

## Review

# Versican in inflammation and tissue remodeling: The impact on lung disorders

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## Abstract

Versican is a proteoglycan that has many different roles in tissue homeostasis and inflammation. The biochemical structure comprises four different types of the core protein with attached glycosaminoglycans (GAGs) that can be sulfated to various extents and has the capacity to regulate differentiation of different cell types, migration, cell adhesion, proliferation, tissue stabilization and inflammation. Versican's regulatory properties are of importance during both homeostasis and changes that lead to disease progression. The GAGs that are attached to the core protein are of the chondroitin sulfate/dermatan sulfate type and are known to be important in inflammation through interactions with cytokines and growth factors. For a more complex understanding of versican, it is of importance to study the tissue niche, where the wound healing process in both healthy and diseased conditions take place. In previous studies, our group has identified changes in the amount of the multifaceted versican in chronic lung disorders such as asthma, chronic obstructive pulmonary disease, and bronchiolitis obliterans syndrome, which could be a result of pathologic, transforming growth factor  $\beta$  driven, on-going remodeling processes. Reversely, the context of versican in its niche is of great importance since versican has been reported to have a beneficial role in other contexts, e.g. emphysema. Here we explore the vast mechanisms of versican in healthy lung and in lung disorders.

**Key words:** extracellular matrix, lung disorders, remodeling, versican

## Introduction

Versican is, as the name implies, a versatile molecule that plays important roles in cell–matrix interactions during adhesion, migration and inflammatory responses. It is readily expressed by fibroblasts and we have observed that versican is involved in remodeling in inflammatory lung disorders such as asthma, chronic obstructive pulmonary disease (COPD) and bronchiolitis obliterans syndrome (BOS). In this review, we therefore aim to explore the molecular role of versican in lung disorders.

Remodeling of the extracellular matrix (ECM) is constantly occurring in the body to meet ever-changing demands on stability and

flexibility of the matrix. Tissue repair and remodeling are processes in wound healing, but these mechanisms also contribute to the aberrant ECM disposition in several lung disorders such as COPD and Asthma (Shimizu et al. 2011; Dournes and Laurent 2012) diseases that affect a large population and range from mild to life-threatening. Remodeling and deposition of ECM molecules are also important events in the development of chronic rejection of transplanted lung (Andersson-Sjöland, Thiman, et al. 2011). The altered matrix along with inflammatory processes contributes to the diminished lung capacity characteristic of these lung disorders.

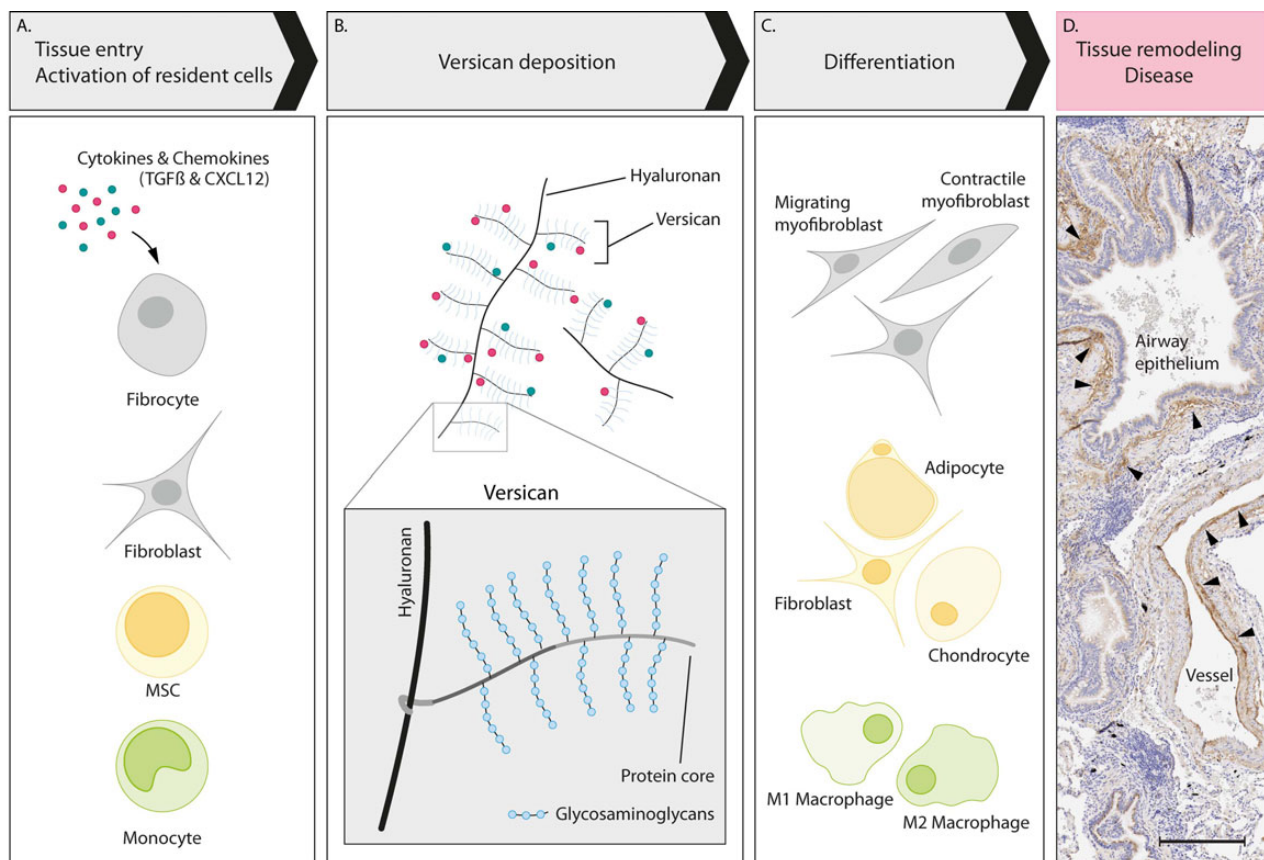
The tissue-remodeling processes are orchestrated by recruited inflammatory cells, resident cells, cytokines and chemokines (see Figure 1). One central player during remodeling in lung disorders is transforming growth factor (TGF)- $\beta$  (Yang et al. 2012), which has been reviewed for COPD (Konigshoff et al. 2009), asthma (Duvernelle et al. 2003), pulmonary fibrosis (Khalil and Greenberg 1991) and BOS (Andersson-Sjöland, Thiman, et al. 2011). Alveolar epithelial cells have the capacity to release a host of cytokines and chemokines, and the derangement of epithelial–macrophage interactions induced by injury may result in persistent inflammation and remodeling (Alber et al. 2012). The inflammatory site in the lung triggers homing and activation of both local and bone marrow-derived progenitor cells that are important in the healing process (Krause 2008).

Remodeling occurs as a result of persistent mechanical stress or hypoxia, but may also be a response to prolonged inflammation since inflammatory processes may affect the tissue. Scar-forming inflammation is thus an important feature of several lung disorders where versican plays an important role. Interestingly, remodeling has also been shown to occur in parallel with inflammation (Rydell-Tormanen et al. 2012), often in both airways and pulmonary vessels (Zanini et al. 2010). During disease progression, the altered blood vessels affect lung structure, and decrease lung function and oxygen saturation (Colombat et al. 2007). The epithelium is also affected and

subjected to increased oxidative stress and other triggers, such as pollen, that cause the epithelium to lose its function and differentiate into mesenchymal cells, with increased deposition of ECM and thickening of the gas exchange layer (Gorowiec et al. 2012). Indeed, stiffening of the ECM during remodeling and development of fibrosis affects cell adhesion and migration so that cells migrate towards stiffer ECM (Plotnikov and Waterman 2013).

Because all these changes contribute to disease progression, it is necessary to study the molecular composition of the ECM niche to understand cell behavior. Fibroblasts are central during remodeling and major contributors to the increased deposition of proteoglycans (PGs). Versican is one of the deposited PGs and is an important player in COPD (Hallgren et al. 2010), asthma (Westergren-Thorsson et al. 2002) and BOS (Andersson-Sjöland et al. 2009).

PGs consist of a core protein with covalently bound glycosaminoglycans (GAGs), which can be sulfated to varying extent. These molecules play crucial roles in lung infection, inflammation and tissue repair as major regulators of cell behavior in the ECM (Gill et al. 2010). The reactive GAG chains result in the ability of certain PGs, such as versican, to control the viscoelastic behavior and stability of the ECM. Different families of PGs contain different GAG side chains; chondroitin sulfate/dermatan sulfate (CS/DS) PGs (lecticans), small leucine-rich repeat PGs (SLRP), and heparan sulfate PGs (HSPGs).



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**Fig. 1.** Events involving versican in the development of lung disease (e.g. COPD). **(A)** As a response to tissue damage and the cytokine/chemokine milieu (dots), mesenchymal (fibroblasts) and inflammatory (monocytes) cells migrate towards injury, and progenitor cells (MSC and fibrocytes) are recruited locally or from the circulation. **(B)** As a result, among other ECM molecules, versican is deposited in the lung tissue, increasing the reserve of cytokines/chemokines that perpetuate the recruitment of inflammatory cells. **(C)** Versican is involved in the differentiation of cells as depicted color coded (monocyte to macrophage, MSC to fibroblast and fibrocyte to myofibroblast). **(D)** Immunohistochemistry visualizes the deposition of versican (brown colors, arrow heads) in lung parenchyma from COPD patients.

Versican belongs to the CS/DS PG gene family along with aggrecan, neurocan, and brevican, each differently distributed: versican in various soft tissues; aggrecan prominent in cartilage; and neurocan and brevican in the central nervous system (Margolis and Margolis 1994). These PGs are involved in infection and inflammation by interacting with, e.g. cytokines and growth factors. There are other CS/DS PGs important in remodeling and inflammation events such as the SLRPs biglycan, fibromodulin and decorin. These PGs are crucial for matrix assembly and regulation of collagen fibrillation. HSPGs are mainly expressed in the alveolar basement membranes and on cell surfaces. The cell surface bound HSPGs are either attached by a glycosylphosphatidylinositol (GPI) anchor (the glypicans) or by a transmembrane part (the syndecans). Also the HSPGs are highly bioactive and implicated in development and disease, including lung emphysema seen in, e.g. COPD (Smits et al. 2010).

Alterations in the expression of PGs directly influences matrix compliance and permeability of vessels, airways and the surrounding tissues. Importantly, the integrity of tissues and stability of the ECM network is supported by interactions between ECM molecules such as versican, and its intimate binding partner hyaluronan. The latter is mainly produced by fibroblasts and binds several proteins. In this respect, hyaluronan, versican and CD44 contribute to the stability of the ECM. In this review, we will explore the current knowledge about the molecular role of versican in the lung niche and how it may be involved in disease.

## Structure and function of versican

Versican encoded on human chromosome 5 and spanning over 90 kb, shares similar globular (G) structures at the N terminal (G1 domain) and C terminal (G3 domain) of the protein core along with the other members of the lectican family. The G1 domain contains an immunoglobulin (Ig)-like domain and a hyaluronan-binding region (HABR), whereas the G3 domain consists of two epidermal growth factor (EGF) repeats, a C-type lectin motif (LC) and a complement-binding protein (CRP)-like motif. Between G1 and G3 versican has CS/DS-binding domains where GAG side chains attach (see Figure 2; Zimmermann and Ruoslahti 1989).

The CS/DS GAG chains are linear anionic polysaccharides consisting of up to ~40 repeating disaccharide units of glucuronic acid (GlcA) and *N*-acetyl-galactosamine (GalNAc). Some of the GlcA can be epimerized into iduronic acid (IdoA) and the polysaccharide may then be referred to as DS or rather CS/DS, due to the mixed content of GlcA and IdoA. The presence of IdoA confers a more flexible structure of the GAGs and allows for binding of growth factors and cytokines. We have demonstrated that IdoA is of importance during directed migration, and the ablation of dermatan epimerase 1 that is responsible for

generation of IdoA led to delayed ability to re-populate wounded areas (Bartolini et al. 2013). Importantly, versican contains only ~10% or less IdoA, and it is not clear whether this content affects cell behavior such as migration.

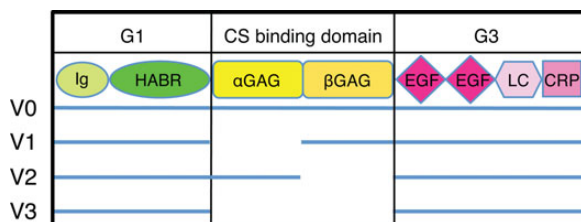
Yet another modification affecting cell behavior is the sulfation of the GAGs to various extents with preference to 4-sulfated GalNAc residues. A substantial amount of 6-sulfated GalNAc is also found. Finally, small amounts of non-sulfated, 2,4-sulfated, 2,6-sulfated and 4,6-sulfated disaccharides have been described (Hitchcock et al. 2006). Importantly, the sulfation pattern is of great importance for cellular events and is crucial for chemokine- and selectin-binding to versican (Kawashima et al. 2002).

Adding complexity, versican can be differentially spliced. Alternative splicing of versican mRNA encoding the CS/DS-binding domain generates four isoforms of versican, namely V0, V1, V2 and V3, which differ in molecular weight. The splice variants are outlined in Figure 2. Recently, an additional isoform, V4, was identified as up-regulated in breast cancer along with the other splice variants (Kischel et al. 2010). The versican isoforms differ in length in their CS/DS-binding domain and therefore also in the number of GAG side chain attachment sites. The V0 is the largest isoform and contains two GAG-binding domains named  $\alpha$ -GAG-binding domain and  $\beta$ -GAG-binding domain. The V1 contains only the  $\beta$ -GAG-binding domain, whereas the V2 only has the  $\alpha$ -GAG-binding domain. The V3 splice form completely lacks GAG attachment sites, and is the smallest of the isoforms (see Figure 2).

TGF- $\beta$  has been shown to induce the expression of proteins that are involved in mRNA splicing and RNA processing in human lung fibroblasts (Hallgren et al. 2012). Importantly, TGF- $\beta$ 2 and TGF- $\beta$ 3 increase the expression of splicing variants V0 and V1 (Berdiaki et al. 2008; Norian et al. 2009). The production of these alternative isoforms of versican by fibroblasts primarily may trigger and perpetuate tissue remodeling and disease progression (Hallgren et al. 2012). Interestingly, different isoforms of versican affect cell behavior differently and could be of importance during pathological progression. Alternative splicing leading to increased levels of V1 thus increased proliferation and also resulted in a resistance to apoptosis in fibroblasts. The V2 isoform on the other hand decreased the proliferation and had no effect on apoptosis (Sheng et al. 2005). Interestingly, the V1 variant had the ability to induce mesenchymal–epithelial transition in fibroblasts, resulting in an expression-shift from N-cadherin to epithelial specific E-cadherin (Sheng et al. 2006).

The complex structure of the core protein invites many binding partners. For example, integrin $\beta$ 1, EGF-R, tenascin, fibulin-1 and -2 as well as fibrillin-1 bind to the G3 domain of versican (Wu et al. 2005). In addition, the negatively charged GAGs create a brush-like structure around the core of versican, and these properties contribute to the long extended shapes of the versican molecules opening up for binding of positively charged molecules such as cytokines, chemokines, growth factors and also selectins and CD44 (Wu et al. 2005). Interestingly, versican can bind specific chemokines such as liver- and activation-regulated chemokine, and secondary lymphoid-tissue chemokine, but not others (e.g. IL-8 and macrophage inflammatory protein-1 $\alpha$ ). The binding occurs through the CS/DS chains of versican, and the binding tends to down-regulate the function of these chemokines (Hirose et al. 2001). It is however important to note that versican only displays a few IdoA residues. The DS part of PGs is of great importance during coagulation and also affects wound healing and inflammation (Malmstrom et al. 2012).

Taken together, the vast biological diversity of versican highly contributes to its important roles in physiological and pathological events.



**Fig. 2.** Structure of versican and its splice variants. Versican has globular domains at the N- (G1) and C-terminal (G3). The G1 contains an Ig-like domain, and an HABR; the G3 contains two EGF repeats; a LC; and a CRP-like motif. Between G1 and G3, CS/DS-binding sites attach GAG side chains to a various extent depending on splice variant (V0, V1, V2 and V3).

## Regulation of versican expression

The biodiversity of versican lies in the different domains of the molecule, and in particular the CS/DS-binding domain contributes highly to the various activities of versican. The specific GAG constitution displayed on the versican molecules is influenced by extracellular signals such as TGF- $\beta$ -, EGF- and platelet-derived growth factor (PDGF)-BB affecting specific GAG synthetic enzymes involved in the process (Tiedemann et al. 1997). TGF- $\beta$ 1 is a key player in regulating ECM production and up-regulates the synthesis of versican in many cells, among those, lung fibroblasts (Westergren-Thorsson et al. 1991). The TGF- $\beta$  signaling pathway is strongly associated with fibrotic and inflammatory lung disorders, and indeed, the binding of TGF- $\beta$  to its type II receptor in concert with the type I receptor leads to formation of a receptor complex and phosphorylation of the type I receptor. Subsequently, the type I receptor phosphorylates Smad2 or 3, which associates with Smad4 and the whole complex translocates into the nucleus. In the nucleus, the Smad complex associates with transcription factors and the complexes bind to specific binding sites within the promoter of versican, biglycan and many other target genes (Kamoto et al. 2013). The versican promoter contains a typical TATA box around 16 bp upstream of the transcription-starting site. The 5' flanking sequence contains promoter, enhancer and repressor elements allowing for specific regulation of versican in different situations. Several transcription factor binding sites have also been revealed, including cAMP response element-binding protein, T-cell factor/lymphoid enhancer-binding factor (TCF/LEF), and activator protein 1 (Sotoodehnejadnematalahi and Burke 2013).

Yet another way to transcribe versican is through the canonical wnt pathway, one of the fundamental pathways involved in activities of development and tissue homeostasis (Logan and Nusse 2004), controlling proliferation, differentiation, cell polarity and motility events of relevance in tissue remodeling. Apart from TGF- $\beta$ , signaling through the Smads also mediates fibrosis through the wnt signaling pathway (Akhmetshina et al. 2012). The key event in the wnt pathway is regulation of the production and stability of  $\beta$ -catenin in the cytosol. In the absence of wnt,  $\beta$ -catenin is phosphorylated by the  $\beta$ -catenin destruction complex and targeted for proteasomal degradation. Wnt proteins stabilize the  $\beta$ -catenins and upon cytosolic  $\beta$ -catenin accumulation, the complex is translocated into the nucleus where it interacts with TCF/LEF (Korinek et al. 1997; Rahmani et al. 2012). This leads to transcription of versican among other wnt target genes (Rahmani et al. 2005; van Amerongen and Nusse 2009). Interestingly, the wnt pathway may be regulated by integrins, and  $\beta$ 1-integrin can activate the wnt pathway via integrin-linked kinase (Maydan et al. 2010). Upon interaction between  $\beta$ 4-integrin and collagen in the ECM, the growth factor bound 2 is recruited; inducing growth factor induced  $\beta$ -catenin accumulation. Recently, aberrant wnt signaling has been proposed as a key pathway in systemic sclerosis pulmonary fibrosis (Lam et al. 2011; Beyer et al. 2012) and studies to inhibit the wnt pathway have unraveled the potential in targeting the tankyrases. The inhibition of tankyrases resulted in reduced nuclear accumulation of  $\beta$ -catenin (Distler et al. 2012) and inhibited wnt signaling along with reduced bleomycin-induced fibrosis.

Another level of control is through microRNA, which are small non-coding RNA molecules involved in the homeostasis and remodeling events of ECM (Rutnam et al. 2013). Interestingly, the 3'UTR of versican can also modulate the function of several microRNAs, signifying the multitude of control mechanisms (Lee et al. 2010). In several lung disorders, we have seen an altered phenotype in the lung smooth muscle cell mass. The transcription factor myocardin in smooth

muscle cells has been shown to coordinate smooth muscle cell differentiation through the induction of microRNA-143. By specifically binding to the 3' UTR of versican, miRNA-143 attenuates versican expression and subsequently, smooth muscle cell migration (Wang et al. 2010).

Fine-tuning of versican production is thus possible through many levels of control in different tissues and during disease. Importantly, this may lead to therapeutic targeting of versican in a specific way to counteract aberrant wound repair in the lung.

## Cellular origins of versican

Versican is expressed by several cell types, and in the lung it is primarily found in elastic fibers in the lamina propria of the central airway wall, predominantly close to the smooth muscle bundles. In the alveolar parenchyma, versican expression is found in irregular and patchy areas in the alveolar septa. Fibroblasts are central producers of the ECM and key regulators of versican during health and even more so during diseases such as COPD (Hallgren et al. 2010), asthma (Westergren-Thorsson et al. 2002) and BOS (Andersson-Sjöland, Thiman, et al. 2011). Human embryonic lung fibroblasts express high levels of versican, pointing towards an important role of fibroblasts and versican during lung development (Tufvesson and Westergren-Thorsson 2000). Versican plays a role in cell-ECM binding and in a study on primary lung fibroblasts obtained from lung-transplanted patients, the migratory properties of these cells had a tendency to decrease, whereas the production of versican increased (Andersson-Sjöland, Thiman, et al. 2011). This could be a result of fibroblasts binding to a versican-rich environment. Versican also has a regulatory effect on cell proliferation, being highly expressed in proliferating dermal fibroblasts (Zimmermann et al. 1994), as well as muscle cell proliferation during development (Velleman et al. 2012). This could be due to the fact that versican is highly regulated by the cytokine/growth factor milieu and, apart from TGF- $\beta$ , PDGF-AB, has been shown to stimulate the expression of versican core protein in arterial smooth muscle cells (Schonherr et al. 1997). On the other hand, proinflammatory cytokines such as IL-1 $\beta$  and IFN- $\gamma$  reduced the expression of versican in arterial smooth muscle cells (Lemire et al. 2007), pointing towards the complex regulation of versican during inflammation.

The multipotent mesenchymal stromal/stem cells (MSCs) exhibit an increase in versican production during differentiation (Foster et al. 2005) and Murphy et al. showed that versican mRNA levels were present already in undifferentiated MSCs, which were maintained during differentiation. Further exploration is required to elucidate the potential role that versican may play in the differentiation of resident lung-derived MSC into cell types that may hamper disease progression, or perhaps the opposite.

Fibrocytes are another type of mesenchymal progenitor cells that derive from bone marrow and home to human lung tissue upon tissue damage (Andersson-Sjöland et al. 2009). When fibrocytes are recruited from the bone marrow to the tissue they can, in conformity with MSC, differentiate into different cell types plausibly including fibroblasts (Andersson-Sjöland, Nihlberg, et al. 2011). Previous studies have reported that the collagen and proteoglycan gene expression profiles of fibrocytes and fibroblasts differ, and that fibrocytes express higher mRNA levels of versican than fibroblasts. Also, the production of high levels of versican together with perlecan, hyaluronan and collagen VI support the hypothesis that fibrocytes are involved in tissue stabilization and modulation of inflammatory responses (Bianchetti et al. 2012; see Figure 1).

## Versican during inflammation

The molecular composition of the niche predisposed by the production of specific ECM molecules such as versican is crucial for a properly mounted inflammatory response. However, in lung disorders, the excessive remodeling processes result in perpetuated inflammation. New insights into how innate immunity influences pathological remodeling are beginning to emerge, revealing interactions between Toll-like receptors (TLRs) and the ECM including damage-associated molecular patterns (DAMPs). A number of endogenous molecules specifically generated upon tissue injury have been identified to activate TLRs, such as versican, biglycan and fragments of hyaluronan and HS (Piccinini and Midwood 2010). Fibroblasts of a different origin and endothelial cells express TLR2 and its co-receptors, thus versican could be a potent trigger for activation of fibroblasts and endothelial cells during inflammation (Wang et al. 2009). Binding of DAMPs to TLRs induces the production of proinflammatory cytokines and upregulates co-stimulatory molecules linking matrix remodeling and innate immune responses to the adaptive immunity (Tufvesson and Westergren-Thorsson 2003; Schaefer et al. 2005; Phipps et al. 2007; Kim et al. 2009; Piccinini and Midwood 2010). Thrombospondin-1, which is up-regulated during wound repair and remodeling, binds to the G1 domain of versican resulting in colocalization into microfibrils containing elastin on vascular smooth muscle cells to further the inflammatory niche (Kuznetsova et al. 2006; see Figure 2). Hyaluronan is enhanced at sites of inflammation, tumor growth and tissue remodeling, and is thought to modulate cell behavior through interaction with several receptors among them being CD44. The hyaluronan–versican interaction is important for T-cell recruitment into inflamed areas and virus infection-induced hyaluronan synthesis induced the concomitant synthesis of versican. Moreover, CD4+ T-cells cultured on versican-rich ECM were retained in culture, although their migration was inhibited (Evanko et al. 2012). Studies of lung fibroblasts treated with polyinosinic:polycytidylic acid (poly I:C), which mimics a viral infection, showed an increase in hyaluronan and versican and a related increase in monocyte adhesion to these matrix structures (Evanko et al. 2009). Versican is thus also important for recruitment of monocytes, which has been demonstrated in a model of myocardial infarction. Here, infiltrating monocytes after stimulation with GM-CSF-induced versican expression (Toeda et al. 2005) and monocytes have been shown to be dependent on versican during adhesion (Potter-Perigo et al. 2010). Indeed, monocytes bind to the ECM during differentiation and have been shown to produce versican along with hyaluronan synthases 2 in this process. In addition, TNF-stimulated gene-6 (TSG-6), encoding for the TSG-6 protein that contributes to matrix stability, was also expressed from monocytes during differentiation into macrophages (Chang et al. 2012). A recent study showed that versican was up-regulated in monocytes in patients with systemic sclerosis and it is possible that versican contributes to the fibrotic processes through a feedback loop involving versican and chemokines, resulting in influx of monocytes (Masuda et al. 2013).

In addition, versican accumulates in tumor stroma and plays an important role in proliferation and metastasis of tumor cells (Du et al. 2013). Relevant in inflammatory states, including cancer and the lung disorders discussed here, versican and especially its C terminus, promotes cell survival and protects cells from H<sub>2</sub>O<sub>2</sub>-induced apoptotic cell death by enhancing cellmatrix interactions (Du et al. 2013).

## Versican in lung disease

Versican is expressed in COPD, asthma and lung-transplanted patients (see Figure 3; Hallgren et al. 2010; Nihlberg et al. 2010;

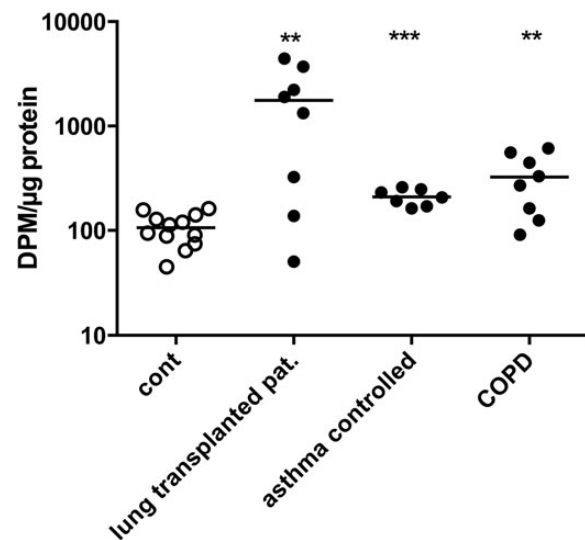


Fig. 3. Graph shows that versican production is increased in lung-transplanted patients, asthma (controlled) and COPD compared with healthy controls. \*\* $P < 0.01$ , \*\*\* $P < 0.005$  compared with controls.

Andersson-Sjoland, Thiman et al. 2011), which indicates that it could be a target for future interventions. Late stage COPD is untreatable and lung transplantation is the only option for these patients and also for other diseases such as cystic fibrosis and IPF. However, lung transplantation is associated with a risk of developing chronic rejection (BOS)—a process involving aberrant wound healing and development of fibrotic plugs in the airways, which leads to insufficient air supply. In a study on lung-transplanted patients, lung fibroblasts produced 16 times more versican half a year after transplantation compared with healthy volunteers. Histology showed that versican was mainly localized in the alveolar walls and thus may contribute to the plug formation (Andersson-Sjoland, Thiman et al. 2011).

## Chronic obstructive pulmonary disorder

COPD is characterized by loss of elastic fibers from small airways and alveolar walls and the decrease in elastin is associated with increased disease severity. Versican is increased in fibroblasts from distal airways from COPD patients (see Figure 3) and indicates that the production is larger than the degradation of versican as seen by immunohistochemistry (Hallgren et al. 2010). Versican in the alveolar wall is also negatively correlated to elastin and elastin-binding protein (EBP; Merrilees et al. 2008), a molecular chaperone important in the fibrillation-process of elastin. These molecular parameters are also correlated to lung function (FEV<sub>1</sub>; Black et al. 2008). Efficient repair by re-synthesis of elastic fibers in alveoli of COPD patients may be hampered by the inhibition of EBP by versican, particularly by its CS/DS chains (Tiedemann et al. 2005). The EBP chaperone escorts tropoelastin from Golgi and endosomal compartments to the cell surface. During states of increased versican in the pericellular compartment, the lectin-domain of EBP interacts with galactosamine in CS/DS of versican, and causes a conformational change in the EBP releasing tropoelastin prematurely. However, since CS/DS GAG-side chains are very variable in the amount and spatial distribution of IdoA it cannot be excluded that it is not the actual amount of versican *per se* but rather the amount of specific CS/DS motifs that regulates the interaction. Normally, following the release of EBP, tropoelastin finds its acceptors, the newly forming microfibrils of elastin. However, during high-versican

microenvironment, new formation of elastic fibers is hampered. The relationship between elastic fiber loss and accumulation of versican has been confirmed in studies showing that modulation of versican influences elastic fiber deposition (Merrilees et al. 2002; Huang et al. 2006, 2008). In these settings, versican was harmful through inhibition of elastic fiber formation, but in an animal model of emphysema increased proteoglycan and in particular versican was associated with protection of the alveolar walls from rupture (Takahashi et al. 2014). In line, in a randomized controlled trial, it was shown that inhaled corticosteroids increased the bronchial expression of versican together with collagen III in COPD patients. This increase in versican was associated with improved lung function. Surprisingly, the smoking status of the patients did not influence versican levels (Kunz et al. 2013), although it may affect tissue remodeling as such through the activation of molecules involved in ECM turnover, such as matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 (Boue et al. 2013). However, the up-regulation of versican in COPD lungs is not consistent. Indeed, Annoni et al. (2012) even showed a decrease in versican expression in alveolar parenchyma in COPD patients compared with healthy non-smokers and may point towards the importance of fine-mapping COPD into subtypes of the disease.

## Asthma

Versican is also involved in asthma and in our studies we have shown a heterogeneous pattern of versican distributed throughout the airway tree. Most studies have so far concentrated on central airways, but intriguingly, we have seen a difference in PG production between centrally and distally isolated fibroblasts. Thus distally derived fibroblasts from patients with mild untreated asthma had increased production of versican (see Figure 3; Nihlberg et al. 2010). Similar results have been obtained from fibroblasts isolated from the distal airways in patients with COPD (Hallgren et al. 2010) and in fibroblast cultures obtained early after lung transplantation (see Figure 3; Andersson-Sjöland, Thiman, et al. 2011), emphasizing the importance of studying the distal airways in all lung disorders. Histological analyses of versican in uncontrolled and controlled mild asthmatics and healthy controls showed increased percentage areas of versican in the group of uncontrolled asthmatics in central airways (Weitof, Andersson et al. 2014).

Remodeling of the airways contributes to the persistent airway obstruction and decline in lung function in asthmatic patients (Chiappara et al. 2001; Lange 2013). Additionally there is a correlation between PGs deposition in the airway wall and reactivity of provocation by inhaled methacholine (provocative concentration required to decrease FEV<sub>1</sub> by 20% of its baseline value [PC<sub>20</sub>] <4 mg/mL) in patients with mild atopic asthma (Huang et al. 1999). Altered deposition of PGs in the asthmatic lung appears to vary between different asthma phenotypes and severities (Roberts 1995; de Medeiros Matsushita et al. 2005; Pini et al. 2007; Nihlberg et al. 2011). Indeed, we have shown that fibroblasts isolated from bronchial biopsies from asthmatic patients with the greatest degree of hyper-responsiveness produced larger amounts of versican (Westergren-Thorsson et al. 2002). In line, several studies of mild, moderate and fatal asthma have reported increased densities of versican in the tissue (Ludwig et al. 2004; Araujo et al. 2008). Patients with fatal asthma had increased versican content in the internal area of large and small airways compared with controls (de Medeiros Matsushita et al. 2005). However, it has not been evaluated if the increased amount of versican and other matrix molecules may have an effect in opposing the contractive properties of increasing smooth muscle layers (Roberts 1995). Respiratory viral infections are known to be

a trigger of exacerbation in both asthma and COPD and could be the catalyst that starts an increased deposition of versican and hyaluronan. Furthermore, the versican-rich environment is known to have an increased capacity for monocyte infiltration and increased immune response (Potter-Perigo et al. 2010). It remains to be explored whether this augmentation in versican in asthma is beneficial or may be a target for future therapies.

## Conclusion

Versican is clearly involved in disease processes in COPD, asthma and BOS. Taken that the inflammatory response is different in these disorders, it becomes evident that ECM remodeling may be a target for future drugs. The role of the ECM niche during inflammation and remodeling events in lung disorders is to serve as an important scaffold for inflammatory and mesenchymal cells and their fate decision, see Figure 1. In this review, we have elucidated versican as an important player in inflammation and remodeling that shows a complex repertoire of cellular actions. An up-regulation of versican in these disorders may perpetuate inflammatory responses and lead to aberrant wound healing processes. The role of versican in innate and adaptive immunity needs further investigations, as does the differential expression of the splice forms. Another structural feature of high potential interest is the function of the CS/DS side chains and its modulation in different inflammatory conditions. We therefore conclude that versican is an interesting target for future research and the dissection of specific roles of its splice variants may be fruitful for finding intervening targets to treat lung disorders such as COPD, asthma and chronic rejection.

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## Conflict of interest statement

None declared.

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## Abbreviations

BOS, bronchiolitis obliterans syndrome; COPD, chronic obstructive pulmonary disease; CREB, cAMP response element-binding protein; CRP, complement-binding protein; CS/DS, chondroitin sulfate/dermatan sulfate; DAMPs, damage-associated molecular patterns; EBP, elastin-binding protein; ECM, extracellular matrix; EGF, epidermal growth factor; GAGs, glycosaminoglycans; GalNAc, N-acetyl-galactosamine; GlcA, glucuronic acid; GPI, glycosyl-phosphatidylinositol; HABR, hyaluronan-binding region; HSPGs, heparan sulfate PGs; IdoA, iduronic acid; Ig, immunoglobulin; MIP-1 $\alpha$ , macrophage inflammatory protein-1 $\alpha$ ; MSCs, mesenchymal stromal/stem cells; PDGF, platelet-derived growth factor; PGs, proteoglycans; SLRP, small leucine-rich

repeat PGs; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; TGF, transforming growth factor; TLRs, Toll-like receptor; TSG-6, TNF-stimulated gene-6.

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