PROTEOGLYCANS AND SKIN

Pr Arnold I. CAPLAN

Director, Skeletal Research Center

Professor of Biology

Case Western Reserve University, Cleveland, Ohio 44106-7080, USA

1. Schmidtchen, AI, Carlstedt, A. Malmstrom, and Fransson, L-A (1990). Inventory of human skin fibroblast proteoglycans. Identification of multiple heparan and chondroitin/dermatan sulphate proteoglycans. Biochem. J. 265:289-300.

This paper provides a comprehensive account of chondroitin sulfate/dermatan sulfate/and heparan sulfate proteoglycans produced by cultured human dermal cells. The weakness of the paper is that it provides no identification of proteoglycans based upon core protein structure.

2. Bianco, P, Fisher, LW, Young, MF, Termine, JD, and Robey, PG (1990). Expression and localization of the two small proteoglycans biglycan and decorin in developing human skeletal and non-skeletal tissues. J. Histochem. Cytochem. 38:1549-1563.

This paper provides an immunohistochemical demonstration that decorin and biglycan are both present in various human tissues. In human skin, these two proteoglycans are differentially expressed. Decorin occurs in the dermis, especially in the DEJ region while biglycan occurs in the epidermis and in vascular endothelial and perivascular regions. Thus, these two proteoglycans may have different functions in skin.

3. Fushimi, H, Kameyama, M, and Shinkai, H (1989). Deficiency of the core proteins of dermatan sulfate proteoglycans in a variant form of Ehlers-Danlos syndrome. J. Int. Med. 226:409-416.

A patient with a variant form of Ehlers-Danlos syndrome, who exhibited skin fragility, hyperextensibility, and bruisability, was found to contain a normal level of collagen, but a reduced level of decorin.

4. Couchman, JR, King, JL, and McCarthy, KJ (l990). Distribution of two basement membrane proteoglycans through hair follicle development and the hair growth cycle in the rat. J. Invest. Dermatol. 94:65-70.

This paper demonstrates that the 3B3-positive basement membrane proteoglycan (bamacan?) is important for hair follicle development and hair growth. This proteoglycan is present, like other basement membrane molecules, in the dermal papilla region of hair follicles.

5. Fine, J-D, and Couchman, JR (1989). Chondroitin 6-sulfate proteoglycan but not heparan sulfate proteoglycan is abnormally expressed in skin basement membrane from patients with dominant and recessive dystrophic epidermolysis bullosa. J. Invest. Dermatol. 92:611-616.

This paper uses 3B3 to identify basement membrane chondroitin sulfate proteoglycan(s) in human skin. In congenital blistering diseases the 3B3-positive proteoglycan is absent or poorly expressed at sites of blisters. Subsequent studies indicate that this proteoglycan is bamacan.

6. Schönherr, E, Beavan, LA, Hausser, H, Kresse H, and Culp, LA (1993). Differences in decorin expression bv papillary and reticular fibroblasts in vivo and in vitro. Biochem. J. 290:893-899.

By immunostaining and in situ hybridization of human skin, decorin and its mRNA, respectively, are more abundant in the papillary dermis compared to the reticular dermis. Results from cultures of papillary and reticular fibroblasts, based on metabolic labeling and northern blot analysis, correlate with findings with in vivo skin.

7. Sanderson, RD, Hinkes, MT, and Bemfield, M (1992). Syndecan-1, a cell-surface proteoglycan, changes in size and abundance when keratinocytes stratify. J. Invest. Dermatol. 99:390-396.

Keratinocytes in culture, growing as a monolayer, produce syndecan-1 which is larger than that made by cultured keratinocytes which are stratified. The larger syndecan-1 has more and larger heparan sulfate chains. Stratified keratinocytes produce more syndecan-1 than unstratified keratinocytes, but do not show an appreciable increase in syndecan-1 mRNA.

8. Zimmermann, DR, Dours-Zimmermann, MT, Schubert, M, and Bruckner-Tuderman, L (1994). Versican is expressed in the proliferating zone in the epidermis and in association with the elastic network of the dermis. J. Cell Biol. 124:817-825.

Immunostaining of human skin shows versican to be present in the basal layer of the epidermis and in the dermis, especially in areas of elastic fibers. Versican mRNA is found by northern blotting of RNA from cultured keratinocytes and dermal fibroblasts.

9. Bernstein, EF, Underhill, CB, Hahn, PJ, Brown, DB, and Uitto, J (1996). Chronic sun exposure alters both the content and distribution of dermal glycosaminoglycans. Br. J. Dermatol. 135:255-262.

Sun-damaged human skin shows increased accumulation of glycosaminoglycans relative to sun-protected skin. The increased glycosaminoglycans are deposited in elastotic areas.

10. Bernstein, EF, Fisher, LW, Li, K, LeBaron, RG, Tan, EML, and Uitto, J (1995). Differential expression of the versican and decorin genes in photoaged and sun-protected skin. Lab. Invest. 72:662-669.

The large chondroitin sulfate proteoglycan, versican, is increased in areas of solar elastosis, while the small dermatan sulfate proteoglycan, decorin, is decreased. Analysis of mRNA levels for versican and decorin in cultures fibroblasts from photoaged and normal skin correlate with the immunostaining results.

11. Westgate, GE, Messnger, AG, Watson, LP, and Gibson, WT (1991). Distribution of proteoglycans during the hair growth cycle in human skin. J. Invest. Dermatol. 96:191-195.

Immunostainingfor 6-sulfated chondroitin sulfate in human skin shows it to be localized to the dermal papilla and the sheath around the hair follicle during anagen. This staining is less intense during catagen and very weak during telogen.

12. deCros, DL, LeBaron, RG, and Couchman, JR (1995). Association of versican with dermal matrices and its potential role in hair follicle development. J. Invest. Dermatol. 105:426-431.

Immunostaining for versican in mouse skin shows differences in distribution during hair follicle development. Versican is present in the dermal papilla during follicle maturation, decreases at the end of anagen, continues to decline during catagen, and is absent from the dermal papilla during telogen. However, during telogen, versican is present in the neck region of the hair follicle. It disappears from the neck region of the follicle and re-appears in the dermal papilla during the next hair growth cycle.

13. Kaplan, ED, and Holbrook, KA (1994). Dynamic expression patterns of tenascin, proteoglycans, and cell adhesion molecules during human hair follicle morphogenesis. Devel. Dyn. 199:141-155.

These two papers and the next paper describe the distribution of chondroitin/dermatan sulfate proteoglycans, as well as other matrix molecules, in human fetal skin.

14. Bertheim, U, and Hellstrom, S (l 994). The distribution of hyaluronan in human skin and mature, hypertrophic and keloid scars. Br. J. Plast. Surg. 47:483-489.

This paper describes the distribution of hyaluronan in normal adult skin and in scar tissue. In normal skin, hyaluronan is primarily confined to the papillary dermis. In scar tissue, hyaluronan remains in the papillary dermis but is confined more exclusively to the DEJ region. In keloids, hyaluronan is poorly expressed in the dermis, but is highly expressed in the epidermis.

15. Ågren, UM, Tammi, M, Ryynänen, M, and Tammi, R (l997). Developmentally programmed expression of hyaluronan. in human skin and its appendages. J. Invest. Dermatol. 109:219-224.

In early fetal human skin, hyaluronan shows a uniform distribution. With increasing age, hyaluronan becomes restricted to discrete areas, such as the dermis subjacent to the basement membrane. There are also fluctuations in hyaluronan in developing skin appendages.

16. Tuhkanen, A-L, Tammi, M, and Tammi, R (1997). CD44 substituted with heparan sulfate and endo-β–galactosidase-sensitive oligosaccharides: a major proteoglycan in adult human epidermis. J. Invest. Dermatol. 109:213-218.

Organ cultures of human epidermis, labeled with $^{35}SO_4$, synthesize heparan sulfate-containing CD44 as a prominent proteoglycan.

17. Weber, IT, Harrison, RW, and lozzo, RV (1996). Model structure of decorin and implications for collagen fibrillogenesis. J. Biol. Chem. 271:31767-31770.

A model for the three-dimensional structure of decorin is derived based on the crystal structure of porcine ribonuclease inhibitor due to similarities in the amino acid sequences of these molecules. The predicted structure for decorin is an arch which has an appropriate size and shape to bind to a single collagen triple helix.

18. Danielson, KG, Baribault, H, Holmes, DF, Graham, H, Kadler, KE, and Iozzo, RV (1997). Targeted disruption of decorin leads to abnormal collagen fibril morphology and skin fragility. J. Cell Biol. 136:729-743.

In decorin knock-out mice, collagen fibrils have irregular outlines and greater polydispersity in diameter relative to the fibrils in normal mice. The skin of decorin knock-out mice has reduced

tensile strength.

19. Lozzo, RV (1997). The family of the small leucine-rich proteoglycans: key regulators of matrix assembly and cellular growth. Crit. Rev. Biochem. Mol. Biol. 32:141-174.

This review examines the small, leucine-rich proteoglycans, of which decorin is a member, and discusses the interactions of decorin with collagen and TGF-β.

20. Hocking, AM, Shinomura, T, and McQuillan, DJ (1998). Leucine-rich repeat glycoproteins of the extracellular matrix. Matrix Biol. 17:1-19.

This review describes the structures and functions of leucine-rich proteoglycans, including decorin.

21. Penc, SF, Pomahac, B, Winkler, T, Dorschner, RA, Eriksson, E, Herndon, M, and Gallo, RL (1998). Dermatan sulfate released after injury is a potent promoter of fibroblast growth factor-2 function. J. Biol. Chem. 273:28116-28121.

Human wound fluid contains dermatan sulfate which binds to FGF-2. Because of the abundance of this dermatan sulfate, it contributes the majority of the binding activity for FGF-2 in wound fluid. This binding mediates the activity of FGF-2 in a cell proliferation assay.

22. Kielty, CM, Whittaker, P, and Shuttleworth, CA (1996). Fibrillin: evidence that chondroitin sulfate proteoglycans are components of microfibrils and associate with newly synthesized monomers. FEBS Lett. 386:169-173.

Microfibrils from bovine nuchal ligament or aorta or produced in explant cultures of bovine aortic smooth muscle cells were found to contain chondroitin sulfate. This was shown by alteration of the electron microscopic appearance of the microfibrils after treatment with chondroitinase ABC or by chondroitinase of treatment of $^{35}SO_{4}$-labeled, immunoprecipitated fibrillin.

23. Sorrell, JM, Carrino, DA, Baber, MA, and Caplan, AI (1999). Versican in human fetal skin development. Anat. Embryol. 199:45-56.

Fetal and adult skin are substantial different in the microarchitecture and microchemistries of their extracellular matrices. Versican becomes restricted to the upper half of the dermis by mid-fetal life although it is quite prominent around hair follicles, glands and vasculature in the lower half of the dermis. Moreover, the microchemistries of the chondroitin sulfate chains show regional differences.

24. Willen, MD, Sorrell, JM, Lekan, CC, Davis, BR and Caplan, AI. (1991). Pattems of glycosaminoglycan/proteoglycan immunostaining in human skin during aging. J. Invest. Derm. 96:968-974.

This study uses glycosaminoglycan specific microchemistry monoclonal antibodies to image epitope distribution in human skin as afunction of age.

25. Sorrell, JM, Carrino, DA and Caplan, AI (1993). Structural domains in chondroitin sulfate identified by anti-chondroitin sulfate monoclonal antibodies: immunosequencing of chondroitin sulfates. Matrix 13:351-361.

This study documents the use of the monoclonal antibodies used in the previous study to sequence

chondroitin sulfate chains.

26. Sorrell, JM, Carrino, DA, and Caplan, AI (1996). Regulated expression of chondroitin sulfates at sites of epithelial-mesenchymal interaction: spatio-temporal patterning identified with anti-chondroitin sulfate monoclonal antibodies. Int. J. Devel. Neurosci. 14:233-248.

This study provides a review and extends the observations using the technology covered in the last two reports above.