Available online at www.sciencedirect.com

SciVerse ScienceDirect

ELSEVIER

Current Opinion in Genetics & Development

Current Comment

Small leucine-rich proteoglycans, at the crossroad of cancer growth and inflammation☆

Liliana Schaefer and Renato V Iozzo

Current Opinion in Genetics & Development 2012, **22**:56–57

Available online 9th February 2012

0959-437X

DOI 10.1016/j.gde.2011.12.002

Liliana Schaefer

Goethe University, Frankfurt, Germany

Liliana Schaefer is currently the Professor of Nephropharmacology at the Institute of Pharmacology and Toxicology, University of Frankfurt/Main with an area of expertise in matrix biology. She is a member of the Editorial Board of The Journal of Biological Chemistry, Associated Editor of the Journal of Histochemistry & Cytochemistry and President of the German Connective Tissue Society. Her science interests are focussed on the role of soluble matrix components as fundamental danger signals signifying tissue injury and on the design of new drugs targeting these danger ligands in inflammation, cancer, and fibrosis.

Renato V Iozzo

Thomas Jefferson University, Philadelphia, PA, USA

Renato Iozzo is currently Professor of Pathology and Cell Biology, and Professor of Biochemistry and Molecular Biology at Thomas Jefferson University, Philadelphia, Pennsylvania. He also holds an *Honorary Professorship* at the School of Life Sciences, University of Manchester, UK. He was the chair of the Gordon Research Conference on Proteoglycans in 2000, and was President of both the American and International Societies for Matrix biology. He has published over 280 articles on proteoglycan biology, cancer and angiogenesis.

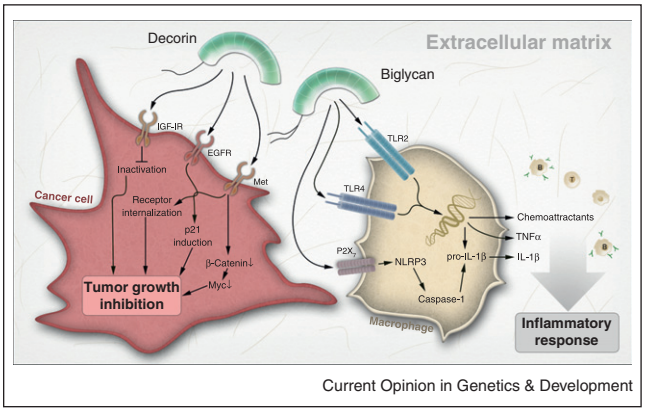
Current Comments are a rapid outlet for scientific opinions on a topic of general interest.

Decorin and biglycan, the two best studied members of the small leucine-rich proteoglycan (SLRP) family, have been implicated in regulating cancer growth and inflammation, respectively. Decorin expression is almost always suppressed by cancer cells but abundantly produced by activated stromal fibroblasts in the tumor microenvironment [1]. Often an inverse relationship exists between cancer growth and decorin expression, suggesting that decorin is an 'endogenous guardian' from the matrix. The mechanism of decorin-evoked tumor repression is linked to its ability to potently induce the endogenous synthesis of p21, a key inhibitor of cyclin-dependent kinases. This is carried out by soluble decorin binding in a paracrine fashion to several receptor tyrosine kinases (RTKs) including the EGFR, IGF-IR and Met (see Figure 1) [2]. Thus, decorin is a natural RTK inhibitor and systemic delivery of recombinant decorin inhibits the growth of various tumor xenografts [3,4]. Currently, it is a matter of debate of how decorin exactly inactivates specific receptors, given the fact that RTKs are ubiquitously expressed. One explanation involves a hierarchical mode of receptor affinity insofar as dissociation constants range from ~1 nM in the case of Met [5] to ~90 nM for EGFR. Thus, it could be envisioned that decorin, by acting as a pan-RTK inhibitor, would target many different types of tumors that exhibit differential RTK binding affinities for decorin. In most cases analyzed thus far, decorin evokes a rapid and protracted internalization of both EGFR and Met via caveolar-mediated endocytosis, a process that often leads to silencing of the receptors. Indeed, decorin blocks several biological processes associated with Met activation, such as cell scatter, evasion and migration [5]. One of the cellular mechanisms affected by this matrix molecule is via downregulation of the non-canonical β-catenin pathway. This leads to suppression of Myc, a downstream target of β-catenin, culminating in Myc proteasomal degradation [6]. Since Myc is a 'master regulator' which can affect up to 1500 genes, it is not surprising to predict that novel functional roles for decorin will be discovered in the near future.

The other SLRP structurally related to decorin, that is, biglycan, acts as a danger signal and triggers both innate and adaptive immune responses. Under physiological conditions, the ubiquitously expressed biglycan is sequestered in the extracellular matrix and is immunologically inert. Upon tissue stress or injury, resident cells secrete proteolytic enzymes, which degrade the extracellular matrix and thus liberate biglycan and fragments thereof. Soluble biglycan and some of its fragments interact with Toll-like receptor (TLR)-2 and TLR4. By activating TLRs, biglycan triggers the synthesis of various proinflammatory cytokines (e.g. TNFα and IL-1β) and chemoattractants, thereby recruiting macrophages into damaged areas in order to resolve the injury (see Figure 1) [7]. Thus, soluble biglycan acts as a danger signal, which

☆ Current Comments contain the personal views of the authors who, as experts, reflect on the direction of future research in their field.

Figure 1



Multiple signaling pathways evoked by decorin and biglycan regulating cancer growth and inflammation. For details see text.

initiates a rapid innate immune response without the need for *de novo* synthesis of 'warning' molecules. In addition, upon stimulation with proinflammatory cytokines, resident cells and infiltrating macrophages synthesize full-length biglycan leading to the recruitment of additional macrophages, which are also capable of synthesizing and secreting biglycan [7]. This creates a feed-forward loop that leads to robust proinflammatory signaling. Moreover, biglycan is capable of clustering TLR2/4 with purinergic $P2X_7$ receptors, thereby autonomously activating the NLRP3 inflammasome and caspase-1 and secretion of mature IL-1β (see Figure 1) [8].

Besides recruiting macrophages, biglycan stimulates the TLR2/4-dependent synthesis of key chemoattractants for T and B lymphocytes and is thus also involved in the adaptive immune response (see Figure 1). Biglycan specifically recruits B1 lymphocytes which are responsible for T cell-independent production of antibodies. This represents an early defense against pathogens, before the adaptive immune response is activated. The biological importance of these mechanisms has been shown in systemic lupus erythematosus (SLE), a prototypic autoimmune disease affecting mainly young women. In SLE, soluble biglycan stimulates the synthesis of autoantibodies and enhances recruitment of macrophages as well as T and B lymphocytes resulting in enhanced inflammation in target organs. Notably, biglycan attracts B cells to chronically inflamed non-lymphoid organs and promotes the development of tertiary lymphoid tissue and acceleration of disease [9].

Collectively, these findings shed new light on the mechanisms of sterile inflammation, which plays a key role in tissue repair and regeneration (e.g., wound healing), ischemia/reperfusion injury (e.g., myocardial infarction) and autoimmune diseases (e.g., rheumatoid arthritis, SLE) among others. There is emerging evidence that soluble biglycan is generated in non-pathogen-mediated inflammatory diseases and autonomously triggers sterile inflammation by orchestrating TLR2/4 and NLRP3 inflammasome signaling [9]. On the other hand, in pathogen-mediated inflammation, the affinity of biglycan to receptors sensing either gram-positive or gram-negative pathogens allows for enhancement of inflammation via a second TLR, which is not involved in pathogen sensing [10].

The SLRPs are emerging as powerful signaling molecules affecting both cancer growth and inflammation. Thus, because cancer and inflammation are closely linked, we envisage that SLRPs such as decorin and biglycan could potentially become valid natural therapeutic agents or target themselves. A novel emerging concept is that, upon release from the extracellular matrix, a 'basically inert' matrix component can turn into either a tumor repressor or a pro-inflammatory danger signal, which can subsequently drive innate and adaptive immune responses. This concept will offer novel perspectives in designing new pharmacological agents for therapeutic interventions in cancer, inflammatory and autoimmune diseases.

References

1. Iozzo RV, Sanderson RD: **Proteoglycans in cancer biology, tumour microenvironment and angiogenesis**. *J. Cell. Mol. Med.* 2011, **15**:1013-1031.
2. Goldoni S, Iozzo RV: **Tumor microenvironment: modulation by decorin and related molecules harboring leucine-rich tandem motifs**. *Int. J. Cancer* 2008, **123**:2473-2479.
3. Seidler DG, Goldoni S, Agnew C, Cardi C, Thakur ML, Owens RA, McQuillan DJ, Iozzo RV: **Decorin protein core inhibits *in vivo* cancer growth and metabolism by hindering epidermal growth factor receptor function and triggering apoptosis via caspase-3 activation**. *J. Biol. Chem.* 2006, **281**:26408-26418.
4. Hu Y, Sun H, Owens RT, Wu J, Chen YQ, Berquin IM, Perry D, O'Flaherty JT, Edwards IJ: **Decorin suppresses prostate tumor growth through inhibition of epidermal growth factor and androgen receptor pathways**. *Neoplasia* 2009, **11**:1042-1053.
5. Goldoni S, Humphries A, Nyström A, Sattar S, Owens RT, McQuillan DJ, Ireton K, Iozzo RV: **Decorin is a novel antagonistic ligand of the Met receptor**. *J. Cell Biol.* 2009, **185**:743-754.
6. Buraschi S, Pal N, Tyler-Rubinstein N, Owens RT, Neill T, Iozzo RV: **Decorin antagonizes Met receptor activity and downregulates β-catenin and Myc levels**. *J. Biol. Chem.* 2010, **285**:42075-42085.
7. Schaefer L, Babelova A, Kiss E, Hausser H-J, Baliova M, Krzyzankova M, Marsche G, Young MF, Mihalik D, Götte M, Malle E, Schaefer RM, Gröne H-J: **The matrix component biglycan is proinflammatory and signals through toll-like receptors 4 and 2 in macrophages**. *J. Clin. Invest.* 2005, **115**:2223-2233.
8. Babelova A, Moreth K, Tsalastra-Greul W, Zeng-Brouwers J, Eickelberg O, Young MF, Bruckner P, Pfeilschifter J, Schaefer RM, Gröne H-J, Schaefer L: **Biglycan, a danger signal that activates the NLRP3 inflammasome via Toll-like and P2X receptors**. *J. Biol. Chem.* 2009, **284**:24035-24048.
9. Moreth K, Brodbeck R, Babelova A, Gretz N, Spieker T, Zeng-Brouwers J, Pfeilschifter J, Young MF, Schaefer RM, Schaefer L: **The proteoglycan biglycan regulates expression of the B cell chemoattractant CXCL13 and aggravates murine lupus nephritis**. *J. Clin. Invest.* 2010, **120**:4251-4272.
10. Iozzo RV, Schaefer L: **Proteoglycans in health and disease: novel regulatory signaling mechanisms evoked by the small leucine-rich proteoglycans**. *FEBS J.* 2010, **277**:3864-3875.