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Review article

Glycosaminoglycan and proteoglycan in skin aging

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ABSTRACT

Glycosaminoglycans (GAGs) and proteoglycans (PGs) are abundant structural components of the extracellular matrix in addition to collagen fibers. Hyaluronic acid (HA), one of GAGs, forms proteoglycan aggregates, which are large complexes of HA and HA-binding PGs. Their crosslinking to other matrix proteins such as the collagen network results in the formation of supermolecular structures and functions to increase tissue stiffness. Skin aging can be classified as intrinsic aging and photoaging based on the phenotypes and putative mechanism. While intrinsic aging is characterized by a thinned epidermis and fine wrinkles caused by advancing age, photoaging is characterized by deep wrinkles, skin laxity, telangiectasias, and appearance of lentigines and is mainly caused by chronic sun exposure. The major molecular mechanism governing skin aging processes has been attributed to the loss of mature collagen and increased matrix metalloproteinase expression. However, various strategies focusing on collagen turnover remain unsatisfactory for the reversal or prevention of skin aging. Although the expression of GAGs and PGs in the skin and their regulatory mechanisms are not fully understood, we and others have elucidated various changes in GAGs and PGs in aged skin, suggesting that these molecules are important contributors to skin aging. In this review, we focus on skin-abundant GAGs and PGs and their changes in human skin during the skin aging process.

Contents

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1. Introduction

Skin aging can be classified as intrinsic aging and photoaging based on the phenotypes and putative mechanism [1]. Intrinsic aging is characterized by a thinned epidermis and fine wrinkles caused by advancing age [1,2], while photoaging is characterized by deep wrinkles, skin laxity, telangiectasias, and appearance of lentigines, and is mainly caused by chronic sun exposure [1,3]. The major molecular mechanism governing skin aging processes has been attributed to the loss of mature collagen and increased matrix metalloproteinase (MMP) expression [1–3]. MMP-1 is known as an initiator collagenase responsible for collagen fragmentation in skin aging process, and MMP-2 and −9 are known to be responsible for further degradation of collagen [1,3]. Impaired TGF-β signaling-caused reduction of collagen synthesis is another reason for collagen loss in aged skin [2,4]. However, various strategies focusing on collagen turnover remain unsatisfactory for the reversal or prevention of skin aging.

2. Structure of glycosaminoglycans (GAGs)

Glycosaminoglycan (GAG) is the name used for six different types of long linear polysaccharide chains composed of specific disaccharide units. The six types of GAG include chondroitin sulfate (CS), dermatan sulfate (DS), keratan sulfate (KS), heparan sulfate (HS), heparin (HP), and hyaluronic acid (HA) [5,6]. Except HA, GAGs are generally heavily glycosylated on their related proteoglycan (PG) core proteins (Table 1) [7–12], and synthesized by various glycosyltransferases and sulfotransferases (Supplementary Table S1)[10–13]. In contrast, HA is synthesized as a single polysaccharide chain without a core protein partner and non-covalently binds to many proteins containing HA-binding domain [13,14]. Because GAG chains contain numerous negatively charged carboxyl and sulfate groups, they may have important roles in maintaining water in tissue [6]. In particular, HA was reported to be able to hold water molecules up to 1000-fold of its molecular weight [14].

2.1. Synthesis of HA

HA is the simplest GAG from the perspective of its synthesis pathway. HA is a linear non-sulfated GAG composed of up to 10,000 repeats of its disaccharide unit D-glucuronic acid (ß1 →3) and *N*-acetyl-D-glucosamine (ß1 →4) [14]. HA synthesis occurs in the plasma membrane by three HA synthases (HAS1–3), and the synthesized HA molecules are directly secreted out of the cell membrane [14]. HAS1 and HAS2 are reported to produce 2–4 × 10^6 Da of HA, while HAS3 produces 0.4–2.5 × 10^5 Da of HA [14]. HAS2 is thought to be the main synthase in the skin [14].

2.2. Synthesis of sulfated GAGs

Other GAGs have more complex structures and synthetic processes than HA and contain their own PGs where they are glycosylated (Table 1). Serine is the only amino acid used for CS/DS and HS/HP glycosylation [5], while serine, threonine, and asparagine are used for KS [12]. Unlike HA, some GAGs can have sulfate groups on their sugars, which are added by various sulfotransferases (**Supplementary Table S1**) [6].

Synthetic processes for CS/DS and HS/HP exhibit many similarities. They share the linkage region composed of common tetrasaccharide, which is responsible for initiating *O*-linked glycosylation on the serine residue [5,15]. The addition of D-xylose to the OH group of serine is mediated by xylosyltransferase (XYLT) 1 and 2 in the endoplasmic reticulum (ER) [5,15]. Addition of the next two D-galactoses to the xylose is sequentially mediated by β1,4-galactosyltransferase (B4GALT) 7 (galactosyltransferase I) and β1,3-galactosyltransferase (B3GALT) 6 (galactosyltransferase

Table 1
Basic disaccharide units of GAGs and their related PGs.

Sugar 1	Sugar 2		
	N-acetyl-D-glucosamine	D-glucosamine	*N*-acetyl-D-galactosamine
D-Glucuronic acid	**Hyaluronic acid (HA)** No core protein	**Heparan sulfate (HS)** Syndecan-1 Syndecan-2 (HSPG1) Syndecan-3 Syndecan-4 Glypican-1 Glypican-2 Glypican-3 Glypican-4 Glypican-5 Glypican-6 Perlecan (HSPG2) Agrin Collagen XVIII Betaglycan (TGFBRIII) Testican-1 Testican-2 Testican-3	**Chondroitin sulfate (CS)** Aggrecan (CSPG1) Versican (CSPG2) Neurocan (CSPG3) Melanoma-Associated Chondroitin Sulfate Proteoglycan (CSPG4) Neuroglycan C (CSPG5) Bamacan (CSPG6) Brevican (CSPG7) CD44 (CSPG8) PG-100 (M-CSF) Bikunin Thrombomodulin
L-Iduronic acid		**Heparin (HP)** Serglycin	**Dermatan sulfate (DS)** Biglycan (DSPG1) Decorin (DSPG2) Epiphycan (DSPG3) Endocan
D-galactose	**Keratan sulfate (KS)** Lumican Fibromodulin Keratocan Osteoglycin (=Mimecan) Osteoadherin (=Osteomodulin)		