ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF ARTIFICIAL INTELLIGENCE

ISSN: 2692-5206, Impact Factor: 12,23
American Academic publishers, volume 05, issue 03,2025

Journal: https://www.academicpublishers.org/journals/index.php/ijai

PROTEOGLYCANS IN NORMAL PHYSIOLOGY AND CARCINOGENESIS

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Abstract: The emergence and development of malignant tumors is associated with numerous disturbances in the physiology of the cell at both the genomic and protein levels and affects many macromolecules involved in various aspects of its vital activity. However, the growth of a malignant tumor and its metastasis are determined not only by the molecular characteristics of the tumor cell itself, but also by its interaction with the surrounding extracellular matrix (ECM) – an important and necessary part of any tissue. A huge role in this is played by complex protein-carbohydrate molecules of proteoglycans (PG), which are one of the main components of the ECM and are present on the surface of almost all cells, largely determining intercellular interactions and interactions of cells with the ECM.
Keywords:proteoglycan, heparan sulfate, glycosaminoglycan, extracellular matrix, chondroitin sulfate, intercellular interactions.

INTRODUCTION

At present, despite intensive research, the causes of malignant tumors and the molecular mechanisms of carcinogenesis remain insufficiently studied. It is known that this process is associated with the functioning of many signaling pathways involving various molecules, the composition, structure and expression of which undergo significant changes in the process of malignant transformation of cells and tissues, which largely determines the initiation and development of the pathological process. Along with the actively studied macromolecules of nucleic acids, proteins, polysaccharides and lipids, protein-carbohydrate molecules called proteoglycans (PG) also play a significant role in the physiology of cells and tissues and their malignant transformation.

MATERIALS AND METHODS

PGs are complex protein-carbohydrate molecules consisting of a core protein and carbohydrate chains of glycosaminoglycans (GAGs) covalently attached to it [1]. They represent a separate class of biological macromolecules that differ fundamentally from glycoproteins precisely in the structure of their carbohydrate chains. Polysaccharide chains of GAGs are linear polymers consisting of repeating disaccharide subunits, each of which includes hexosamine (D-glucosamine or D-galactosamine) and uronic acid (D-glucuronic or L-iduronic). Each disaccharide can undergo selective modification at various positions (sulfation at the 2-, 3- and 6-O-positions and acetylation/sulfation at the N-position), which leads to a high anionic charge of the disaccharides themselves and the GAG carbohydrate chain formed from them and the PG molecule as a whole.

RESULTS AND DISCUSSION

GS is one of the main classes of GAGs. Its carbohydrate chains consist of N-acetylated or N-sulfated D-glucosamine (GlcNAc), which is linked to D-glucuronic (GlcA) or L-iduronic acid (IdoUA) [2]. A special type of GS is heparin, which is characterized by a high degree of sulfation of iduronic acid (at carbon 2 (IdoA2S)) and N-sulfated glucosamine (at position 6 (GlcNS6S)). The degree of sulfation of heparin is much higher than GS, which makes heparin the most charged of all known biomolecules, which is a widely used pharmaceutical anticoagulant.

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CS contain alternating residues of glucuronic acid (GlcUA) and N-acetylgalactosamine (GalNAc). They vary significantly in chain length and molecular weight: their weight fluctuates in the range from 5 to 70 kDa, even when isolated from the same source [3]. Like GS, CS can be N- and/or O-sulfated or acetylated at the 2, 3, 4 and/or 6 positions and are highly anionic molecules with a heterogeneous structure, and the pattern of their sulfation directly affects their biological functions. DS is completely identical to the CS molecule in its composition, but contains a stereoisomer of glucuronic acid (D-GlcUA) – iduronic acid (L-IdoUA). It is the presence of the L-IdoUA stereoisomer that allows such a molecule to be called DS and not CS. Glucuronic (GlcA) or iduronic (IdoA) acid in DS can be partially sulfated at the C2 position, and N-acetylgalactosamine (GalNAc) at the C4 or C6 position [4].

Structure of keratan sulfates

The main disaccharide of keratan sulfates consists of N-acetylglucosamine (GlcNAc) and galactose, both of which can be sulfated at the C6 position. Therefore, keratan sulfate is the only type of GAG that lacks a carboxyl group [2]. The molecular weight of keratan sulfate ranges from 5 to 25 kDa and strongly depends on the tissue origin. The highest concentration of keratan sulfate is found in the cornea. Keratan sulfate is a structural component of several PGs – aggrecan, contained in cartilage, and small leucine-rich PGs (lumican, keratocan, fibromodulin). In addition to the extracellular matrix (ECM), keratan sulfates are also found intracellularly in eosinophil-specific granules and as part of cellular transmembrane proteins such as CD44 and MUC1 [4]. It is the structure of disaccharides that determines the type of GAG carbohydrate chain, which in turn is reflected in the name of the complex protein-carbohydrate PG molecule. It should be noted that different GAG chains can be present simultaneously on the same core protein, in which case the name of the complex PG molecule is determined by the dominant GAG chains present on its protein core.

PGs are present in virtually all tissues of all living organisms, from trilobites to mammals [1]. Their main location is the cell surface and ECM. It is their localization that determines the main functional role of PGs in mammalian tissues – maintaining cell contacts with the surrounding ECM cells [4]. The importance of this function cannot be overestimated, because without maintaining close functional relationships, the existence of any tissue of the organism and the organism as a whole is impossible. PGs also take an active part in the processes of differentiation and development of the organism [4]. Their carbohydrate chains can specifically interact with growth factors, such as fibroblast growth factors FGF-1, FGF-2 and transforming growth factors (TGF), which have a heparin-binding domain and are actively involved in the processes of inflammation, wound healing and tumor development [3].

CONCLUSION

Protein-carbohydrate molecules of PG are an integral component of any tissue, which plays an important role both in the normal physiology of cells and in the formation and maintenance of the surrounding ECM. The complex structure of PG and their high negative charge ensure their interaction with numerous ligands, the transmission of signal information, the maintenance of intercellular interactions and the interaction of cells with their microenvironment.

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