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Perspective

Chondroitin Sulfate Disaccharides, a Serum Marker for Primary Serous Epithelial Ovarian Cancer

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ABSTRACT

Glycosaminoglycans are long polysaccharidic chains, which are mostly present in connective tissues. Modified GAG expression in tissues surrounding malignant cells has been shown to contribute to tumor progression, aggressive status and metastasis in many types of cancer. Ovarian cancer is one of the most lethal gynecological malignancies due to its late diagnosis because of the absence of clear symptoms and unavailability of early disease markers. We investigated for the first time GAG changes at the molecular level as a novel biomarker for primary epithelial ovarian cancer. To this end, serum of a cohort of 68 samples was digested with chondroitinase ABC, which releases chondroitin sulfate into disaccharides. After labelling and purification, they were measured by HPLC, yielding a profile of eight disaccharides. We proposed a novel GAG-based score named "CS-bio" from the measured abundance of disaccharides present that were of statistical relevance. CS-bio's performance was compared with CA125, the clinically used serum tumor marker in routine diagnostics. CS-bio had a better sensitivity and specificity than CA125. It was more apt in differentiating early-stage patients from healthy controls, which is of high interest for oncologists.

Keywords: Chondroitin sulfate; Disaccharide; Glycosaminoglycan; Ovarian cancer; Biomarker; HPLC

INTRODUCTION

Although surgical techniques and therapies have improved in the past years, Ovarian Cancer (OC), one of the rarer gynecological carcinoma types, remains the most lethal gynecological malignancy. The reason for the high mortality rate is that the disease remains clinically silent in the early stages and tends to be diagnosed only when the late stages are reached. Hence, only 10%-20% of patients are diagnosed in the early stages (stage I: localized in the ovary, stage II: localized in the pelvis) whereas approx. 80% of patients are diagnosed at a late stage of the disease (stages III and IV). For decades, the standard of care has been de bulking surgery followed by platinum- or taxane-based chemotherapy. Prognosis directly correlates with the presence and size of residual tumors remaining after surgery. Indeed, most patients initially respond to chemotherapy but will become chemo-resistant upon relapse. As a result, insufficient screening methods and late-stage detection are the primary causes of poor prognosis. OC is diagnosed using pelvic examination and transvaginal ultrasound in combination with the measurement of the serum levels of Carbohydrate Antigen 125 (CA125). Regarding primary diagnosis, CA125 alone has a low sensitivity of 57%, especially in early stages of OC and a specificity of 97%. The other routine biomarker available is Human Epididymis 4 (HE4). It shows slightly better performance than CA125 in pre-menopausal women but has otherwise low sensitivity. Modeling simulations estimated that early diagnosis could not only improve survival by 10%-30% but also be cost-effective.

As glycosylation is modulated at the onset and the course of cancer, it is an interesting source of biomarkers. Glycosaminoglycans (GAG) are glycoconjugates, which are mostly present in connective tissues. They are found either in free form or as constituents of proteoglycans in the extracellular matrix. Being composed of long polysaccharidic chains, GAG are key components of the extracellular matrix in healthy connective tissues and play an important role in homeostasis, regulation of cell growth, angiogenesis, migration, recognition and disease. Due to their structural diversity, GAG actively take part in cellular events by binding a wide range of different molecules (for instance growth factors, cytokines, chemokines, enzymes) at the surface of cells and tissues. As a consequence, GAG promote inflammation that accompanies many types of inherited and acquired diseases. GAG modulations are observed during the development of many diseases (cancer, neuroinflammation, atherosclerosis, diabetes) within tissues and, as a result, in blood that is in circulation.

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Biological processing of glycoconjugates unlike proteins is not template-driven and results from the availability of activated monosaccharides, glycosidases, glycosyltransferases, sulfotransferases and epimerases. GAG are negatively charged linear polysaccharide chains that are built of disaccharide repeating units. This study concentrates on the analysis of non-sulfated Hyaluronic Acid (HA)-consisting of β (1-3)-GlcNAcβ (1-4)-GlcA-as well as Chondroitin Sulfate (CS)-consisting of β (1-3)-GalNAc β (1-4)-GlcA. CS-0S denotes a non-sulfated disaccharide. CS sulfation can occur at the C2 position of Glucuronic Acid (GlcA), (named CS-2S) and the C4 and C6 position of *N*-acetylgalactosamine (GalNAc), named CS-4S or CS-6S. Combinations of these sulfation patterns are possible, resulting in the disaccharides CS-2S4S, CS-2S6S, CS-4S6S, CS-2S4S6S.

Modified GAG expression in tissues surrounding malignant cells has been shown to contribute to tumor progression, aggressive status and metastasis for many types of cancer, namely ovarian cancer, breast cancer, colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, pancreatic cancer, and gastric carcinoma. In addition, elevated levels of chondroitin synthase I and III, which synthesize CS chains, were measured in various types of cancer. CS chains interact with growth factors or are stored in the extracellular matrix and released gradually within the matrix, promoting cell signalling. In other words, CS over expression as well as modulated sulfation are hallmarks of cancer development. Moreover, CS-proteoglycan expression has been shown to correlate with both tumor differentiation and prognosis. In this work, we investigated for the first time GAG changes at the molecular level as a novel biomarker for primary epithelial ovarian cancer.