

CUTANEOUS MUCINOSIS

Thesis

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Dermatology and Venereology

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A handwritten signature in black ink, consisting of a stylized, cursive script that appears to read 'H. Moharrem'.



C O N T E N T S

	<u>Page</u>
<i>Introduction</i>	1
<i>Mucin</i>	3
<i>Generalized Myxoedema</i>	12
<i>Pretibial Myxoedema</i>	17
<i>Lichen Myxoedematous</i>	25
<i>Scleredema Adultorum</i>	38
<i>Follicular Mucinosis F.M.</i>	54
<i>Reticular Erythematous Mucinosis</i>	65
<i>Summary and Conclusion</i>	70
<i>References</i>	73
<i>Arabic Summary</i>	

INTRODUCTION

CUTANEOUS MUCINOSIS

Cutaneous mucinosis are conditions that have in common an increased dermal deposition of acid glycosaminoglycans (GAG).

These disorders are characterized by induration and thickening of the skin attributable to the considerable water-binding capacity of GAGs. (Matsuoka et al., 1984).

Cutaneous muconosis include:

- 1) Generalized myxoedema which frequently accompanies hyperthyroidism or hypothyroidism (Lever and Schaumburg-Lever, 1983).
- 2) Pretibial myxoedema, this localized variety involves preferentially the pretibial areas and is resistant to treatment (Matsuoka et al, 1984).
- 3) Scleredema and lichen myxoedematosus (scleromyxoedema) represent generalized cutaneous mucinosis unrelated to thyroid disease (Perry et al, 1960 and Cohn et al., 1970).

Lichenmyxoedematosus which is an uncommon chronic, progressive, cutaneous disease of unknown cause (Howden et al., 1975).
- 4) Follicular mucinosis is an idiopathic inflammatory dermatosis characterized histologically by accumulation of acid mucopolysaccharides in the outer root sheath of the hair follicles and within the sebaceous glands (Snyder et al., 1984).

- 5) Reticular erythematous mucinosis which is characterized by reticular erythema and deposition of mucin in the skin (Steigleder et al., 1974).

In generalized myxoedema, the amount of mucin is too small to be demonstrable and in scleredema, mucin may be present only in the early stage but regular demonstration of the presence of mucin in the dermis is possible only in pretibial myxoedema and in lichen myxoedematosus. In reticular erythematous mucinosis, it is possible in most cases to be found (Lever and Schaumburg Lever, 1983).

MUCIN

MUCIN

What are Mucins?

Mucins are jelly-like materials concerned with the hydration of the ground substances and probably play a part in the extravascular exchange of metabolites.

The ground substance which contains the fibres and cells contains a variety of carbohydrates, proteins and lipids, and dermal mucin is formed of acid mucopolysaccharides. In the skin the major mucopolysaccharides are hyaluronic acid and dermatan sulphate (Chondroitin Sulphate B), there is in addition a small amount of Chondroitin-6-Sulphate. Heparin is also a mucopolysaccharide but it normally remains within the mast cells which produce it and does not contribute to the ground substance (Ebling, 1979).

Histochemistry of the Mucin:

Historically, the term mucopolysaccharide has been applied to hyaluronic acid, dermatan sulphate, chondroitin-6-sulphate and heparin in order to describe a polysaccharide material that was viscous or mucinous. Initially only the structure of the mucopolysaccharide (glycosaminoglycan) portions of those molecules was recognized, but subsequently it became clear that polysaccharides are usually linked covalently to protein (Silbert, 1983).

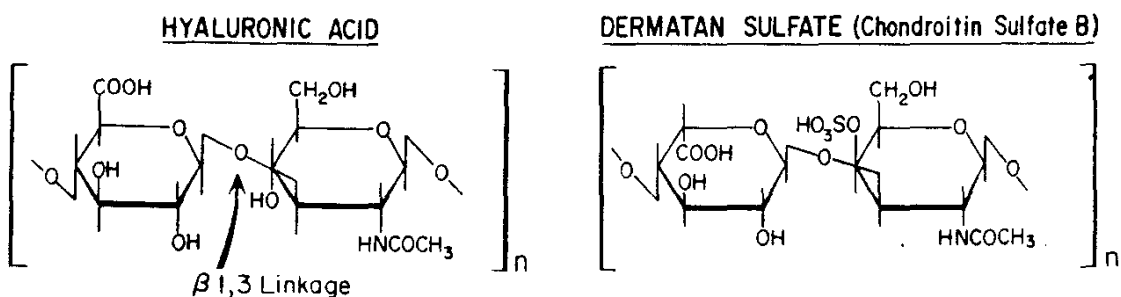
Thus the term mucopolysaccharide is sometimes used for the polysaccharide portion alone, or for the entire polysaccharide protein (proteoglycan) combination.

The term glycosaminoglycan was introduced in order to describe the polysaccharide (glycan) structure containing hexosamines (glycosamine) and does not include protein moiety. Hyaluronic acid, Chondroitin-6-Sulphate, Dermatan Sulphate and heparin are substances in vertebrates that satisfy the structural criteria of glycosaminoglycan (Silbert, 1983).

Structure of:

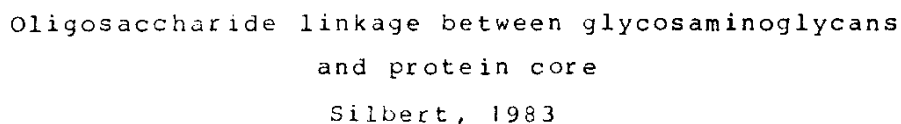
I Glycosaminoglycan:

It is formed of chains consisting of hexosamine (either glucosamine or galactosamine) alternating with another sugar (glucuronic acid or iduronic acid). Although an individual chain may have a mixture of uronic acid (i.e. some glucuronic acid and some iduronic acid) the hexosamine will always be all glucosamine or all galactosamine, because the hexosamine occurs as every other sugar it is most convenient to think of the glycosaminoglycans as compounds consisting of multiple disaccharides repeating units as shown below



Silbert, 1983

The glycosaminoglycan portions of Chondroitin-4-Sulphate and 6-Sulphate, dermatan sulphate and heparin are each linked at their reducing end to a trisaccharide consisting of galactosyl-galactosyl-xylose (Lindahl and Roden, 1972).



The xylose is glycosidically linked to the hydroxyl of serine in the protein chain; the first sugar of the glycosaminoglycan chain (linked to the galactose) is always a glucuronic acid. This first glucuronic acid could be considered a part of the linkage oligosaccharide since it is added by a specific enzyme different from the enzyme that is involved in the incorporation of glucuronic acid into the polysaccharide chain (Helting and Roden, 1969) .

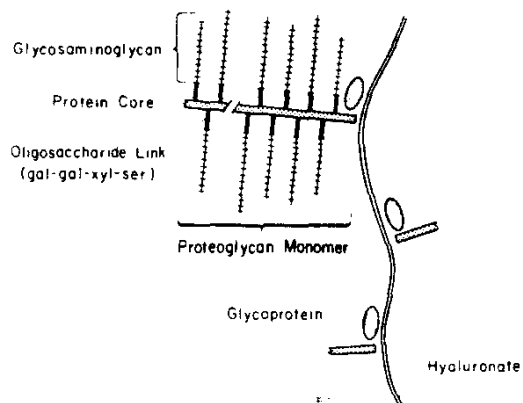
III Proteoglycan

The proteoglycan structure has only been described in detail for cartilage. However, skin proteoglycan is probably similar (Hascall, 1977).

In cartilage the glycosaminoglycan chains are connected through the oligosaccharide linkage to a protein core molecule forming a proteoglycan unit or monomer. Each proteoglycan may have 50 or more similar glycosaminoglycan chains attached to this core in a "bottle brush" configuration, so the total molecular weight may be more than 10^6 . As many as 100 individual proteoglycan monomers in turn can be attached non covalently around a core of hyaluronic acid to form aggregates of $100-150 \times 10^6$ M.W. The proteoglycans are spaced along the chain at interval of 10 disaccharide units (Hascall and Heinegard, 1974 and Hardingham and Murt, 1973).

The aggregate can be dissociated to proteoglycan monomer by high salt concentration, and at least part can be reaggregated by lowering the salt concentration.

PROTEOGLYCAN AGGREGATE



Biosynthesis of Cutaneous Mucopolysaccharides:

Experimentally it appears that glucose is the precursor of both the hexosamine and uronic acid parts of the hyaluronic acid molecules. Mucopolysaccharides of the ground substance are either formed inside the fibroblasts or the mast cells, and that formed inside the fibroblasts are secreted. On the other hand, the mucopolysaccharide which is produced by the mast cells is stored within the cell and it is mainly heparin (Ebling, 1979).

Degradation:

Turnover:

The half life of skin hyaluronic acid in vivo (young rabbit and rat) has been shown to be 2-5 days, skin chondroitin sulphate has been shown to have a half-life of 7-14 days and that of dermatan sulphate in young animals is 7-10 days and in older animals was somewhat longer (Silbert, 1983).

Endoglycosidases

The best defined glycosaminoglycan-lyase is the hyaluronidase that is found in testicular tissue.

This enzyme degrades hyaluronic acid to a family of oligo-saccharides ranging in size from tetrasaccharide to larger even-numbered oligo-saccharides (Weissman et al., 1954).

Initially the hyaluronic acid molecule can be depolymerized rapidly with consequent loss of viscosity. Further degradation results in release of measurable amount of reducing sugars but completion of degradation requires a longer time (Weissman, 1955 and Hoffman et al., 1956).

Desulphated chondroitin, chondroitin-4-sulphate and chondroitin-6-sulphate have also been shown to be degraded by testicular enzyme, resulting in oligosaccharide products similar in size to those from hyaluronic acid (Meyer and Rapport, 1950 and Hoffman et al., 1956).

Another hydronidase has been discovered from the skin of rat. It has been found that the amount of hyaluronidase obtained in fractions from skin is sufficient to account for all the necessary degradation of hyaluronic acid in the known turnover of hyaluronic acid in skin tissue (Cashman et al., 1969).

The effect of Hormones on Mycopolysaccharides:

Cortisone and cortisol reduce the spreading capacity of the hyaluronidase. Androgens such as testosterone greatly increase the concentration of hyaluronic acid without much affecting the sulphated polysaccharides. Oestradiol appears to have a specific inhibitory effect on the synthesis of dermatan sulphate. Growth hormone exerts an anabolic effect

especially in cartilage and the turnover of chondroitin sulphate is increased (Asbo-Hanssen, 1963).

Thyroxin increases the turnover, though this generally leads to reduction in mucopolysaccharide concentration, it must be recognized, however, that exophthalmos occurring in hyperthyroidism is associated with increased hyaluronic acid (Ebling, 1979).

Role of Mucin in the Skin:

Glycosaminoglycans which represent the main components of mucin play an important role as part of the supporting matrix of connective tissue. They function in maintaining salt and water distribution, so that a volume of water as much as 1000 times the volume of the proteoglycan can be contained within the molecule. In addition it would appear that these molecules may be directly involved in cell-cell and cell-matrix interactions and may be of importance in directing cell behaviour (Silbert, 1983).

The water is largely removed during the process of dehydration of the specimen, consequently, in routine sections, the mucin because of its marked shrinkage, appears largely as threads and granules (Lever and Schaumberg-lever, 1983).

Glycosaminoglycans by their interaction with collagen provide for the considerable plasticity of the derma. These components are polyanions i.e. they have many negative charges by which they bind to basic dyes such as alcian blue (Vanugtrecht-Henderiekx et al., 1984).