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REVIEW

Selective recognition of a saccharide-type tumor marker with natural and synthetic ligands: a new trend in cancer diagnosis

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Abstract It is well known that saccharides and their glycoconjugates can have an important influence on various serious pathologic stages such as cancer. They can regulate tumor proliferation, invasion, hematogenous metastasis, and angiogenesis. These facts clearly show the importance of cancer saccharide recognition. In medicine, sensor analysis is one of the best methods for recognition and determination of biologically important analytes. The development and study of sensors for saccharide tumor markers can open a new way for their detection. Therefore, this review is focused on recognition of saccharide-based cancer markers by natural or synthetic selective ligands working as bio- and chemosensors. The design and application of these ligands for cancer diagnosis is a useful direction of research. Moreover, it also opens the possibility of using these agents for the targeted drug transport required for advanced anticancer therapy.

Keywords Saccharide cancer marker · Chemical sensors · Biosensors · Optical sensor · Cancer diagnosis · Glycomic

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Introduction

Recently, a slight decline in the incidence of cancer has been achieved worldwide, but long-term mortality rates still remain high [1]. For successful therapy, early diagnosis of cancer plays the key role. Implementation of early detection in traditionally used clinical methods is necessary for significant reduction of the morbidity and mortality caused by cancer [2].

For decades, microscopy of biopsy samples was the principal diagnostic method. However, this method suffers from subjectivity and a limited ability to detect the early events of cancer [3]. To fulfill the demand for the earliest possible diagnosis, new tools have to be found and applied. It is well known that when a tumor is detected, certain changes at the molecular level have already occurred. The main goal of the new diagnostic approaches is to recognize these changes as early as possible. This recognition can be based on a specific interaction of diagnostic agents with suitable molecular partners, i.e., cancer biomarkers [4]. Biomarkers, divided by several structural motifs (e.g., proteins, saccharides, metabolites, and nucleic acids), represent molecular signatures of the cell phenotype. They can be used for specific detection and recognition of

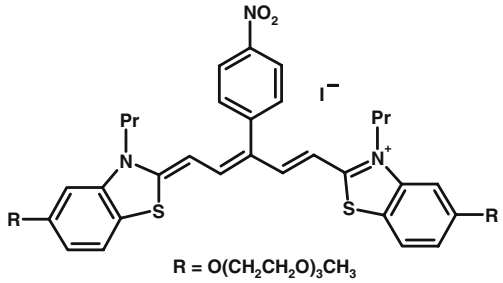

Fig. 1 Cyanine dye sensor [54] for heparin

particular cell types, such as cancer cells. In addition, biomarkers can be used for prediction of disease progress for chosen and optimized therapy.

The development of molecular tools for cancer diagnosis and prognosis is already in progress and it is still evolving [5]. Many biomarkers of cancers have been identified [4, 5]. An ideal recognition preferably employs biomarkers (targets) which are overexpressed on all tumor cells but not on the normal cells, and at the same time are required for cell survival, proliferation, or other critical functions [6]. The recognition component of a diagnostic agent can also be used in the drug delivery system to enhance its efficacy of medication [7].

Methodological approach

In research and clinical practice genomic, proteomic, and metabolic methods are usually used [8]. The genomic method [9] (microarays, serial analysis of gene expression, or PCR) provides information about the expression profile and mutation of the genes. Such information can be used for the prognosis of the patient (level of messenger RNA) or to pursue the effect of targeted therapies (somatic change of DNA). Proteomic methods [4] (ELISA, radioimmunoassay, MudPIT, surface-enhanced laser desorption/ionization time-of-flight analysis) can be used for the diagnosis of blood malignancies and for the determination of protein translation modification (phosphorylation). Metabolomics (analysis of metabolic pattern) reflects a global change of cancer cells and therefore metabolic analysis can be used for cancer recognition (low intracellular and extracellular pH) [10] and higher levels of some bioanalytes [11] (pyruvate [12], lactate [12, 13], metals [14, 15], and others). Effective diagnostic methodology requires determination of more biomarkers by a different diagnostic method [16]. Therefore, the identification of new cancer markers and the development of methods for their selective recognition and determination are intensively sought. Besides the methods mentioned above, there is a new emerging field of glycomic research, which can be a useful tool for cancer diagnosis and a good starting point for the development of a controlled and targeted drug delivery system [7].

In glycomics, cancer recognition is focused on saccharide patterns of cancer cells [17, 18]. It is well known that the saccharide substitution pattern of cell receptors is significantly changed during oncogenic transformation [18]. Such a change was observed in various stages of many cancer types and provides important information about cancer progress, immune response, drug resistance, metastatic capacity, and malignancy. It includes overexpression of the cell-surface polysaccharides (glycosaminoglycans [19, 20], polysialic acid [21]) and oligosaccharides (Lewis antigene [22], saccharide part of gangliosides [23]), and modification of the surface receptors (e.g., sialylation of glycolipids) [24].

Glycan cancer markers

Glycans are covalent assemblies of sugars (oligosaccharides and polysaccharides) that exist in either free form or in covalent complexes with proteins or lipids. These glycans might be regarded as part of a larger array of "metastatic codes" that a tumor's glycan profile (or "glycotype") might represent. For example, the serological markers CA125, CA19-9, and CA15-3 are mucin glycoconjugates that are commonly overexpressed by ovarian, pancreatic, and breast adenocarcinomas, respectively, and their serum levels correlate with tumor burden and prognosis [18, 25, 26]. Mass spectrometry [25, 26], chromatography [25], or sophisticated methods such as lectin/antibody microarrays [26, 27] are used for recognition and determination of glycan markers. Important saccharide markers include glycosaminoglycans, polysialic acid, gangliosides, and Lewis antigens.

Glycosaminoglycans are one of the most important cancer saccharides. They are functional linear heteropolysaccharides which participate in and regulate a number of cellular events and physiological/pathological processes [28]. Glycosaminoglycans can undoubtedly influence tumor cell proliferation, metastasis, and cancer progression. Polysulfated glycosaminoglycans (heparan sulfate, chondroitin sulfate, dermatan sulfate, and keratin sulfate) [19, 29, 30] are polysaccharides with high structural variability and negative charge. Inhibition of the expression of their

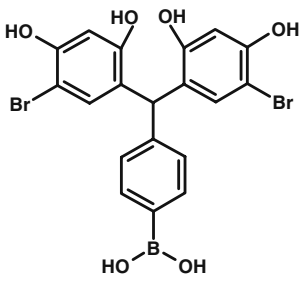

Fig. 2 Boronic acid sensor [56]

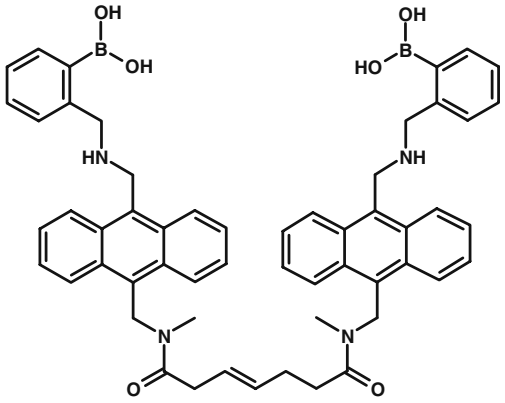

Fig. 3 Diboronic acid probe [67]

receptors [31] or their glycosylation [32, 33] can be useful way for reduction of tumorigenic phenotype and angiogenesis. They can be used for recognition of pancreatic carcinoma [34], breast cancer [35], prostate cancer [36], thyroid cancer [30], astrocyte tumor [37], and glycoblastoma [38]. Hyaluronic acid is a nonsulfated glycosaminoglycan composed of repeating units of alternating uronic acids and *N*-acetylglucosamine [20, 39]. The overexpresion of hyaluronic acid was found in cancer of the neck, head, thyroid gland, liver, lung, prostate gland, and ovary among other organs and structures [40] and to be involved in stimulation of metastatic activity, angiogenesis, and tumor cell resistance.

Polysialic acid [41] is a large negatively charged linear homopolymer of a 2,8-sialic acid residue mainly associated with neural cell adhesion molecule. Medulloblastoma, neuroblastoma, and alveolar rhabdomyosarcoma are characterized by a high level of polysialic acid [21]. The elevated expression can cause higher migration ability of cancer cells [42]. In brain tumors, high expression of polysialic acid correlates with high tumor invasiveness and high risk of metastasis.

Gangliosides are sialic acid containing glycosphingolipids that are primarily expressed in the plasma membrane, and play an important role in cell growth and differentiation [43]. Overexpression of some gangliosides was observed in many tumors of neuroectodermal or epithelial origin, such as glioma, medulloblastoma, neuroblastoma, melanoma, head and neck tumors, breast cancer, and teratomas [23]. GD1a expression is used as marker for ovarian cancers [44]. In tumor biological processes, glycosylated molecules play key roles in protection of cancer cells from immune system regulation, in cell adhesion/motility, and thus in the initiation of tumor metastasis. Inhibition of cancer ganglioside function is a useful method for the reduction of tumor aggressiveness, immumoprotection, and angiogenesis [45].

Lewis blood group antigens are also common for various types of malignancies [22]. Le^a and Le^b antigens are important tissue blood groups, whereas Le^x and Le^y antigens in healthy individuals are only expressed, at relatively low levels, by a few tissues (epithelial cells). Lewis antigens can be synthesized de novo or overexpressed in the majority of human carcinomas of the colon, bladder, breast, and lungs, and are often associated with advanced forms of malignancies [46]. The presence of sialyl-Le^a and sialyl-Le^x is associated with bad prognosis in various types of cancers [22].

Selective ligands for recognition of glycan tumor markers

The development and study of selective ligands (biosensor and chemosensors) for glycan tumor markers can open a new

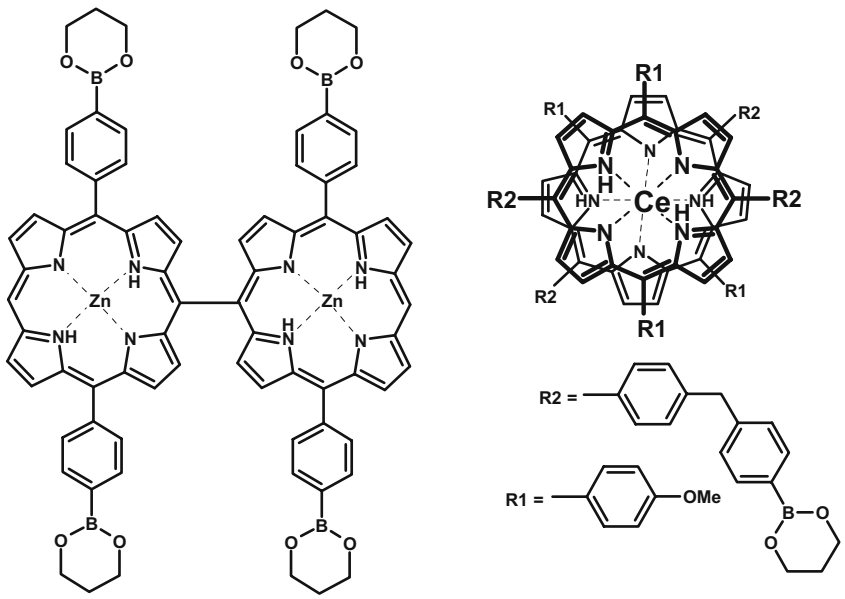

Fig. 4 Porphyrin dimer sensors [69, 70]

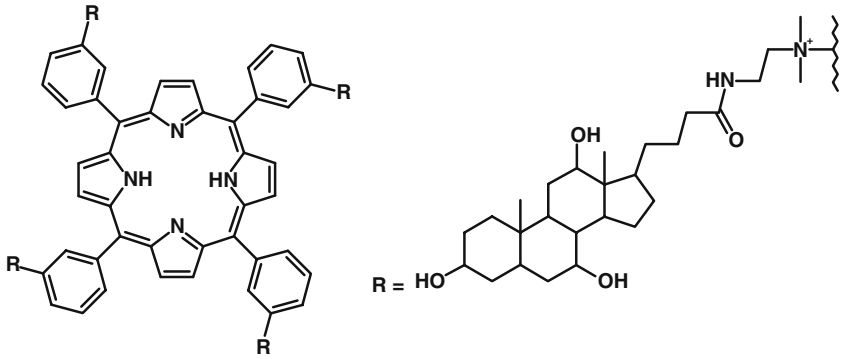

Fig. 5 Bile acid–porphyrin sensor [63]

way of their detection. A biosensor for cancer saccharide recognition can be represented by fluorescence-labeled monoclonal antibody directed against cancer saccharide receptors or by certain lectins with specificity for cancer saccharide markers [47].

A similar principle utilizing antibody or lectin conjugates [48] has been applied in various drug delivery systems for anticancer drugs. The development of lectin supramolecular complexes with metal porphyrins for targeted photodynamic therapy [49, 50], of lectin with galactose specificity, or of galactose–cyclodextrin for targeted transport of doxorubicin [51] represent other options for lectin-mediated drug delivery systems. Lectin/antibody carriers with suitable selectivity recognize and bind target cancer markers and thereby they provide a high level of slowly liberated anticancer agents in the cancer cells and a low level in normal cells. In addition, some lectins exhibit their anticancer effect by activation of cell death receptors [52].

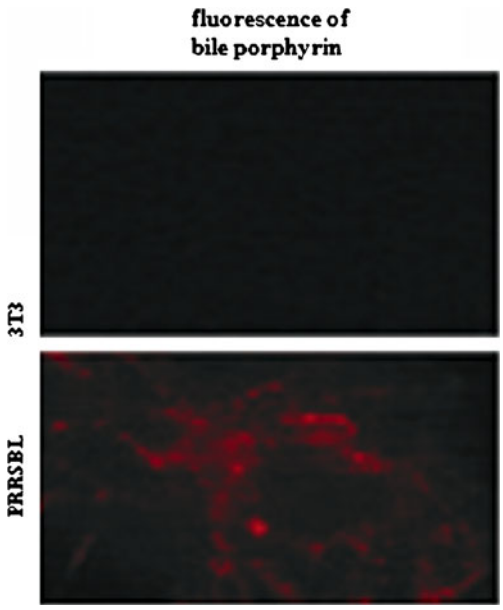

Fig. 6 Comparison of porphyrin affinity for normal 3T3 (murine embryo fibroblast) cells and transformed PRRSBL cells (murine sarcoma cell line)

Design of optical chemosensors is based on CH/π saccharide interaction [53]. Construction of these sensors can be based on smaller aromatic systems, a hydrophobic cavity, or metallocomplexes. Their function can be further improved by introduction of cationic charge and saccharide binding groups (e.g., boronic acid).

The ligands enabling cationic recognition are suitable for recognition of anionic polymers as are some saccharide cancer markers (glycosaminoglycans and polysialic acid). Good inspiration in this field might come from known sensors recognizing heparin (e.g., cyanine bases [54], cationic polymer [55]) for anionic saccharide polymers, mainly heparin (Fig. 1).

Some of those structural motifs such as cyanine bases have potential in anticancer treatment (photodynamic therapy and chemotherapy). For saccharide recognition, simple sensors based on boronic acid are usually applied [56] (Fig. 2). Recently, a colorimetric sensor with high selectivity for sialic acid was discovered.

The idea of a hydrophobic cavity was inspired by nature's design of lectins [57]. The hydrophobic cavity reduces the negative influence of water on the stability of the ligand–receptor complex. This phenomenon can be exploited to couple chemosensors with lectins [58]. It is based on reduction of the negative influence of water on the stability of the ligand–receptor complex. This goal can be achieved by coupling chemosensors with lectins. The idea of a hydrophobic cavity can be also applied to chemosensor design. These sensors use polyaromatic or better a heteroaromatic core as a signal and central unit (porphyrin

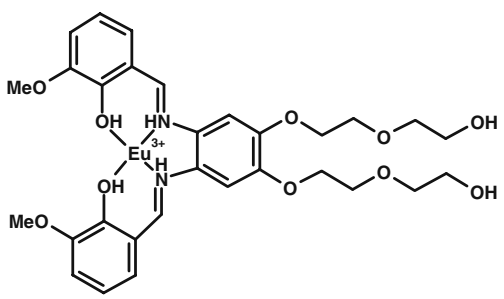

Fig. 7 Europium complex [72]

derivatives [59–65], cryptan system [66], and others) with substitution of hydrophilic and analyte binding groups (binaphthols [59] phosphonates [60] steroids [61], boronic acids [62] bile acid [63], PEG [64], cyclodextrin [64], and others). Similarly, Yang et al [67, 68]. prepared fluorescent diboronic acid probes for specific determination of cancer cells with overexpressed sialyl Le^x carbohydrate (Fig. 3).

They observed high selectivity for the target analyte and human hepatocellular carcinoma cells with overexpression of this marker as compared with modified cells without expression of the marker studied.

A metal–porphyrin dimer could be a possible sensor structural motif for Le^x and Le^a antigens [69, 70] (Fig. 4).

Promising results were also obtained in our laboratory by using bile acid–porphyrin conjugates [63] (Fig. 5). The conjugates showed high affinity for the cancer saccharide marker (heparin sulfate, hyaluronic acid, and sialic acid) and unique selectivity for transformed tumor cells (murine sarcoma, human colorectal adenocarcinoma, and chick embryo fibroblast sarcoma) in comparison with normal nontransformed cells (Fig. 6).

Such selectivity resulted in high photodynamic efficacy of this structural motif for cancer cells and very low photodynamic efficacy for normal cells.

The affinity of the saccharide motif for some fluorescent metal ions such as lanthanides [71] is a good basic point of sensor design. For example, Alpturk et al [72]. developed a europium complex for effective detection of a sialic acid cancer marker as GD1a (Fig. 7). This promising work showed the strong potential of this sensor type in cancer diagnosis.

In the branch of target transport, these ligands can be used for improving drug delivery selectivity as the recognition part of these systems, or as a conjugate with anticancer agents. For example, our study focusing on bile–porphyrin conjugates clearly showed high potential of targeted anticancer therapy based on cancer saccharide recognition [63]. In the field advanced drug delivery, Lee et al [7]. studied the influence of a conjugated specific chondroitin sulfate ligand on drug delivery selectivity for the human renal adenocarcinoma cell line and its anticancer effectiveness. They observed a significant improvement of the drug delivery property for cancer cells with overexpressed target marker and an inconsiderable change for cancer cells with a reduced marker level.

Conclusion

Knowledge of tumor saccharide pattern can be also exploited for the development of diagnostic methods and targeted anticancer systems. We presented in this review the use of glycomics, mainly optical biochemical and chemical sensors, for recognition of cancer saccharide markers. The examples discussed help to highlight the design principle of natural or synthetic selective ligands as optical sensors for cancer diagnosis. The sensors described clearly demonstrate the high potential of this approach for cancer diagnosis. This review also focused on the exploitation of cancer saccharide ligands as targeted anticancer therapy. Their in vivo and in vitro study demonstrated the strong potential of this approach in targeted anticancer treatment.

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