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Review

Keratan sulfate: An up-to-date review

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ABSTRACT

Keratan sulfate (KS) is a glycosaminoglycan (GAG) type consisted of a sulfated poly-*N*-acetyl lactosamine chain. Besides acting as a constitutive molecule of the extracellular matrices, this GAG also plays a role as a hydrating and signaling agent in cornea and cartilage tissues. Inasmuch, KS is widely explored in the pharmaceutical industry. This review will cover the major achievements described in the literature of 2010–2014 concerning this GAG. Discussion about KS' roles in physiopathological conditions, as target or therapeutic molecule in diseases, methods of analysis and detection as well as KS-related enzymes, metabolism and developmental biology is properly provided.

Contents

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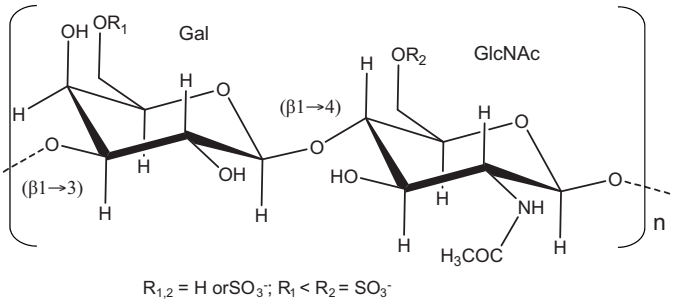

$R_{1,2}$ = H or SO_3^-; $R_1 < R_2 = SO_3^-$

Fig. 1. Structural representation of keratan sulfate. It is a polymer composed of disaccharide repetitions of alternating 3-linked β-galactopyranose (Gal) and 4-linked *N*-acetylglucosamine (GlcNAc). Sulfation occurs at 6-position of any monosaccharide but more often at the GlcNAc.

1. Introduction

1.1. Structure

Keratan sulfate (KS) is a glycosaminoglycan (GAG) type widely found in the extracellular matrices (ECM) of certain tissues, such as cornea, cartilages and bone. KS is composed of a sulfated poly-*N*-acetyl lactosamine backbone. Its structure is formed by alternating 3-linked β-galactose (Gal) and 4-linked *N*-acetyl-β-glucosamine (GlcNAc) units displayed in disaccharide repeating building blocks within a polysaccharide chain [1,2]. Although both units can be 6-*O*-sulfated, this modification occurs more often at the GlcNAc units [3] (Fig. 1). KS is the only GAG type which does not bear an acidic residue [1–3] such as glucuronic acid commonly seen in chondroitin sulfates, dermatan sulfate, hyaluronic acid, and heparin/heparan sulfate [4]; or iduronic acid commonly seen in dermatan sulfate and heparin/heparan sulfate [4]. Instead of these acidic units, KS has the neutral sugar Gal [1–4], and this characteristic gives to KS a less acidic potential in solution, once sulfation is the only acidic component of its structure.

KS chains are generally found structurally attached to a protein core forming thus proteoglycans (PGs) [5]. KS chains can be either *N*-linked to asparagine residues (named as KS I) or *O*-linked to serine or threonine residues (named as KS II) [6]. While KS I occurs more often at the corneal tissue, KS II happens more frequently at the cartilages [1]. Both KS I and II possess a mixture of non-sulfated (Gal-GlcNAc), mono-sulfated (Gal-GlcNAc6S), and di-sulfated (Gal6S-GlcNAc6S) disaccharide units within their chains [6]. The keratan sulfate PGs (KSPGs) can be either primarily composed of KS chains like the family of small leucine-rich ECM PGs such as keratocan, mimecan, lumican, fibromodulin, osteomodulin, and osteoadherin, or just containing few KS chains, as the least abundant GAG type, like aggrecan, which is largely composed of chondroitin sulfate [1,5,6].

1.2. Function

In terms of biological actions, KS is a functional component of PGs from cornea, cartilage and bone tissues. In cornea, the high abundance of KSPGs is related in maintaining the proper hydration levels of this tissue. This is relevant in order to keep constant the transparency of the tissue [1,7]. This factor is extremely important to allow the light beams passing through and converging precisely at the retina in order to generate the right visual effect [1,7]. Anyone could assume unexpected if undesirable structural changes on KS chains of the corneal PGs led to visual dysfunctions. And that is exactly what happens in certain visual disorders like macular corneal dystrophy and keratoconus [1,6,7]. While the former is characterized by defections or changes on the patterns of sulfation, the latter is occasioned by malfunctioning in KS chain formation. Nonetheless, both disorders are occasioned by distortions in fibrils (collagens and PGs) organization in the cornea resulting increased opacity of the tissue [1,6,7]. The use of KS as an active ingredient in eye drops may help to restore the healthier condition. This explains why KS is widely explored in the market as an active ingredient of eye drops. Like in cornea, in cartilages KS is also well-known to play a role in keeping balanced the hydration properties of the tissue, especially as a component of aggrecan which is considerably efficient in confer resistance to physical stress and loads on the tissue. Aggrecan is considered the molecular assembly of the highest molecular weight of the body. In bones, KS seems to play a primary role as structural component of certain KSPGs endowed with cell binding properties [8].

Aside from KS principal function in cornea, this GAG type also participates in developmental biology, cellular signaling and migration, like the other GAGs chondroitin, dermatan and heparan sulfates [1]. For example, as opposed to chondroitin sulfates that are known to induced neurite growth and guide neurite migration during neural development, KS-containing molecules comprise a barrier to neurite growth *in vitro* [1,9,10]. KS and chondroitin sulfate seem to be working altogether, with opposite functions, to keep balanced the mechanisms involved in neural development. Nonetheless, in certain occasions, KS can also help direction of axons in neural development and regeneration *in vivo* [1,9,10].

1.3. Scope of the review

Due to the biological and medical roles of KS, as discussed above, as either naturally occurring functional molecules of the body, or as active ingredients in pharmaceutical formulations, a review paper outlining the major recent findings about this biological macromolecule seems to be relevant in the literature nowadays, especially, considering the rapid growing success of glycomics, and the importance of GAGs to this project. The inexistence of any review paper concerning KS in the literature of the last five years is an additional contributing factor to this publication. In this study, I discuss the major achievements made in the science of KS that have been deposited in the literature database within the 2010–2014 timeframe. This review is systematically divided into the following topics about KS: (i) its role in physiopathological conditions; (ii) as therapeutic or target molecule in diseases; (iii) methods of analysis and detection; and (iv) related enzymes, metabolism, and developmental biology.

2. Role in physiopathological conditions

2.1. Inflammation

It is well-known that pro-inflammatory chemikones, and their consequential effects in leukocyte recruitment and activation, are at a first moment, regulated by GAGs found on cell surface PGs [11,12]. Based on this premise, Carlson and co-authors have investigated the role of KSPGs in the cornea as regulators of chemokine gradient and the neutrophil-dependent inflammatory process of this tissue [13]. The authors have postulated that KSPGs in cornea play a key role in controlling the chemokine gradient, its breakdown, and consequent resolution of the corneal inflammation. Experimentally, bacterial immunogenic lipopolisaccharide (LPS) was injected into the corneal stroma of mice. Extracts from this particular tissue were examined based on immunoblot methods. After 6 h of injection, while the amounts of 52 kDa protein core of keratocan were observed significantly reduced, the amounts of the 34/37 kDa products were proportionally increased. The appearance of these products of reduced molecular weights is coincident with the event of neutrophil infiltration in the corneal stroma.