Proteoglycans: the “Teflon” of the airways?

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Abstract

Proteoglycans are a family of structurally distinct, polyanionic complex carbohydrates composed of repeating disaccharide units. Proteoglycans include heparin, heparan sulphate, chondroitin 4-sulphate, chondroitin 6-sulphate, dermatan sulphate, and hyaluronic acid. Heparin is found in the granules of a subset of mast cells where it is bound to various mediators including histamine. Heparan sulphate has a much wider distribution in the body, being associated with stromal matrices, basement membrane and many cell surfaces, particularly the surface of endothelial cells. Heparin is an anticoagulant, but it is now very apparent that it possesses many other biological activities that have relevance to our understanding of lung diseases, particularly inflammatory diseases of the airway. Recent evidence suggests that heparin may have beneficial effects in the airway when administered by inhalation that could be exploited therapeutically.

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There is now increasing evidence that the naturally occurring glycosaminoglycan, heparin, has a wide range of biological properties that can be considered beneficial in the context of regulation of the inflammatory response.

Heparin can inhibit the influx of neutrophils into certain tissues and inhibit T cell trafficking, partly by an inhibitory effect on the heparinase enzyme secreted by T cells as part of the mechanisms whereby these cells travel across the vascular endothelium.¹ Heparin has been reported to inhibit delayed hypersensitivity responses,¹ allergic encephalomyelitis,² graft rejection,³ and to provide remission of ulcerative colitis.⁴

Scientific basis: heparin and the lung

Heparin has been shown to be released from human lung mast cells in response to allergen exposure,⁵ and increased levels of a heparin-like substance have been reported in the plasma of asthmatic subjects when compared with non-asthmatic, non-allergic control subjects.⁶ It has long been recognised that – “paradoxically”

– heparin, a mast cell product, could inhibit anaphylaxis⁷ and more recently it has been shown by some,⁸ but not all,⁹ investigators to inhibit mast cell mediated bronchoconstriction and skin responses. It is also now apparent from several studies that heparin can inhibit allergen induced eosinophil infiltration into the airways of experimental animals following intravenous administration or inhalation.^{1,10} Furthermore, in allergic rabbits and sheep heparin can attenuate allergen induced airways hyperresponsiveness.¹

For inflammatory cells to enter tissue such as the lung it is now recognised that there are a number of stages involved including: (1) adhesion to the vascular endothelium, (2) diapedesis across the endothelial cells, and (3) chemotaxis within tissues. It is clear that heparin can inhibit all the stages of cell migration including the carbohydrate-selectin interactions between endothelial cells and leucocytes, the presentation of specific chemoattractants to activated leucocytes, and leucocyte trafficking.¹ Whilst mechanisms underlying the effect of heparin on neutrophil migration are well understood,¹ the ability of heparin to interfere with eosinophil adherence and diapedesis is less well understood. Nonetheless, heparin is able to inhibit the actions of several important eosinophil chemoattractants such as platelet factor 4 (PF-4) and regulated upon activation, normal T expressed and secreted (RANTES).¹

One of the consequences of activated eosinophils in the airways is damage to the respiratory epithelial cell layer. Eosinophil derived substances such as major basic protein and eosinophil peroxidase are known to be capable of eliciting ciliastasis and frank epithelial damage.¹ It is of interest therefore that heparin has been shown to inhibit such cytotoxic activity *in vitro*¹ and to protect against changes in the airway following exposure to cationic proteins.¹

Furthermore, heparin may be capable of modulating the extent of remodelling of the airway wall seen in chronic lung diseases such as asthma. Heparin is capable of modulating the actions of a range of proteins including extracellular matrix proteins, growth factors, and certain enzymes.¹ Recent evidence has suggested that heparin can inhibit the proliferation of lung fibroblasts and airway smooth muscle cells in a number of species including humans.¹ It therefore remains plausible that heparin is released in the airways physiologically as a homeostatic mechanism to provide a “non-

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Figure 1 The release of heparin by activated mast cells may serve as a homeostatic mechanism to limit the extent of cellular recruitment into tissues, the extent of tissue damage induced by cationic molecules released by infiltrating leucocytes and the extent of tissue remodelling resulting from injury to mucosal surfaces. (–) = inhibitory effects of heparin.

stick", Teflon-like surface to limit the extent of the cellular adhesion and diapedesis. Furthermore, the release of heparin provides a plausible homeostatic mechanism to limit tissue damage and remodelling following an inflammatory insult to the mucosal surface of the lung (fig 1).

Therapeutic potential and conclusions

Clinically, heparin administered by inhalation has been shown to inhibit allergen induced late onset airway responses in asthmatic subjects⁹ and exercise induced bronchoconstriction.¹¹ Furthermore, topical heparin has been shown to inhibit the recruitment of eosinophils into the nose of allergic subjects following allergen exposure.¹² Heparin clearly exhibits a range of biological properties beyond its ability to act as an anticoagulant, and it is now apparent that many of these properties are unrelated to anticoagulant activity. It is evident that the use of heparin-like molecules that lack anticoagulant activity could have therapeutic potential as anti-inflammatory drugs and in limiting airways remodelling. A better understanding of the role of endogenous heparin and heparan may well lead to a better understanding of disease mechanisms and the normal homeostatic control of the inflammatory process.

Hopefully such research will ultimately lead to a new class of drug for the treatment of chronic inflammatory disease of the lung.

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