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Small proteoglycans

H. Kresse, H. Hausser and E. Schönherr

Institute of Physiological Chemistry and Pathobiochemistry, University of Münster, Waldeyerstr. 15, D-W-4400 Münster (Germany)

Abstract. In this review the structure and functions of two non-related proteoglycan families are discussed. One family represents a group of extracellular matrix macromolecules characterized by core proteins with leucine-rich repeat motifs. Within this family special attention is given to those members which carry chondroitin or dermatan sulfate glycosaminoglycan chains. The second family is characterized by repeat sequences of serine and glycine. Their members are products of a single core protein gene and are characteristic constituents of secretory vesicles in cells of the haematopoietic lineage.
Key words. Biglycan; decorin; extracellular matrix; secretory vesicles; serglycin.

Introduction

The definition of a proteoglycan – a protein that is covalently linked with at least one glycosaminoglycan chain – is fulfilled by a wide variety of diverse macromolecules. Proteoglycans, like other glycoproteins, do not possess a unifying functional feature, nor are they unique members of subcellular or extracellular compartments. With the unravelling of the core protein structures of many proteoglycans, it is now recognized that proteoglycans could best be divided into distinct families which share structural properties of their protein backbone. One can anticipate that in the near future these common structural features will help to define common functions within the different proteoglycan families (see references 34, 43, 52, 59, 72, 134 and 135 for reviews).

This article deals with two non-related proteoglycan families. One family – leucine-rich proteoglycans of the extracellular matrix – is characterized by long arrays of leucine-rich repeat motifs of about 24 amino acids in length. A striking feature of these motifs is an amphipathic sequence which has been proposed to be involved in protein-protein and protein-lipid interactions[79]. These structural motifs have been detected in many species, from yeast to man[53]. In this article, however, we will focus on the description of leucine-rich proteoglycans of the extracellular matrix which carry chondroitin or dermatan sulfate glycosaminoglycan chains. The second family covered in this review is characterized by repeat sequences of serine and glycine, hence the name serglycin proteoglycans. These proteoglycans are characteristic constituents of secretory vesicles in cells of the haematopoietic lineage, and it is, therefore, assumed that they fulfill their functions primarily intracellularly.

Leucine-rich proteoglycans of the extracellular matrix

Structural features

Structural features of the core proteins. Protein and cDNA sequencing established that biglycan[37,99], decorin[29,30,83], fibromodulin[108] and lumican[13] belong to the family of leucine-rich proteoglycans of the extracellular matrix. Another small dermatan sulfate proteoglycan, proteoglycan-Lb, which is expressed in embryonic chick epiphyseal cartilage, can also be characterized by leucine-rich repeats, but it has been proposed that this proteoglycan shows a higher homology to human osteoinductive factor rather than to the other small proteoglycans[150]. Immunological cross-reactivity was the reason for tentatively listing another recently discovered proteoglycan, proteoglycan-100, in the group of small interstitial proteoglycans[142,176].

Biglycan and decorin are interstitial chondroitin/dermatan sulfate proteoglycans with globular core proteins[98]. Biglycan, which has also been named proteoglycan I, PG-I and PG-S1, received its name because it is substituted most often with two glycosaminoglycan chains. Decorin, which carries a single glycosaminoglycan chain only, decorates the surface of type I and II collagen fibrils[144]. Other names are small proteoglycan II, PG-S2 and PG-40. Fibromodulin, which is a keratan sulfate proteoglycan in bovine tissues[116], got its name because of its inhibitory effect on collagen fibril formation, whereas lumican, which is a keratan sulfate proteoglycan, too, was named because of its role in the acquisition and maintenance of corneal transparency.

As almost all secretory proteins, the core proteins of the small proteoglycans contain a signal peptide. Biglycan and decorin are furthermore characterized by a putative propeptide of 18 and 14 amino acids in length, respectively. It is shown in figure 1 that the mature

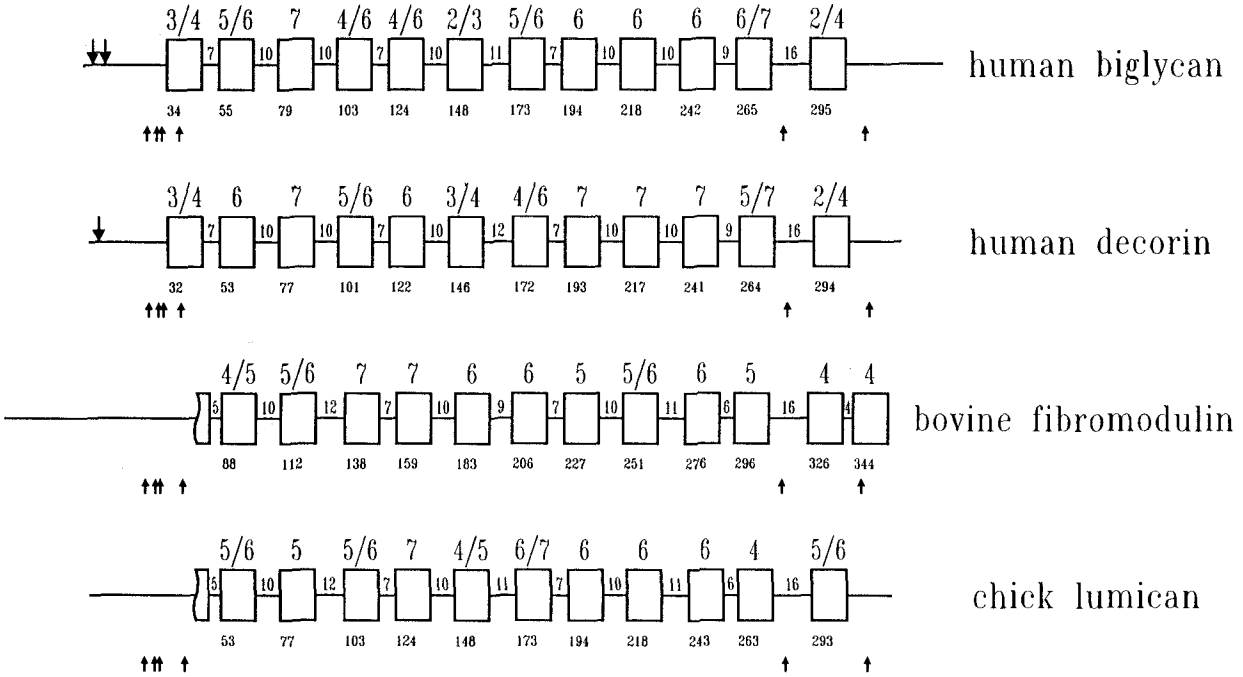

Figure 1. Comparison of the core protein structures of small proteoglycans containing leucine-rich repeats with the consensus sequence Leu - Xaa - Xaa - Leu - Xaa - Leu - Xaa - Xaa - Asn - Xaa - [Leu/Ile]-[Ser/Thr]-Xaa-[Val/Ile]. The conserved 14 amino acid units are boxed, with numerals above the boxes giving the degree of conservation of the 7 specified residues without (first numeral) or with (second numeral) taking into account conservative exchanges. Small numerals between the boxes indicate the number of amino acids between the boxed units, numerals below the boxes designate the position of their first residues (in the mature proteoglycan in case of biglycan and decorin and in the primary translation product in case of fibromodulin and lumican, respectively). Glycosaminoglycan chain attachment sites are indicated by large arrows in biglycan and decorin, the positions of cysteine residues are indicated by the smaller ones.

proteoglycans can be characterized as follows. The glycosaminoglycan attachment sites are located near the N-terminus. The sequences around these attachment sites show relatively large interspecies variations[29,31,88] and are of low homology between the proteoglycan family members. This site is followed by a cysteine-rich region. The central portion of the core protein is characterized by up to 12 repeats of the sequence Leu - Xaa - Xaa - Leu - Xaa - Leu - Xaa - Xaa - Asn - Xaa - [Leu,Ile] - [Ser,Thr] - Xaa - [Val,Ile] followed by a less homologous sequence of 7–10 amino acids. In both biglycan and decorin the consensus sequence is least clearly expressed in the first, sixth and twelfth unit. Asparagine is the most highly conserved residue. The 14 amino acid leucine-rich consensus sequence is followed by proline residues in 41% of the sequences used to generate figure 1. Within the sequences of the 14 amino acids there are proline residues only in the sixth and twelfth units of biglycan and decorin, respectively. In analogy to studies on the leucine-rich α_2-glycoprotein of human serum[160], it appears that the α-helical or β-sheet structure of the first 14 amino acids of the repeats is followed by a β-turn, and that domains are formed which are capable of bipolar surface orientation. It is also noteworthy that the spacing between the leucine repeats suggests that three times three units are tandemly linked with each other.

Repeat structures have not yet been detected in the C-terminal portion of biglycan and decorin but there is a conserved disulfide loop. An additional interesting feature of the core proteins is their surprisingly high isoelectric point (9.8 in case of decorin) due to the presence of several sequences rich in basic amino acids. The human biglycan gene has been mapped by in-situ hybridization to the Xq27–q28 region[93,163] and the decorin gene locus to 12q21–q22[120]. The human biglycan gene consists of 8 exons including one that encodes the 5′ untranslated region of the mRNA[36]. All the introns are spread throughout the leucine-rich repeat domain. The gene promoter lacks both CAAT- and TATA-boxes but contains 5 putative SP1 and one AP2 trans-acting factor binding site consensus sequences. Details of the organization of the decorin gene have not yet been published. Preliminary evidence, however, suggests that the decorin gene is organized in a similar manner as the biglycan gene (U. Vetter, R. Iozzo, personal communications, 1992).

Normally, biglycan contains two glycosaminoglycan chains which are linked with serine 5 and serine 10 of the mature core protein[37]. However, neither of these sites are necessarily used to 100%[99]. Figure 2 gives an example where about 50% of the biglycan core protein appears as a 'monoglycan'. In decorin, the single glycosaminoglycan chain is linked to serine 4 of the mature

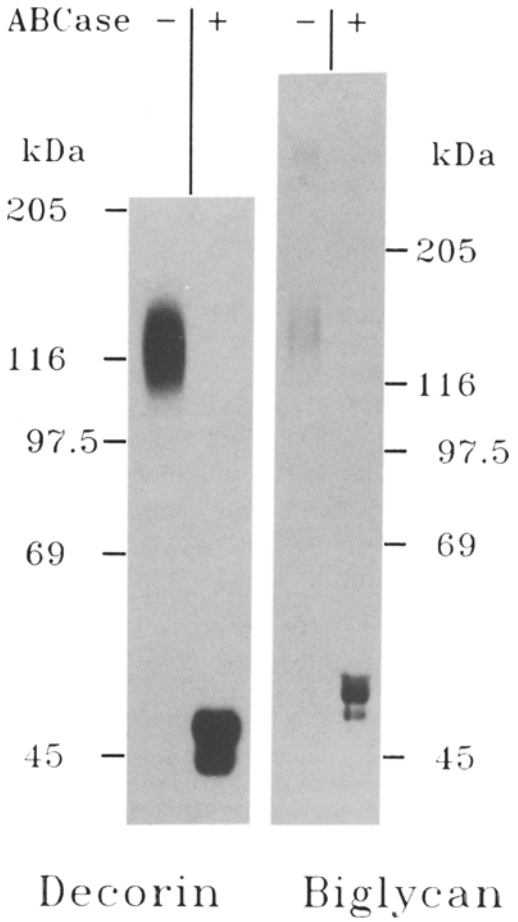

Figure 2. Comparison by SDS-polyacryamide gel electrophoresis of decorin and biglycan in their proteoglycan and core glycoprotein forms. [^{35}S] Methionine-labeled decorin (left panel) and biglycan (right panel) from human fibroblasts before and after chondroitin ABC lyase (ABCase) digestion. It is evident that biglycan exists as a proteoglycan in a 'monoglycanated' as well as in a 'biglycanated' form. Note that the core glycoprotein of biglycan has a higher mol. wt than the core glycoprotein of decorin.

core protein[24]. As postulated for glycosaminoglycan attachment sites[17], all these serine residues are preceded by one or more acidic amino acids. There are two other Ser-Gly sequences in the decorin core protein which do not meet this requirement and do not serve as acceptor sites for glycosaminogycan chains. When in recombinant decorin serine-4 was converted to alanine, no glycosylation occurred[91]. It should be noted, however, that the postulated Ser-Gly-Xaa-Gly sequence, which has been considered as part of the recognition signal for glycosaminoglycan transfer[17], is not present in biglycan, and chick decorin contains a Gly-Ser instead of a Ser-Gly sequence[88]. This sequence reversal is also present in the attachment site of the glycosaminoglycan chain in type IX collagen-proteoglycan[94].

In addition to glycosaminoglycan chains, biglycan and decorin are also substituted with asparagine-bound oligosaccharides. Human biglycan contains N-linked oligosaccharide attachment sites at asparagine residues 233 and 274, respectively. In decorin, three such sites are present at amino acids 181, 232 and 273, respectively. It appears that in biglycan either all or none of these sites are used[128]. Decorin from secretions of human fibroblasts is either substituted with three or only with two Asn-linked oligosaccharides[45] whereas the secretion product of chondrocytes appears to be fully substituted with oligosaccharides[136]. Most of the oligosaccharides are of the complex type, but high mannose-type oligosaccharides have also been detected. Evidence for the substitution with glycoprotein-type O-linked oligosaccharides has not been obtained[45]. Furthermore, at least in case of decorin, the core protein contains phosphorylated serine[46] and sulfated tyrosine[124] residues.

Glycosaminoglycan composition. Biglycan and decorin always carry galactosamine containing glycosaminoglycan chains. In no case have these chains been replaced by glucosamine containing glycosaminoglycan chains. However, since the glycosaminoglycan chain composition is not under direct genetic control, a tremendous variability of the fine structure of the polysaccharide has been reported. It is not the intention of the present review to describe this wealth of information in detail. In general, the structural features can be summarized as follows. 1) When biglycan and decorin are produced by a single cell type, the composition of the glycosaminoglycan chains is similar[23] and may even be identical[40]. However, other small proteoglycans like proteoglycan-100, which is synthesized in cultured osteosarcoma cells together with decorin and biglycan, may have a different carbohydrate composition[142]. 2) The glycosaminoglycan composition is influenced primarily by the type of producing tissue. Many studies have shown that the degree of epimerization of D-glucuronic acid residues to L-iduronic acid residues may cover the range between 0% and more than 90%. For example, small proteoglycans from skin contain the highest proportion of L-iduronic acid residues[23], whereas small proteoglycans containing about 35% iduronic acid residues have been isolated from bovine tendon[137]. About equimolar amounts of both hexuronic acid residues were found in bovine sclera[25] and arterial tissue[123], whereas chondroitin sulfate-type glycosaminoglycans were noted in bovine bone[41]. Interestingly, small proteoglycans from articular cartilage contain a significant proportion of iduronosyl residues[23] (about 30–40%), but the ones from nasal cartilage do not[60]. The ratio of glucuronosyl and iduronosyl residues is of importance for the secondary structure. Glucuronosyl residues exist predominantly in the $^4C_1$-conformation, whereas iduronosyl-residues show an equilibrium of $^4C_1$-, $^1C_4$- and skew-boat conformers[67]. 3) The molecular size of the glycosaminoglycan chains in small proteoglycans may vary considerably[43]. Values between 15 kDa[103,111] and greater than 56 kDa[148] have been reported. Decorin from the vitreous

may even have a glycosaminoglycan chain with a molecular mass of about 5×10^5. In the few reports on the glycosaminoglycan chain length of decorin and biglycan, being produced by a homogeneous cell population, it appeared that the chain length of biglycan was shorter than that of decorin[71,142].

Metabolism

Core protein expression of the small proteoglycans. The expression and tissue localization of decorin has been studied most intensively[11,85,117,170]. In general, decorin could be associated with all connective tissues being rich in type I and type II collagen. In the epidermis it was seen only in early stages of chick development. Endothelial cells were negative in situ and in culture[68]. Reports on the production of decorin by endothelial cells[71] could either be explained by the production of a monoglycanated form of biglycan or by the expression of decorin in 'sprouting' endothelial cell cultures. It is noteworthy that decorin containing filaments have been shown to approach basement membranes in a variety of organs[170]. Decorin was localized in the fibrous connective tissue septa of developing skeletal and cardiac muscle. However, the source of this proteoglycan is not precisely known since it is not initially deposited around myogenic cells. Fibroblastic cells have been assumed to be responsible for decorin deposition[85], but Parthasaraty et al.[110] were only able to detect a proteoglycan in rabbit skeletal muscle which was related to but not identical with decorin. Brandan et al.[20], however, proposed that decorin is synthesized and secreted by differentiated myotubes. Decorin was also observed in the stratum moleculare of the cerebellum and in the cerebral cortex[170].

Biglycan, on the other hand, is preferentially expressed in specialized cell types including skeletal myofibers, differentiating cells of the epidermis[11] and endothelial cells[11,68]. However, it is also expressed in the decorin producing cells of the arterial wall[5,11,68], in fibroblasts[69,165] and chondrocytes[54]. There is a developmentally regulated expression of biglycan and decorin in bone and cartilage. In fetal human femora, hypertrophic cartilagenous matrix did not stain with decorin-specific antibody[11], but staining of similar chick tissue was noted[85]. Decorin was found in hypertrophic zones of metacarpal, phalangeal and vertebral human bones. In human developing diarthrodial joints, an outer cap of prospective articular cartilage and articular soft tissues stained positively for biglycan but not for decorin[11]. A very carefully conducted study on age-related changes in the expression of extracellular matrix proteins by human bone cells revealed that biglycan levels were high in fetal cells and in cells derived from pubescent donors. Decorin was maximally produced in cells from adolescent donors but was much lower in osteoblasts from newborn persons[35]. The observation that both biglycan and decorin transcripts could be detected in fat-storing cells of rat liver[97] could be of relevance for our understanding of the pathogenesis of liver fibrosis. Fetal kidney mesangial cells appeared to produce only biglycan[74] whereas mesangial cells from adult rats synthesized biglycan as well as decorin[107].

The expression of proteoglycan-100 in fetal human tissues has recently been compared with that of decorin[16]. Proteoglycan-100 and decorin co-localized in osteoblasts and occasionally in osteoclasts. Individual chondrocytes exhibited a positive staining for proteoglycan-100 but were negative for decorin. The basal and the prickle cell layer of the epidermis were positive for the former proteoglycan. Additionally, proteoglycan-100 was found in striated muscle, nerve fibres and synovial tissue.

The regulation of the expression of the small proteoglycans is not understood in detail. As mentioned above, at least in case of osteoblasts, there is a developmental program of the expression of biglycan and decorin core proteins. Strong evidence has been obtained that the extracellular matrix influences decorin expression to a much greater extent than the expression of cell surface-associated heparan sulfate proteoglycans. A dramatic down-regulation was observed when skin fibroblasts were maintained in a type I collagen lattice[49].

There are several reports on the influence of cytokines on small proteoglycan expression. Transforming growth factor-β (TGF-β) appears to be a potent reagent in up-regulating biglycan in all cell types studied so far[14,21,69,131,172]. Only myofibroblast-like cells obtained after long term culture of fat-storing liver cells (Ito cells) did not respond to TGF-β with an increased biglycan production[97]. Divergent results, however, were found when the influence of the cytokine on decorin expression was investigated. In mesangial cells[14] and in rat liver fat-storing cells in primary culture, TGF-β up-regulated the expression of decorin to a similar extent to that of biglycan. Marginal effects or even a down-regulation were observed in all other studies quoted above. This clearly indicates a cell type specific control of decorin production, the molecular basis of which, however, is not understood. The multifactorial regulation of small proteoglycan expression is also exemplified by the observation that in mesangial cells platelet-derived growth factor, which increased small proteoglycan production, was able to block the effect of TGF-β[15].

A similar cell type specific effect of cytokines was observed for interleukin-1 treatment of gingival[9] and skin fibroblasts[61] which led to a moderate stimulation of decorin expression. On the other hand, long term infusion of interleukin-1α into rabbit knee joints caused a dramatic reduction in decorin biosynthesis in weight bearing cartilage but not in patellar cartilage[175]. A further example for the separate control of the expression

of various small proteoglycans is the observation that TGF-β selectively suppressed the expression of proteoglycan-100 in human osteosarcoma cells[21], whereas this proteoglycan could be selectively up-regulated by tumor necrosis factor-α (H. Kresse and E. Schönherr, unpublished observation).

Intracellular mediators of small proteoglycan expression seem to include prostaglandin $F_{2\alpha}$[75] and retinoic acid[105], the former leading to an increase and the latter to a decrease of decorin production.

Co- and post-translational modifications. Studies on the biosynthesis of small proteoglycans focussed on decorin biosynthesis. Since the secretion kinetics of decorin and biglycan are very similar, at least in fibroblasts and osteosarcoma cells, and since the glycosaminoglycan composition of the two proteoglycans is also very similar, it is assumed that the co- and post-translational reactions take place in identical subcellular compartments and in a similar order of events. Pulse chase experiments of fibroblast[45] and chondrocyte cultures[136] indicated the expected co-translational attachment of high mannose-type oligosaccharides on decorin core protein. Early post-translational events include the removal of the propeptide[136], the phosphorylation of serine residues[46] and, at least in fibroblasts and normal chondrocytes, the transfer of components of the linkage region between the glycosaminoglycan chain and the core protein[81,136]. Since xylosylated core protein without repetitive glycosaminoglycan disaccharide units could be isolated from fibroblasts and chondrocytes and since intermediates of the chain-elongation process have only very short half-lives[63], it is hypothesized that the components of the linkage region become attached to the core protein in a compartment proximal to the Golgi cisternae where the glycosaminoglycan chains are polymerized. This conclusion is supported by the observation that xylosyltransferase is localized in chondrocytes in the rough endoplasmic reticulum[62]. In rat hepatocytes, however, strong evidence was obtained that xylosyl transfer to the heparan sulfate proteoglycan core protein occurred in the Golgi apparatus and not in the endoplasmic reticulum[102]. Some xylose residues of decorin are also phosphorylated[46] as has been observed in case of aggrecan[104,156]. It has not yet been elucidated whether this modification reaction is an early or late post-translational event and whether it plays a role in the intracellular routing of the proteoglycans.

In fibroblasts the conversion of decorin core protein to a mature glycosaminoglycan chain bearing proteoglycan occurred with a half-life of approximately 12 min. However, intermediates of the maturation process could not be identified, indicating the rapid action of the glycosyl transferases, the glucuronosyl epimerase and the sulfotransferases. Since epimerization of glucuronic acid residues to L-iduronic acid residues has to be followed by 4-sulfation of adjacent N-acetylgalactosamine residues, both epimerization and 4-sulfation have to be tightly coupled. This is not necessarily true for 6-sulfation. In this context it is notable that proteoglycan-100 lacks iduronic acid residues and contains mainly N-acetylgalactosamine 6-sulfate units[142]. Considering that the ionophor monensin, which blocks the secretory route in the medial part of the Golgi apparatus[51], has only a minor influence on 6-sulfation of decorin but a dramatic influence on epimerization and 4-sulfation, it appears that glycosaminoglycan chain polymerization and 6-sulfation are occurring in an earlier compartment than the other two processes[63]. Sulfation of some tyrosine residues seems to be the latest event in small proteoglycan biosynthesis[124]. Table 1 summarizes the course of the modification reactions.

Sequence of events during decorin biosynthesis in fibroblasts[81] and chondrocytes[136]

Co-translational	Removal of signal peptide Transfer of 2–3 high mannose-type oligosaccharides to asparagine residues
Early post-translational	Removal of propeptide Assembly of the linkage region? Phosphorylation of serine residues Phosphorylation of xylose residues? Trimming of asparagine-bound oligosaccharides
Late post-translational	Glycosaminoglycan chain-polymerisation 6-Sulfation of GalNAc residues Epimerization of GlcA residues 4-Sulfation of GalNAc residues 2-Sulfation of L-IdoA residues Conversion of high mannose-type to complex-type oligosaccharides
Very late post-translational	O-Sulfation of tyrosine residues

Secretion of small proteoglycans appears as a constitutive, non-regulated process. Secretion rates are not influenced by the presence of asparagine-bound oligosaccharides[45], by the presence or absence of the glycosaminoglycan chains[82] or by the sulfation degree of the chains[50]. However, a minor proportion of decorin resides in an undefined intracellular compartment for one or more hours prior to secretion[45,180].

Endocytosis, extracellular and intralysosomal degradation. As it will be shown below, small proteoglycans bind to a variety of extracellular and cell-associated macromolecules. In the absence of these binding molecules, e.g. in tissue culture where an extracellular matrix is lacking, a considerable proportion of secreted small proteoglycan is recaptured by receptor-mediated endocytosis[137]. However, when fibroblasts are embedded in a collageneous meshwork, small proteoglycan turnover is slowed down and half-lives of 3–4 days for decorin have been measured[49]. In an intact tissue the half-life of decorin may even be longer. No significant degradation of decorin in explant cultures of bovine

tendon has been detected within 12 days[78]. Studies on the turnover of biglycan are not available in the literature. Studies on seemingly normal cartilage tissues have indicated that up to 15% of the extractable core proteins are partially degraded. The heterogeneity of the glycosaminoglycan chain size also suggests a limited degradation[175,176]. Furthermore, free glycosaminoglycan chains have been recovered from the external plasma membrane of cultured fibroblasts and keratinocytes where they are possibly retained by glycosaminoglycan-binding proteins[113,114]. Though free glycosaminoglycan chains could possibly be the result of intracellular proteolysis, it seems more likely that degradation occurred by extracellular proteases and/or reactive oxygen species[96]. At the moment, however, it is completely unknown what type of proteases might be involved in small proteoglycan degradation and to what extent reactive oxygen is also responsible for the fragmentation of the glycosaminoglycan chains. An extracellular action of lysosomal hyaluronidase has not yet been demonstrated.

As mentioned above, small proteoglycans may undergo a secretion-recapture pathway, and a variety of cells of mesenchymal origin are known to internalize biglycan and decorin efficiently by receptor-mediated endocytosis[47,57,119]. It is the core protein of the small proteoglycans which serves as a ligand for 51 and 26 kDa binding proteins which have been found in endosomes and at the plasma membrane of skin fibroblasts, osteosarcoma cells and chondrocytes. They have been implicated to participate in the endocytotic process due to their high affinity binding to the core proteins[55,57]. The process of endocytosis of small proteoglycans appears to be under the regulation of heparan sulfate on the cell surface. Heparin and oversulfated heparan sulfate species have been shown to bind to the same endocytosis receptor proteins[56] and hence to inhibit decorin and biglycan endocytosis. However, the bulk of endocytosed heparin is not delivered to the lysosomes for degradation. Recycling back to the cell surface seems to be due to the insensitivity of the ligand receptor complex to the acidic pH of the endosome. Cell membrane-intercalated heparan sulfate proteoglycans are considered to block the transport of the receptor proteins and indeed considerable augmentation of small proteoglycan endocytosis could be observed after enzymatic removal of heparan sulfate from the cell surface (H. Hausser, unpublished result). Endocytosis of small proteoglycans is followed by endosomal and lysosomal degradation to monomeric constituents. It appears that a critical proteolytic step occurring in endosomes is required before the dermatan sulfate chain becomes accessible to hydrolytic enzymes[64]. Details of the enzymatic degradation of the glycosaminoglycan chains are not presented in this article. A fairly complete picture of the sequential degradative steps emerged from studies on the genetic mucopolysaccharidoses which are characterized by deficiencies in enzymes required for these catabolic steps. Reviews are given in references 65, 80 and 100. It has not yet been established to what extent recently described endoglycosidases, which act on the glycosaminoglycan protein linkage region, participate in the intralysosomal degradation of the small proteoglycans[158,159].

Functions

Interactions with collagens. The specific association of decorin with type I and/or type II collagen has clearly been shown by specific immunostaining of mammalian tissue[38], of fibroblast cultures embedded in a collagen lattice[49] and by in vitro studies[167–169]. On the electron microscopic level the binding of small proteoglycans, indirectly identified as decorin, was most impressively shown using electron-dense dyes in the critical electrolyte concentration mode[143,144,147]. In soft connective tissues decorin appeared regularly and orthogonally arrayed at the d- or e-band of type I collagen fibrils. However, in bone the proteoglycan was not found in this particular location which is the first place where apatite crystals are deposited along the fibrils. Hence, it was assumed that decorin-collagen interactions in soft connective tissues are responsible for preventing mineralization.

Clear evidence was obtained that it is the core protein and not the glycosaminoglycan chain which binds to the fibril. A relatively high affinity constant of $3.3 \times 10^{-7}\ M^{-1}$ was found in vitro[22], and one decorin molecule per 20 collagen molecules were found at saturation.

As decorin binds to the suface of collagen fibrils, the lateral assembly of individual tripel helical collagen molecules is delayed[168], and the final diameter of the collagen fibrils becomes thinner[169]. These two effects are also obtained when a glycosaminoglycan-free core protein is used in the fibril-forming assay but not when large proteoglycans or protein-free glycosaminoglycan chains are used.

In spite of the observation that it is the core protein which binds to fibrillar collagen, the glycosaminoglycan chain seems also to be of importance. Dermatan sulfate chains are able to self-associate especially when they consist of alternate repeats of D-glucuronic and L-iduronic acid residues[39]. In corneal stroma the thickness of glycosaminoglycan chains was greater than expected[145], possibly due to self-association of the glycosaminoglycan chains of decorin molecules bound on opposite collagen fibrils[146]. Since corneal decorin contains glycosaminoglycans of constant length[146], this self-association is a means to maintain a constant interfibrillar distance. An analogous conclusion on the importance of the glycosaminoglycan chains was drawn from investigations on the contractions of fibroblast-

populated collagen lattices. When these fibroblast cultures were kept in the presence of a dermatan sulfate-degrading enzyme or when the interaction between decorin core protein and type I collagen was interrupted by a decorin core protein specific antibody, a delay of collagen gel retraction was observed. This delay was interpreted as being caused by a failure of decorin to bridge collagen fibrils and to transmit the forces caused by the migrating fibroblasts from one fibril to another (H. Kresse, unpublished result).

In human skin, biglycan could not be found in association with collagen fibrils[38]. Likewise, biglycan did not show any specific effect on collagen fibril formation in vitro[58]. On the other hand, biglycan co-localizes with collagen fibers in collagen lattices populated with biglycan producing osteosarcoma cells (P. Witsch-Prehm, unpublished result). It seems possible that biglycan-collagen interactions depend on the ionic composition of the incubation media (K. G. Vogel, personal communication).

The specifity of the interaction between decorin and type I collagen has recently been questioned[12]. In a solid phase binding assay decorin interacted efficiently only with type VI and not with type I collagen. These conflicting results could be explained by the proposal of an unidentified linking component binding both extracellular matrix molecules. Its presence remains to be established.

Interactions with fibronectin and thrombospondin. Decorin core protein has been shown to co-localize with fibronectin fibrils on the surface of cultured human fibroblasts[139]. In a solid phase assay procedure decorin core protein bound to the two high affinity heparin-binding domains of fibronectin with similar efficiency as the intact proteoglycan. K_D-values of about 10–20 nM were calculated. The sequence Asn-Lys-Ile-Ser-Lys in positions 85–89 of the mature core protein was shown to be involved in, but not alone sufficient for the interaction of decorin with the heparin-binding domains of fibronectin[138]. Subsequent studies also revealed an interaction between decorin core protein and the cell-binding domain of fibronectin[173]. It had already been shown before that a mixture of biglycan and decorin, prepared from bovine cartilage, inhibited the attachment of fibroblasts to a fibronectin substrate[87]. It was suggested that the inhibition was mediated by a concerted action of core proteins and glycosaminoglycan chains. Somewhat different results were obtained by using decorin from fibroblast secretions being prepared under non-denaturing conditions. The glycosaminoglycan-free core protein alone as well as the intact proteoglycan were found to be able to interact with the cell-binding domain of fibronectin. This interaction was considered to be responsible for the anti-adhesive properties of the proteoglycan[173]. The binding domain of the core protein for interaction with the cell-binding domain of fibronectin is located in the C-terminal disulfide loop and, hence, is different from the amino acid sequence interacting with the heparin-binding domains (M. Winnemöller and H. Kresse, unpublished results).

Another high affinity interaction with K_D-values in the nanomolar range was shown for the mutual binding between thrombospondin and decorin[174]. Complex features were found in a search of the respective binding domains because both the decorin core protein and its protein-free glycosaminoglycan chain could interact with thrombospondin, which itself exhibited more than one binding site for the core protein. As in case of the decorin fibronectin interaction, the consequence of the binding of decorin to thrombospondin was also an inhibition of fibroblast attachment on a thrombospondin substrate. It could, therefore, be concluded that decorin exhibits anti-adhesive properties for cultured fibroblasts. This property contrasts with the finding that the overexpression of decorin in Chinese hamster ovary cells led these cells to spread more on the substrate and to become quiescent at lower saturation density[178]. In figure 3 the putative binding domains of decorin for extracellular matrix components are indicated.

Interactions with growth factors. Studies on the expression of human decorin in Chinese hamster ovary cells led to the discovery that decorin and biglycan core proteins bind TGF-β with high affinity. In case of decorin the dissociation constant was 1.5×10^{-9} M[177]. The inhibition of TGF-β activity was assumed to be due to competition by decorin and the TGF-β receptors for the same or adjacent binding sites on the growth factor[135]. It is interesting to note that in the interactions of TGF-β with small proteoglycans the core protein exhibits binding activity which contrasts with the growth factor binding activities of the glycosaminoglycan chains of heparan sulfate proteoglycans (see Gallagher[42] for a review). Since heparan sulfate proteoglycans are also

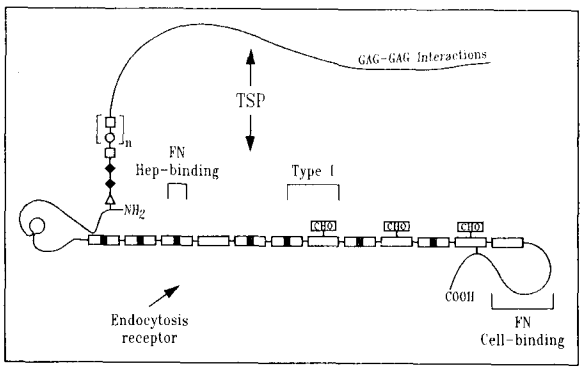

Figure 3. Schematic drawing of decorin showing putative functional domains. Note that the model is not shown true to scale. TSP, thrombospondin; FN, fibronectin; type I, type I collagen; Hep, heparin. The black box in the core protein repeats indicates the sequence Asn-Lys-Ile-Ser-Lys, striped boxes designate homologous sequences.

involved in cell adhesion it seems possible that the effect of overexpression of decorin on the spreading behavior of Chinese hamster ovary cells is the result of competition between decorin and heparan sulfate for the endocytosis receptor proteins (see above).

Another link between proteoglycans and growth factors is observed in case of proteoglycan-100. Partial amino acid sequencing of its core protein revealed its relation to but not an identity with macrophage colony-stimulating factor, CSF-1 (K. Schwarz, unpublished result). CSF-1 has been shown recently to be a proteoglycan, too [188,157].

Pathology

Considering the importance of the family of small proteoglycans in the assembly of the extracellular matrix, in cell adhesion and growth control, it is suprising how scanty the reports are on the involvement of these proteoglycans in pathological processes. There are some precise data on the involvement of small proteoglycans in monogenetic disorders, but the vast majority of reports on the involvement of proteoglycans in multifactorial, acquired diseases deals with alterations in the amount and distribution pattern of glycosaminoglycans only. They will not be considered here. We have observed an isolated patient who represented a progeroid variant with signs of the Ehlers-Danlos syndrome[82]. In addition to aged appearance, developmental delay, dwarfism and a generalized osteopenia, defective wound healing was a major symptom. The patient's disorder was traced back to a mutant galactosyltransferase I protein[122]. This enzyme catalyzes the second glycosyl transfer reaction in the assembly of dermatan sulfate chains. Its partial inactivity resulted in the secretion of mature and of unglycanated small proteoglycans. Although evidence for the existence of more than one galactosyltransferase I is lacking[33], the patient's skin fibroblasts produced normally behaving heparan sulfate proteoglycans and large proteoglycans. Since the patient could produce a considerable proportion of mature decorin and biglycan, it seems reasonable to postulate a sufficient residual activity for a seemingly normal production of proteoglycans carrying several glycosaminoglycan chains.

In accordance with the phenotype of the patient mentioned above, we found deficient expression of the decorin gene in several fibroblast cell lines from patients with progeroidal appearance who also exhibited connective tissue anomalies (Beavan, L., Quentin-Hoffmann, E. and Kresse, H., submitted for publication). However, anomalous expression of decorin in these cases may reflect an unknown primary defect and maybe a secondary phenomenon. Deficient expression of decorin and overexpression of biglycan has similarly been observed in fibroblasts from patients with Marfan syndrome[121].

Of special importance seems to be the observation that the expression of biglycan in osteoblasts correlate with skeletal growth. Patients with Turner syndrome, an XO-chromosomal abnormality, produce only half of the amount of biglycan compared with individuals with normal chromosome number in clonal cultures of osteoblasts (U. Vetter, personal communication). Patients with Turner syndrome are characterized by a short stature. It remains to be established, however, whether biglycan expression is indeed a key factor in skeletal growth.

As stated above, only a few studies exist describing small proteoglycan alterations in common disorders involving inflammation, tissue repair and fibrosis. Yeo et al.[179] observed an increase in decorin biosynthesis in healing wounds and during tumor stroma generation. Along the same lines was the notion of hypomethylation of the decorin gene in human colon cancer[2]. An increased expression of both biglycan and decorin was found in experimentally induced liver fibrosis[97]. However, in bleomycine-induced lung fibrosis only an increased biglycan production and a decrease in the biosynthesis of decorin was found[171]. Immunohistochemical investigations in human liver fibrosis indicated that biglycan was preferentially localized perisinusoidally, whereas decorin was mainly but not exclusively present in fibrous scars (B. Högemann, G. Edel, K. Schwarz and H. Kresse, unpublished result). In a model of acute mesangial proliferative glomerulonephritis it was found that the elevated expression of TGF-β gave rise to increased small proteoglycan production[107]. In this respect an increased production of small proteoglycans in inflammation and repair processes could be advantageous because of the ability of the proteoglycans to suppress TGF-β activity. Injections of decorin have been used to successfully suppress the glomerulonephritic disease in rats[15].

Intravesicular serglycin proteoglycans

Structural features

Serglycin proteoglycans represent a group of largely intracellular proteoglycans which are named because of the presence of extended sequences of alternating serine and glycine residues which can be heavily substituted with chondroitin sulfate and/or heparin chains. cDNA sequences have originally been obtained from rat yolk sac tumor cells[18,19], but it then turned out that these proteoglycans are present in many hematopoietic cells, i.e. in mast cells[4,8,73,161], basophilic[7] and promyelocytic leukemia cells[101,150], eosinophils[133], natural killer cells[44], platelets[3,112] and possibly T cells[27]. There is only a single serglycin gene, located on chromosome 10q22.1 in the human[92,150] and on chromosome 10 in the mouse[7]. In rat, mouse and human, the gene consists of three exons, the third one encoding the characteristic serine/glycine-repeat sequence which serves as the glycosaminoglycan attachment site. Different promoters have been detected, being active in parietal yolk sac and in mast

cells, respectively[4]. Negative and positive cis-acting elements in the promoter of the mouse gene were identified[6]. Recently, the complete sequence of the human gene has been obtained[66].

The primary translation products have relative molecular masses of 17,000 (human), 16,700 (mouse) and 18,600 (rat), and proteolytic processing of the propeptide may occur[19]. The proteoglycan core proteins undergo an extreme variety of post-translational events (see also references 77 and 153 or reviews). It can be summarized that in rat and mouse serosal mast cells serglycins mature to proteoglycans of 750–1000 kDa, whereas mucosal mast cells contain a 150 kDa and bone marrow mast cells a 200 kDa proteoglycan[161]. This indicates that the number and/or the length of the glycosaminoglycan chains may vary considerably. Furthermore, the type of the glycosaminoglycan moiety strongly depends on the cellular source of the proteoglycan and on the exposure of the synthesizing cells to various cytokines or other agents. Many cells obviously have a latent capability to switch the type of glycosaminoglycan chains that are synthesized, and hence the core protein does not determine the chemical nature of the glycosaminoglycan chain. Only a few examples of the variability can be given in this review.

It was calculated that 10–15 glycosaminoglycan chains are attached to the serglycin core protein in yolk sac tumor cells[26]. The respective estimates were 7–9 chains in human eosinophils[133], 6–7 chains in the human promyelocytic leukemia cell line HL-60[90] and 3–5 chains in murine monocytic leukemic cells[95]. Most remarkable is the finding that heparin, heparan sulfate and different N-acetylgalactosamine-containing polymers can be assembled on the same core protein. The latter glycosaminoglycans are still named by capital letters: chondroitin sulfate A ([GalNAc-4-sulfate-GlcA]$_n$), chondroitin sulfate B ([GalNAc-4-sulfate-IdoA]$_n$), chondroitin sulfate di-B (GalNAc-4-sulfate-IdoA-2-sulfate]$_n$), chondroitin sulfate C ([GalNAc-6-sulfate-GlcA]$_n$), chondroitin sulfate D ([GalNAc-6-sulfate-GlcA-2-sulfate]$_n$), and chondroitin sulfate E ([GalNAc-4,6-bissulfate-GlcA]$_n$). Mast cells exhibited the greatest diversity. In rodents, where connective tissue and mucosal mast cells are distinguished, serglycin from connective tissue mast cells contains heparin chains of 60-100 kDa[130,181]. A specific endoglucuronidase splits the polymers before secretion[109,162]. These cells, however, have a latent capacity also to synthesize chondroitin sulfate E-type glycosaminoglycane[155]. Mucosal mast cells of rodents, on the other hand, have been found to synthesize chondroitin sulfates A[126], B/di-B[84,154] and E[84,126]. The same mast cell type may produce heparin and chondroitin sulfate E-containing proteoglycans simultaneously[125,149], but the two glycosaminoglycans are bound to individual core protein molecules. It had been shown additionally that interleukin-3 causes differentiation of murine bone marrow progenitor cells into chondroitin sulfate E-containing immature mast cells which can further differentiate under the influence of fibroblast-derived factors into heparin-containing cells[132]. With refined analytical tools, chondroitin sulfate D-type glycosaminoglycans were detected in murine lymph node-derived mast cells[28].

In the human, mucosal and connective tissue-type mast cells cannot be clearly distinguished. Heparan sulfate proteoglycans were found in mast cells from nasal mucosa[115], but heparin and chondroitin sulfate E-containing proteoglycans were detected in skin, lung and intestine[32,115,152]. Chondroitin sulfate E proteoglycans were also found in human eosinophils[133]. The molecular size of the glycosaminoglycan chains, but not their composition, was strongly influenced by several cytokines. Cultured human monocytes mainly produced chondroitin sulfate A[165] as did promyelocytes[10] and platelets[106], but in neoplastic monocytes the proteoglycan was much larger in molecular size[76]. Differentiation into macrophages resulted in an increased expression of chondroitin sulfate E[164].

Functions

Serglycins are of functional importance while they are stored in secretory vesicles and after their release into the extracellular space. A couple of basic proteases are complexed to the proteoglycans in monocytes and granules of thrombocytes resulting in enzyme inactivation or modulation of proteolytic activity[70,86,141]. The polyanionic properties of serglycins may serve to maintain electrical neutrality, to efficiently concentrate secretory material and to reduce the osmotic pressure in histamine-rich vacuoles. In natural killer cells complex formation between perforins and heparin proteoglycans at the acidic pH of the secretory granule possibly prevents autolysis. After specific release this complex dissociates, thereby allowing target cell lysis[140]. In other instances the complexes may remain stable, and the proteoglycan may serve to delay diffusion and to retain the complex in the extracellular matrix[149].

It is not the intention of the present article to cover the spectrum of potential actions of secreted serglycins and of glycosaminoglycans derived therefrom. The actions of heparin and dermatan sulfate on antithrombin and heparin cofactor II have been reviewed in detail recently[89], but it should be noted that the effects may occur predominantly at extravascular sites. It remains to be seen to what extent serglycin derivatives, in contrast to cell surface proteoglycans, are involved in such important functions as inhibition of leukocyte elastase[127], tissue fixation of extracellular superoxide dismutase[1] and compartmentalization of haematopoietic growth factors[48,129].

Perspectives and summary

In recent years great progress has been made in elucidating the core protein structures and the genomic

organization of the proteoglycans discusses in this review. However, basic features as to the regulation of core protein expression, to the factors controlling the glycosoaminoglycan chain assembly, to the characterization of functional domains on the core proteins and on the glycosaminoglycan chains, and to the pathobiochemical importance of the proteoglycans are still to be elucidated. With the advent of the modern methods of molecular and cell biology, at least some of these questions will be answered in the coming years.

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Note added in proof: Details of the organization of the decorin gene have now been published:

Danielson, K. G., Fazzio, A., Cohen, I., Cannizzaro, L. A., Eichstetter, I., and Iozzo, R., The human decorin gene: intron-exon organization, discovery of two alternatively spliced exons in the 5′ untranslated region, and mapping of the gene to chromosome 12q23. Genomics *15* (1993) 146–160.
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