHAMM* receptor for hyaluronan-mediated motility; *GFRs* growth factor receptors; *HA* hyaluronan; *HAS* hyaluronan synthase

4.7 Conclusions

Versican, true to its name, is a versatile molecule of many functional roles in cell and tumor biology. It plays a significant role in five of the six hallmarks of cancer originally described by Hanahan and Weinberg (2000). Versican supports sustained cell proliferation, chemoresistance, the evasion of growth suppression, tissue invasion and metastasis, angiogenesis, and apoptotic resistance (Fig. 4.2). The role of

versican in cancer progression involves both its impact on cancer cell phenotype (proliferation, migration, metastasis) and how it impacts the surrounding microenvironment and the ability of the immune system to identify and remove cancerous cells. In light of this, not only can versican be used as a diagnostic or prognostic marker in a wide variety of cancers, it may also serve as a potential therapeutic target for cancer therapies.

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