Current Comments

Glycosaminoglycans: from “cellular glue” to novel therapeutic agents

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Glycosaminoglycans (GAGs), linear macromolecular heteropolysaccharides consisting of disaccharide repeating units, are classified into several types. Hexuronic acid based GAGs include heparin (HP) and heparan sulfate (HS), which are glucosamine containing sulfated GAGs, chondroitin and dermatan sulfates (CS and DS), based on galactosamine, and hyaluronan which is a glucosamine based non-sulfated GAG. Keratan sulfate is a non-hexuronic acid galactose containing sulfated GAG. They were originally defined as inert ‘glue’ surrounding the cells and were thus positioned on the side-track of ‘cutting-edge’ research efforts for decades. During the last years, however, a huge leap in the field has been accomplished and these macromolecules are now recognized as essential players in critical biological processes regulating cellular properties; tissue development and remodelling; homeostasis; and disease progression.

The unique structural characteristics at the level of sulfation within the GAG chains are closely related with their diverse functions. The evidence that GAGs have a key role in various pathological conditions, have led to the conclusion that understanding the changes in GAG expression and fine structure that occur in disease may lead to opportunities to develop innovative and selective therapies (reviewed by [1]). This has initiated numerous and novel approaches to exploit pluripotent characteristics of GAGs in the ongoing battle against disease.

Acknowledgement of GAGs as potential therapeutic agents dates from the beginning of 19th century. The highly sulfated, free GAG, heparin was discovered in 1916 to have potent anticoagulation properties, whereas the first clinical trials in 1941, introduced heparin as a pioneer drug in the field of GAG therapeutics. The extensive use of this wonder agent, has promoted the progress and development of vascular and cardiac surgery, the extracorporeal circulation, the haemodialysis, the organ transplantation and the treatment and prevention of arterial and venous thromboembolism. This impressive track history is based on heparins’ ability to interact with antithrombin III and heparin cofactor II, promoting their activation and increasing their ability to inhibit thrombin.

Frequent use of heparin in the treatment of cancer-associated thromboembolism initially pointed out its anti-cancer potential. Accumulating clinical evidence indicates that cancer patients treated with unfractionated and low-molecular weight heparin (LMWHP) survive longer than patients treated by...
other anticoagulants, especially patients in the early stage of the disease. The non-anticoagulant activity of heparin on metastasis includes the ability to inhibit cell–cell interaction through blocking of P-selectin and L-selectin, to inhibit the extracellular matrix enzyme heparanase, to modulate the binding of growth factors involved in epithelial to mesenchymal transition during tumor invasion and to inhibit angiogenesis [2]. Notably, the inhibition of melanoma cell adhesion and migration by LMWHP via the PKCa/JNK signaling axis affecting actin cytoskeleton changes opens another area in GAG therapeutics for the future [3].

The extraordinary possibilities of GAG applications in targeted disease treatment are further illustrated by the ability of heparin to regulate processes correlated with inflammation. Heparin participates in the regulation of the inflammatory response by inhibiting the influx of neutrophils into certain tissues and attenuating T-cell trafficking, partly by an inhibitory effect on the heparanase secreted by T-cells. In the lung, it has been suggested that inhibition of the interaction between pro-inflammatory cytokines and membrane-associated GAGs by heparin may provide a mechanism for inducing clinically useful immunosuppression (reviewed by [4]).

Structurally similar to heparin, HS, which in the cellular milieu is bound into proteoglycans (PGs), facilitates both angiogenesis and the activity of the HS-cleaving heparanase. The HS side chains of PGs present in basal membrane contribute not only to storing and preserving the biological activity of various HS-binding cytokines and growth factors, but also in presenting them in a more ‘active conformation’ to their cognate receptors. Abnormal expression or deregulated function of these PGs affect cancer and angiogenesis, and are critical for the evolution of the tumor microenvironment [5]. Furthermore, GAGs as binding partners for matrix metalloproteinases and protease inhibitors, regulate the proteolytic microenvironment of tumors, thus modulating metastatic spread.

Heparan sulfate mimetics, that have been developed to inhibit these processes, are currently undergoing formal preclinical development as a novel treatment for advanced cancer [6]. Heparan sulfate membrane PGs may also be a scaffold that facilitates the interaction of intracellular pathogens with secondary receptors that mediate host cell entry, a key step in the infection process. Consistent with this mechanism, application of HS or heparin as well as modulation of host cell membrane HS inhibits microbial attachment and entry [7].

Chondroitin and dermatan sulfates also have intriguing biological activities, which in turn should help the development of CS/DS-based therapeutics (reviewed by [8]). In the milieu of cancer deregulation, the observation that CS is overexpressed in several highly metastatic tumors led to the suggestion that CS may well be used as a target for the selective delivery of anti-cancer drugs by polyethylene glycol-coated liposomes.

Hyaluronan matrices are ubiquitous in normal and pathological biological processes. Indeed, many cell stress responses initiate the synthesis of a monocyte-adhesive hyaluronan extracellular matrix, which forms a central focus for subsequent inflammatory processes that are modulated by the dialogue between the matrix and the inflammatory cells [9].

The specific physicochemical properties of GAGs allow these molecules to support and re-establish structural tissue homeostasis which resulted in their extensive use in orthopaedic clinical practice as well as in reconstructive and cosmetic surgery. Chondroitin sulfate belongs to the oral symptomatic slow-acting drugs for the treatment of osteoarthritis. The evidence for clinical efficacy of oral CS as a drug comes from sets of clinical trials which document their good tolerability and safety aspects [10]. Moreover, HA has been extensively used in both reconstructive and cosmetic surgery due to its effectiveness, ease of administration, and safety profile.

The endeavours of the ‘wonder’ drug heparin are well known. Encouraging studies, briefly outlined above, strongly indicate the potential use of GAGs as potent therapeutic agents in this promising field of targeted disease therapy.

References


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