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Review article

Dual and antagonic therapeutic effects of sulfated glycans

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ABSTRACT

Sulfated glycans currently explored in medicine like glycosaminoglycans (GAGs) or those of potential medical application like algal sulfated galactans (SGs) and fucoidans exhibit significant effects in numerous pathophysiological systems. According to the structure of these sulfated glycans, sample concentration and the method utilized in the approach opposite effects can be achieved. The effects aimed at down-regulating the events usually dominate. These effects are expected in most clinical endeavors. However, the effects capable of accelerating the events can be also beneficial in certain circumstances. Besides discoursing about the paradoxical effects of sulfated glycans in coagulation/thrombosis, angiogenesis, inflammation and microbial infections; this report aims primarily at highlighting the possible contribution of the neglected activities of some well-known sulfated glycans in up-regulating the events of these pathophysiological systems. The representative sulfated glycans taken here are the mammalian-derived GAGs, the unique holothurian GAG, the red algal SGs and the brown algal fucoidans. The current discussion is highly relevant in light of the future strategies for developing novel sulfated glycan-based therapies.

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1. Introduction

Sulfated glycans like glycosaminoglycans (GAGs), sulfated galactans (SGs) and fucoidans exhibit medical effects in several pathophysiological systems including, but not limited to, inflammation,[1–3] vascular biology,[4] cancer growth and metastasis,[2,5–7] coagulation/thrombosis,[8–12] microbial infections,[13,14] and angiogenesis.[15] The medical effects of these molecules result from their inherent capacity of interacting and regulating key functional proteins of such pathophysiological systems.[16] For instance, due to the great affinity of heparin (Hp) for antithrombin (AT),[17] Hp is heavily explored in the global pharmaceutical market as an anticoagulant agent.[18] Hp–AT is one the most studied sulfated glycan–protein complexes. However, GAGs and other sulfated glycans show the capacity of interacting not just with AT in coagulation/thrombosis, but in fact with many other proteins from this and other systems. For example, they display the capacity of binding to other blood (co)-factors, like IIa, Xa and heparin cofactor II (HCII)[19] to vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF or FGF-2), and the canonical receptors of these growth factors in angiogenesis and tumor progression.[19] Sulfated glycans are also able to interact with multiple chemokines and P- and L-selectins in inflammation,[1,19] besides with the glycoprotein 120 (gp120) of human immunodeficiency virus (HIV) infections on $CD4^+$ T cells during acquired immunodeficiency syndrome (AIDS).[20,21]

Administration of exogenous sulfated glycans in in vivo experimental models simulating the clinical conditions in which the sulfated glycan-binding proteins have to be regulated leads very often to a therapeutic outcome.[1,19] The clinical outcome depends on the chemical properties of the sulfated glycans like specific structural features (anomeric configuration, glycosidic linkage, sulfation pattern),[1,19] conformational preference at both the free and protein-bound states,[22] polysaccharide concentrations utilized in the assays[23,24] and binding affinities of the sulfated glycan ligands in interactions with the functional proteins.[16] Besides some sulfated glycans already explored in the global market such as mammalian-derived GAGs like Hp,[25] chondroitin sulfate (CS),[26] and hyaluronic acid,[27] other less-known sulfated glycans like SGs are also available in research programs aimed at studying their medical activities.[1,19,28]

As highlighted, sulfated glycans are able to interact with numerous functional proteins whose activities must be down-regulated during the pathological events. However, they can also interact unspecifically with other proteins related or not related with the pathophysiological system targeted during the treatment. Sometimes, these unspecific interactions worsen the pathological conditions and this comprises a serious side effect. For example, during the anticoagulant therapy of Hp, this GAG displays also the capacity of interacting with platelet factor-4 resulting, therefore, in an immunological reaction named thrombocytopenic which the platelet amounts circulating in the blood in considerably reduced.[29] The unintended sulfated glycan–protein interactions can produce even a contrary response in the system. For example, procoagulant and prothrombotic effects can be achieved in a specific dose range of certain anticoagulant/antithrombotic sulfated glycans when tested in in vivo or in vitro experiments.[23,24,30,31]

This report presents a different perspective in light of dealing with these two opposite effects of the sulfated glycans in therapies. The article attempts to demonstrate that the opposite clinical effect can be beneficial in certain circumstances if isolated and properly explored. For example, the procoagulant effects achieved with certain doses of some anticoagulant sulfated glycans may be medically useful in events of hemophilia, in which coagulation is seen compromised due to the absence or low-availability of specific blood procoagulant co-factors.[32] A report specifically dedicated to discuss the neglected contrary therapeutic outcomes of certain sulfated glycans is virtually inexistent. This report aims therefore at filling this emptiness of the literature by discussing the upstream therapeutic potentials of key sulfated glycan representatives, here conventionally named as '*pro-effects*'. The sulfated glycan types taken herein are the mammalian-derived GAGs, the unique holothurian GAG named fucosylated chondroitin sulfate, the red algal SGs and the brown algal fucoidans. The pathophysiological systems dealt are the coagulation/thrombosis, angiogenesis, inflammation and microbial infections. In order to accomplish the principal aim of this work which is to demonstrate the possible therapeutic outcome from the '*pro-effects*' as compared to the '*anti-effects*' usually expected for most biomedical sulfated glycans, a brief introduction on the four above-mentioned pathophysiological systems is presented. Discussion then turns to the dual and antagonic effects of the mostly-known sulfated glycans. Reasons and methods to selectively explore each kind of effect ('*anti-effects*' and '*pro-effects*') are justified at the end of the article. This type of report is valuable in light of the strategies currently available for developing novel carbohydrate-based drug candidates.

2. Coagulation and thrombosis

2.1. Overview

Amongst all medicinal activities reported so far for the sulfated glycans, their anticoagulant and antithrombotic effects have been the most investigated and explored ones.[19,33,34] This is likely due to the growing needs for new antithrombotic agents as a result from the increasing incidence of diseases related with thromboembolism. In fact, diseases related with disorders of the heart-and-blood system are the leading cause of death in the world, close to 30% of total deaths.[35] The anticoagulant/antithrombotic mechanisms of action of the sulfated glycans is centered mainly on their capacity of potentiating the inhibitory activity of natural plasma serine proteases inhibitors (serpins) such as AT and HCII.[36] The serpins physiologically down-regulate the blood coagulation process through inhibition of procoagulant/prothrombotic plasma serine proteases like the activated factor II (IIa or thrombin) and activated factor X (Xa). Certain sulfated glycans such as Hp,[37] whose structure is depicted in Figure 1A, have the ability to enhance the inhibitory activities of the serpins in several orders of magnitude. This catalytic effect can be mechanistically seen through two distinct events, although both occur simultaneously in the system: (i) the template mechanism in which the sulfated glycan polymeric chain act as a '*molecular bridge*' to bring together both protease and serpin into a resultant ternary complex;[38] and (ii) the sulfated glycan-driven allosteric conformational change on serpins to a more active form.[39]

2.2. Antagonic effects

Figure 2 depicts bars obtained by in vivo experiments of venous thrombosis in the presence of diverse sulfated glycans such as the standard unfractionated Hp (~15 kDa), and SGs of two red algal species named *Botryocladia occidentalis* (>100 kDa) and *Acanthophora muscoides* (~20 kDa).[23] Structures of these three polysaccharides are represented in Figure 1. At the doses of 0.5 mg kg^{-1} or higher, the SGs showed the capacity of losing their antithrombotic effect while at lower doses (up to 0.25 mg kg^{-1} of rat weight), except Hp which shows a descendent effect up to 0.5 mg kg^{-1}, both native SGs from red algae exhibit antithrombotic property. In the curve of *B. occidentalis* SG, thrombus weight can be even heavier than control while for the *A. muscoides* SG the