Preface

Proteoglycans: Complex Diversity in Structure and Functions

Scientific interest and curiosity for proteoglycan research has dramatically increased over the past decades, these molecules being no more considered as a scaffold for the cells of a given tissue, but more as a reservoir for growth factors and cytokines modulating their activation status and turnover. For example, heparin and other related heparan sulfate molecules are increasingly being recognized as important modulators of many signaling pathways.

The evolution and accuracy of methodologies specific to their complex structure allow a better knowledge of their structure together with a more precise definition of their functions and involvement in physiology and pathologies. The huge increase of original research articles on proteoglycans reflects the increasing interest for these molecules.

There is no unifying structure for proteoglycans (PGs), such as collagen triple helix for example, and they display a great diversity of protein forms. However, their basic structure is defined as a protein portion and long unbranched polysaccharides (named glycosaminoglycans or GAGs). PGs were initially grouped together because of the high negative charges of their GAG chains; it makes them easily separable from other molecules by ion-exchange chromatography. However, PGs are not that similar. The core protein size ranges from 10 to >500 kDa, and the number of GAG chains attached varies from 1 to >100. In addition, several PGs carry GAG chains of more than one type (hybrid PGs: aggrecan, syndecans…) and/or have additional *N*- or *O*-linked sugar modifications. Not all PGs are "full-time" PGs. There are also a growing number of matrix molecules which may or may not be linked with GAG chains, depending on the developmental stage or due to regulatory factors. They are called "part-time" PGs, such as MHC class II invariant chain, thrombomodulin, CD44, macrophage colony-stimulating factor, amyloid precursor protein, collagen type IX, XII, XIV, and XVIII, and the transferring receptor, with alternatively spliced variants having GAG-initiation sites. Some PGs such as versican or CD44 also occur as alternatively spliced forms with varying sugar modifications. Versican can also be considered as part-time PGs because a variant of versican without GAG attachment sites has been discovered.

The protein forms have complex modular structures with protein motifs that are of similar sequence to those found in other protein families: several PGs thus contain distinct protein and carbohydrate domain structures that confer specific functional properties. The protein domains are often the products of separate exons. Recent studies have identified approximately 30 different PG protein cores; these cores are not only scaffolds for GAGs but they also contain domains that have particular biological activities. Many PGs are thus multifunctional molecules that engage in several different specific interactions at the same time.

In addition, numerous variations also occur in GAG chain structure; GAGs are large extended structures with highly charged sulfate and carbohydrate groups, and they dominate the physical properties of the protein to which they are attached. PGs in the extracellular matrix thus function physically as creators of a water-filled compartment. Their high fixed negative charge attracts counter ions, and the osmotic imbalance caused by a local

high concentration of ions draws water from the surrounding areas. PGs thus keep the matrix hydrated and create a water compartment because they exclude other macromolecules while retaining permeability to low molecular weight solutes. This property increases the concentration of the macromolecules and therefore may increase reaction rates and promote all interactions that are concentration-dependent. Thus, PGs have important physical effects on events in the concentrated milieu around the cells and in the extracellular matrix.

The GAG side chains covalently linked to the core protein may be chondroitin sulfate (CS), or its epimerized homolog dermatan sulfate (DS), or keratan sulfate (KS), heparan sulfate (HS), or heparin (HP). Except KS, GAG synthesis is initiated by sequential addition of four monosaccharides: xylose (xyl), galactose (Gal), galactose and glucuronic acid (GlcUA). From this linker tetrasaccharide, the sugar chains are extended by addition of two alternating monosaccharides: an aminosugar and GlcUA. In HP and HS, the aminosugar is *N*-acetyl-glucosamine (GlcNAc) and in CS/DS, it is *N*-acetyl-galactosamine (GalNAc). The extent of epimerization of GlcUA to iduronic acid (IdUA) and the sulfation pattern of the disaccharide units distinguish HP from HS, and CS from DS. In KS, the GAGs are initiated as *N*-linked or *O*-linked oligosaccharides and extended by addition of GlcNAc and Gal. There is also regional variability to the epimerization and sulfation in each GAG chain. Studies of these patterns have defined the motifs required for specific interactions with growth factors, cytokines, matrix components, enzymes, and other proteins.

Divided into three categories, the volume first covers issues of basic concepts and up to date analysis methods for (I)proteoglycan and (II)glycosaminoglycan respectively at the protein and saccharide levels. Then the multifunctional aspect of proteoglycans is highlighted through three relevant examples of proteoglycans with highly different structures: serglycin, aggrecan, and heparin sulfate proteoglycans. The final chapter describes proteoglycan involvement in the pathogenesis of various disorders (kidney, corneal epithelial wound healing,…) and their potential therapeutic value in osteo-articular diseases.

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