Gynecologic Oncology 135 (2014) 371–381

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Sulfated sugars in the extracellular matrix orchestrate ovarian cancer development: 'When sweet turns sour'

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HIGHLIGHTS

- Chondroitin sulfate glycosaminoglycans are multifaceted key molecules in ovarian carcinogenesis.
- Chondroitin sulfates are potential targets for novel diagnostic and therapeutic modalities.
- Chondroitin sulfates may be used as micro-environmental hooks for targeted drug-therapy.

ARTICLE INFO

Article history:
Received 15 June 2014
Accepted 16 August 2014
Available online 23 August 2014

Keywords:
Chondroitin sulfate
Glycosaminoglycans
Biomarkers
Therapeutic targeting
Carcinogenesis

ABSTRACT

Considering the high mortality of ovarian cancer, novel approaches for diagnostics and therapy are urgently needed. Cancer initiation, progression, and invasion occur in a complex and dynamic microenvironment which depends on the interplay between host cell responses and tumor activity. Chondroitin sulfate (CS), a special highly sulfated sugar, forms an important intermediate player in this respect. Depending on the (micro)structural diversity of chondroitin sulfate chains, various ligands interact with this special group of glycosaminoglycans, making it a key molecule for many physiological and pathological processes, including cancer development.
This review focuses on the various functions of chondroitin sulfate in tumor growth, angiogenesis, dissemination and immunosilencing of ovarian cancer. We also shed light on possible future diagnostic and therapeutic modalities for ovarian cancer based on the large variety in chondroitin sulfate microstructure and function. It is concluded that the class of chondroitin sulfate represents an attractive target to interfere with the process of ovarian tumorigenesis.

Contents

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http://dx.doi.org/10.1016/j.ygyno.2014.08.023
0090-8258/

Introduction

Ovarian cancer is a major health threat in women, causing more deaths than all other gynecologic cancers combined. Worldwide, about 226,000 new patients and approximately 140,000 ovarian cancer related deaths are recorded each year [1]. Due to absence of clear symptoms at an early stage and the lack of sufficient screening methods, over 70% of ovarian cancer patients are diagnosed with advanced stage (Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) III and IV) of disease, and have a poor 5-year survival [2]. First-line treatment, consisting of cytoreductive surgery and platinum-based chemotherapy, initially shows good response. Unfortunately, 70% of the patients with advanced disease quickly develop recurrent disease and eventually succumb [3].

In the past, efforts in cancer research were predominantly focused on genetic changes in tumor cells that initiate cancer development. However, solely uncontrolled proliferation of tumor cells does not result in cancer. For tumor cells, in order to invade and disseminate, numerous hurdles in the surrounding micro-environment have to be taken. For example, preservation of normal tissue architecture surrounding tumor lesions prevents tumor cells from invading and metastasizing [4]. As a consequence, tumor cells evolve and through proteolytic and glycosidic degradation of normal extracellular matrix (ECM) and de-novo-synthesis of 'tumoral' ECM they create a more protective environment. A large intratumoral ECM proportion has shown to correlate with poor prognosis in different types of cancer, including ovarian cancer [5].

The ECM is made up of many different types of proteins and glycoproteins. Chondroitin sulfate (CS), a special class of glycosaminoglycans, is a major constituent of the ECM. Mainly positioned as side chains on the protein core of proteoglycans (PGs), they regulate many biological and pathological processes including cell differentiation, migration, adhesion and metastasis. An increase of CS and its different subfamilies has been noted in various types of cancer, including ovarian cancer (Table 1). Moreover, elevated levels of unique CS epitopes in ovarian cancer tissue and patient sera are associated with adverse prognostic factors and poor patient outcome [6,7]. The functional significance of CS accumulation is largely unknown. Nevertheless, many mechanistic roles in the (tumoral) micro-environment have been indicated. A better understanding of the interplay between tumor cells and its surroundings could eventually lead to improved diagnostic and therapeutic modalities.

In this review, we discuss the manifold roles of CS in the (ovarian) cancer micro-environment and discuss its potential clinical value in detection and treatment of ovarian cancer. The intricate play between core protein and glycosaminoglycan chains within proteoglycans is still unclear and core-mediated effects cannot always be separated from glycosaminoglycan-mediated effects. Therefore, we have included CS proteoglycans in this survey as well.

Chondroitin sulfate in the extracellular matrix

A 'sweet' side to the extracellular micro-environment

The ECM is a highly organized three-dimensional mesh of fibrous proteins and glycoproteins. A well-operating ECM provides architectural support and molecular cues to the tissue. A ubiquitous component of the ECM are proteoglycans, highly versatile glycoproteins with a high degree of heterogeneity especially on the part of the glycosaminoglycan side chains [8]. Glycosaminoglycans are linear polysaccharides that consist of a backbone of repeating disaccharide units composed of an amino sugar and an uronic acid. Four major families of glycosaminoglycans have been identified: chondroitin/dermatan sulfate, heparan sulfate/heparin, hyaluronan and keratan sulfate. To a large extent, the biological functions that proteoglycans possess mediate on the interactions of the glycosaminoglycan chains with various ligands. Moreover, the function of glycosaminoglycans is closely related to their spacial configuration and location. For instance, in the ECM they may form growth factor deposits, whereas at the cell surface they can function as (co)receptors regulating a wide range of cellular events. Through the binding of glycosaminoglycans with effector molecules such as cytokines, chemokines, and growth factors, glycosaminoglycans are able to regulate cell adhesion, proliferation, migration and angiogenesis [9].

The ECM is critical for everyday maintenance of all healthy organs. A "healthy" ECM surrounding cancer cells, can restrain or even overcome cancer progression [4,10], by retaining malignant tumors in an in situ situation. Conversely, the ECM also provides a scaffold to tumor cells and is therefore an essential intermediate player in tumor progression. Compared with non-neoplastic ECM, tumor associated ECM contains higher concentrations of various growth factors and high amounts of specific proteoglycans and glycosaminoglycans (Table 1). Moreover, tumor associated ECM is characterized by a predominant presence of (highly sulfated) CS, which outshines the other glycosaminoglycan families. Abnormal compilation of ECM facilitates tumor growth and cancer progression [9].

Chondroitin sulfate and its proteoglycans

The biosynthesis of glycosaminoglycan chains is a complex process and, unlike protein synthesis, not template driven. Instead, glycosaminoglycan formation relies on the activity of a group of specific glycosyltransferase, sulfotransferase and epimerase enzymes which are present in the Golgi apparatus. Only little is known about their regulation. The basic structure of the CS backbone is composed of a linear chain of repeating disaccharide units of glucuronic acid (GlcA) and N-acetylgalactosamine (GalNAc) (Fig. 1A). Chain elongation occurs by sequential transfer of the appropriate monosaccharide by different glycosyltransferases (Fig. 1B) [11]. Subsequent modifications involve C5-epimerization of GlcA to iduronic acid, thereby forming dermatan sulfate, and O-sulfation at C2 of GlcA/IdoA and/or C4 and/or C6 of GalNAc [11]. The main structural categories of CS are illustrated in Fig. 1A. Di-sulfation at C4 and C6 constitutes CS-E. Generally, CS is composed of various disaccharides. In addition, chains differ in length and special domains exist within one chain bearing high and low sulfated substitutions. The structural variation makes CS an information-dense molecule containing a large number of distinct oligosaccharide 'motifs'. These domains are the key-elements on which growth factors and their receptors act, enabling them to specifically promote various biological and pathological effects [12].