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From the Editor's Desk

# Proteoglycans, key regulators of cell–matrix dynamics

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A B S T R A C T

In this special issue of *Matrix Biology* centered on proteoglycan biology we have assembled a blend of articles focused on the state-of-the-art of proteoglycanology. The field has greatly expanded in the past three decades and now encompasses all the areas of biology. This special issue is divided into five chapters describing hyaluronan metabolism, biosynthetic and catabolic pathways of proteoglycans and their roles in inflammation, cancer, repair and development. We hope that the new original work and the reviews from recognized leaders will stimulate investigations in this exciting and fertile field of research.



Proteoglycans (PGs) represent a heterogenous group of molecules that collectively display a multifaceted nature and possess the common feature of a protein core upon which one or more glycosaminoglycan (GAG) chains, such as chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS), heparin (He) or heparan sulfate (HS) are covalently bound (Iozzo, 1998; Schaefer and Schaefer, 2010; Schaefer, 2012; Couchman and Pataki, 2012). An exception to this rule is hyaluronan (HA), which lacks a protein core (Schaefer, 2012). The numerous physiological processes reflect the versatility of PGs and the pathological conditions they were found to be involved in, and also the nature of their roles as both structural components of the extracellular matrix (ECM) and signaling molecules (Schaefer and Schaefer, 2010; Schaefer, 2011; Moreth et al., 2012; Frey et al., 2013; Nastase et al., 2014). Many PGs such as decorin or versican are present in all tissues as components of the ECM, while others, such as brevican, neurocan, or phosphacan are seemingly tissue specific (Schaefer and Schaefer, 2010).

PGs can be classified into three groups based on the properties of their protein core, size, localization, and the molecular composition of their GAG chains (Schaefer, 2012). The first group, modular PGs, share a common feature that permits the assembly of various protein modules into a single structure. This group can be further subdivided into HA-binding PGs known as hyalectans (*e.g.* aggrecan, versican, brevican, neurocan) and non-hyaluronan-binding PGs (*e.g.* perlecan, agrin, collagen XVIII) (Iozzo and Murdoch, 1996; Schaefer, 2012). The second group, small leucine-rich proteoglycans (SLRPs) are characterized by the presence of leucine-rich-repeats in their primary structure and are further subdivided into five distinct classes (Nastase et al., 2014). Decorin and biglycan are the SLRPs towards which most of the studies so far have been directed. The final group, cell surface PGs, are segregated into syndecans and glypicans. Serglycin is an exception, as it is an intracellular PG and the only one that carries heparin (Schaefer, 2012).

This special issue of *Matrix Biology* summarizes recent developments concerning the biology of selected proteoglycans and hyaluronan, assembled during the 8th International Conference on Proteoglycans, organized by Liliana Schaefer (Frankfurt, Germany) and John R. Couchman (Copenhagen, Denmark) in Frankfurt/Main, Germany, August 25–29, 2013. The International Conference on Proteoglycans was founded about 16 years ago to allow presentation of new research in the odd years relative to the highly-popular Gordon Research Conference on Proteglycans, which is held in the even years in New Hampshire. The conference in Glashütten, a rural place near Frankfurt, was highly successful and included a large number of young investigators from four continents.

The present issue contains a diverse blend of 31 contributions including original research articles, short reports, and mini-reviews. Opening this issue is a personal retrospective overview of proteoglycan research accrued over several decades by Ulf Lindahl, with a particular emphasis on the impact of GAG structure on interactions with proteins and the control of GAG structure by the "GAGosome". A perspective by Hascall et al. postulating the role of HA metabolism as a rheostat for controlling cytosolic UDP-GlcNAc concentrations to maintain normal cell functions highlights the first chapter on *Hyaluronan Metabolism*. The following chapters provide overviews and reports on novel findings regarding *Proteoglycan Synthesis and Catabolism*, *Structure–Function Analysis of Proteoglycans*, impact of *Proteoglycans in Inflammation and*

*Abbreviations:* CS, chondroitin sulfate; DS, dermatan sulfate; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; GAG, glycosaminoglycan; HA, hyaluronan; HS, heparan sulfate; IGF-IR, insulin-like growth factor 1 receptor; IR-A, insulin receptor A isoform; KS, keratan sulfate; MyD88, myeloid differentiation primary response gene 88; PG, proteoglycan; SLRP, small leucine-rich proteoglycan; TLR, toll-like receptor; TRIF, TIR-domain-containing adapter-inducing interferon-β; VEGF, vascular endothelial growth factor.

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*Cancer* and the role of *Proteoglycans in Skeletal Differentiation, Repair and Development*.

The second chapter on *Proteoglycan Synthesis and Catabolism* addresses the role of *EXTL2*, encoding *N*-acetylhexosaminyltransferase, in GAG biosynthesis by providing data in *EXTL2*-knockout mice. Next, Busse-Wicher et al. summarize the current knowledge on the enzymatic properties of the EXT family of proteins that harbors glycosyltransferase activities relevant for HS chain polymerization and the functions of EXT/L-proteins not related to HS. Regarding catabolism, Sumeda Nandadasa et al. address the crucial role of versican cleavage by ADAMTS proteases for embryonic remodeling. Keeping in the theme of catabolic processes, the newly described signaling mechanisms of decorin-mediated endothelial cell autophagy are presented by Goyal et al. Finally, the last publication in this chapter deals with the HSPG as a cell-surface endocytosis receptor involved in infectious diseases, lipid metabolism, and cancer as an interesting target for macromolecular drug delivery.

The chapter on *Structure–Function Analysis of Proteoglycans* begins with a review by Stewart and Sanderson concerning the functions that HS and HSPGs serve in the nucleus and their impact on the expression of genes within normal or diseased cells. Then, Thacker et al. review the prevalence, structure, and biological role of HS 3-*O*-sulfation as well as the expression and specificity of the 3-*O*-sulfotransferase family. Peysselon et al. describe the correlation between the affinity and kinetics of protein interactions with heparin and the localization and biological functions of these proteins with a focus on cancer. The chapter continues with novel findings provided by Morcavallo et al. concerning the capacity of the class I SLRP decorin to bind the insulin receptor A isoform (IR-A), its ligands, and the biological consequences of these interactions. The following study by Nikolovska et al. reports the effects of decorin deficiency in mouse skin and the possible correlation with human patients suffering from Ehlers–Danlos syndrome. A study by Chen et al. reports on the effect that interactions between class I and class II SLRPs have in regulating corneal transparency following investigations on mice deficient in either biglycan, lumican, or both SLRPs. Finally, this chapter concludes with two studies by Lord et al. The first reports on the differential roles of perlecan synthesized by either smooth muscle cells or epithelial cells on cell adhesion, proliferation, and growth factor signaling. The second report concerns the alternative splicing of the *HSPG2* gene that encodes perlecan in a human mast cell line and proposes that the smaller perlecan transcripts observed are important for the biological function of mast cells.

The chapter on *Proteoglycans in Inflammation and Cancer* reports on the inflammatory effects of biglycan and versican, two PG-derived endogenous ligands of innate immunity receptors Toll-like receptor (TLR)2/4. In a transient transgenic mouse model, where soluble biglycan is overproduced by hepatocytes and released into the circulation, *in vivo* signaling of biglycan differentially triggering TLR2/4 and myeloid differentiation primary response gene 88 (MyD88) or TIR-domain-containing adapter-inducing interferon-β (TRIF) adaptor proteins in leukocytic chemoattraction is described by Zeng-Brouwers and coauthors. Furthermore, Moreth et al. show that overexpression of soluble biglycan worsens the pathophysiology of renal ischemia–reperfusion injury and impairing the biglycan-triggered TLR2/4 signaling is renoprotective. The review by Wight et al. summarizes our current knowledge about the importance of versican in inflammation, acting as a ligand for myeloid and lymphoid cells *via* multiple binding sites. Further, Chang and collaborators describe a TLR4-dependent increase of versican and hyaluronan in the lungs after a response to gram-negative bacterial infection. Finally, Zhang et al. summarize the roles of HS in neuroinflammation incurred by the structural modifications of HS due to heparanase. Next, the focus switches away from inflammation to cancer. The study by Skandalis et al. concerns the crosstalk between the estradiol receptor and the epidermal growth factor receptor (EGFR)/insulin-like growth factor 1 receptor (IGF-IR) and its consequences on proteoglycan expression in breast cancer. Horváth et al. then report the effects of decorin deficiency in two different mouse models of hepatocarcinogenesis, where loss of decorin permits globally increased RTK phosphorylation, even under basal conditions. The following review by Nikitovic et al. presents the multifunctional role of lumican in tumorigenesis. Finally, this chapter closes with a report of Ramani and Sanderson on an unintended consequence of chemotherapy; chiefly, the shedding and release of syndecan-1 in myeloma, which may cause tumor relapse and accelerate tumor progression.

The last chapter of this special issue is the role of *Proteoglycans in Skeletal Differentiation, Repair and Development* and starts with two investigations into the structurally related SLRPs, biglycan and decorin. In the first report, Berendsen et al. reveal the role of biglycan in the bone repair process by promoting vascular endothelial growth factor (VEGF) signaling, while the second study by Dunkman et al. concerns the age-dependent impact of decorin and biglycan on tendon healing. Jochmann et al. then summarize the existing knowledge of the roles of HS in skeleton differentiation. Filmus et al. then review the role glypicans play in various embryonic processes and human pathologies regulated by Hedgehog signaling. Pan et al. present the consequences of impaired HS synthesis on cardiogenesis in mice deficient in the HS-generating enzyme GlcNAc N-deacetylase/GlcN N-sulfotransferase 1. Finally, in the last publication, Wu et al. show how biglycan and decorincan manipulate fetal membrane stability in mice during distinct gestation stages.

Collectively, this assembly of research articles and timely reviews included in this special issue of *Matrix Biology* underscores the biological relevance and significance concerning the multidisciplinary nature of PGs as structural components of the ECM and major players in signal transduction that are critical for maintaining intracellular homeostatic processes. Thus, PGs are key regulators of cell–matrix dynamics. Furthermore, this issue reflects the tremendous progress in our understanding of PG biology in health and disease and should thereby attract a broad readership, ranging from basic research scientists to clinicians.

This issue resulted as a collective work of well-known specialists and leaders in the matrix biology field. The effort of all 139 contributors to this issue is highly appreciated. I would like to express my gratitude to the Editor in Chief of *Matrix Biology*, Dr. Renato V. Iozzo, and to the Managing Guest Editor, Dr. Ralph Sanderson for their help in editing this special issue. We are all grateful to the publisher of *Matrix Biology*, Kaia Motter, and to Elsevier for promoting publicity in the field of proteoglycan biology and for their contribution to the successful realization of this project. The attractive cover of this special issue is based on the picture of an original art-work by K. Schmidt *The New Frankfurter* provided by courtesy of Michael Gärtner from the *Gallery M* in Frankfurt.

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