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Advances in glycosylation-mediated cancer-targeted drug delivery

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To enhance efficacy and safety, therapeutic antitumor agents are expected to target the desired locations where the ligand–receptor binding acts as a typical recognition approach. Among the various ligands, carbohydrates represent a crucial structure of tumor cell membranes and have been shown effective for cell-selective drug delivery. Recently, glycosylation-mediated therapeutic targeting strategies have been increasingly developed to form a variety of nanoscale delivery carriers. In this review, a variety of glycosylated drug delivery systems and their applications for cancer therapy have been surveyed. The future perspectives, including opportunities and challenges in this field, are also discussed.

Introduction

Q2 Numerous drug delivery systems (DDSs) have been developed to improve the therapeutic efficacy of cancer treatments, but it can be challenging to satisfy clinical requirements in most cases [1,2]. Limited delivery efficacy to the targeted sites is one of the main problems. To this end, many approaches have been investigated to improve DDSs with enhanced safety, stability and efficiency [3,4]. One promising strategy is to actively target the specific objectives and moieties at the desired locations [3]. Among distinct targeting methods, many efforts have been directed at the glycosylation-mediated strategy [5–7]. Glycan structures have been incorporated into various nanocarriers to achieve tumor-targeting abilities [8] due to aberrant glycosylation in tumors and the tumor-associated microenvironment [9]. As shown in Fig. 1, differing from normal cellular glycosylation, tumor cells often display high expression levels of overall sialylation, truncated glycans, *N*-linked glycans and glycosphingolipids during this process [10,11]. The aberrant glycosylation associated with tumors often includes an increase in overall sialylation. Meanwhile, the abnormal expression of truncated glycans in the malignancy is attributed to the incomplete synthesis of *O*-glycans [12]. *N*-linked glycans occur in the consensus Q3 peptide sequences Asn-X-Ser/Thr. The aberrant expression of *N*-linked glycans on the tumor cell surface highly influences tumorigenesis and metastasis [13]. In addition, glycosphingolipids, the carrier of one or several sialic acids, could regulate receptor tyrosine kinase (RTK) signaling. Aberrant expression of glycosphingolipid markers has also been defined in tumor cells [14]. Therefore, the mentioned aberrant tumor glycosylation can be used to design glycosylation-mediated tumor-targeted DDSs. The design should take into account different regulatory checkpoints of the glycosylation machinery without affecting material properties inherent to them. Taking advantage of these glycosylation approaches, various glycosylated DDSs have emerged as useful diagnostic, prognostic and targeting strategies for malignant tissues and thus provide novel therapeutic opportunities for cancer treatments [15,16].

The existence of diverse glycosylation sites in materials leads to different regulation of the intracellular segregation, localization and turnover of glycoprotein receptors, which have significant roles in cellular recognition, communication and signaling [17].

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1359-6446/
https://doi.org/10.1016/j.drudis.2018.02.009

Please cite this article in press as: Cai, L. et al. Advances in glycosylation-mediated cancer-targeted drug delivery, Drug Discov Today (2018), https://doi.org/10.1016/j.drudis.2018.02.009

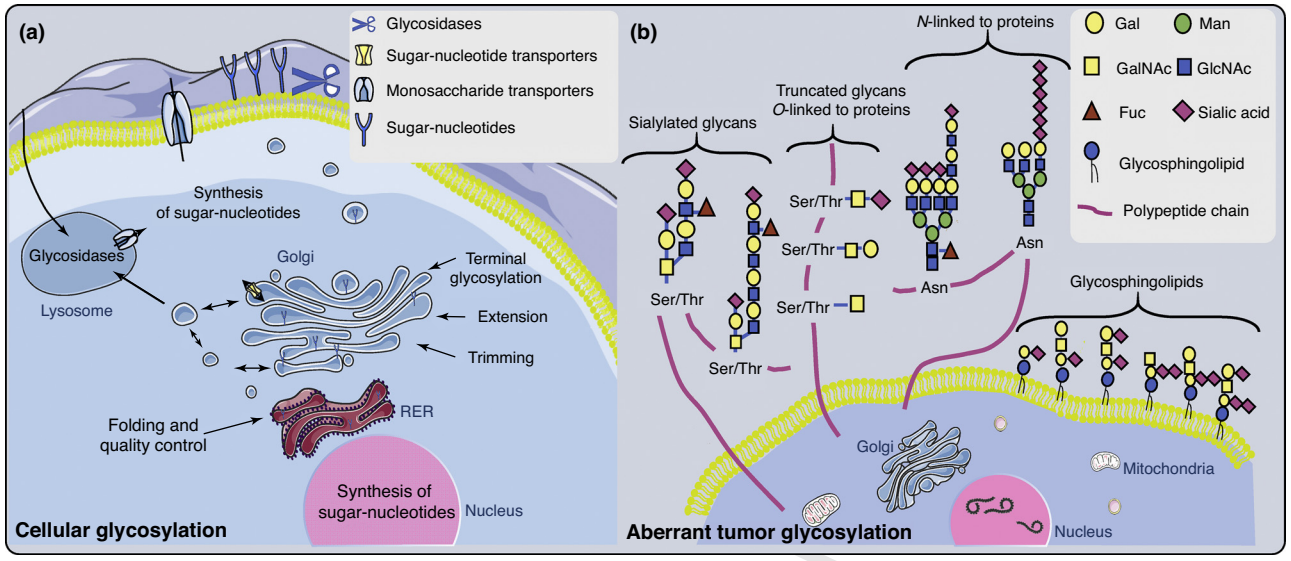

FIGURE 1

Schematic of **(a)** cellular glycosylation and **(b)** aberrant tumor glycosylation. Differing from normal cellular glycosylation, tumor cells often display high expression levels of overall sialylation, truncated glycans, *N*-linked glycans and glycosphingolipid. Gal, galactose; Man, mannose; GalNAc, *N*-Acetyl-D-galactosamine; GlcNAc, *N*-acetylglucosamine; Fuc, fucose.

Furthermore, the glycoside effect with enhanced binding capacities is often achieved by the use of multiple interactions by multivalent carbohydrates [18]. Therefore, various glycosylated materials have been widely employed in anticancer drug development because the therapeutic targets of glycosylation in tumor cells or the tumor-associated microenvironment have been well verified [19–23]. However, only a few efforts have been made to integrate and assess the rapidly amassing knowledge on glycosylated structures into a broader context of targeting chemistry [12,24,25]. Hence, this review aims to translate the emerging knowledge of glycosylation strategies into a common set of structure-targeting relationships based on amounts of experimental results and theoretical backgrounds.

The receptors for glycosylation

As reported in previous studies [26], reversible interactions between carbohydrates and protein receptors have been widely involved in many biological and pathological processes, ranging from cellular communication to bacterial invasion to tumor metastasis. Many pieces of evidence indicate that endogenous lectins and galectins are the main recognition molecules responsible for translating the glycan-containing information into a broad spectrum of cellular responses [27,28]. It is well-documented that carbohydrates participate in numerous fundamental biological processes of cancer development, such as cell–cell adhesion in the process of tumor cell dissociation and invasion associated with tumor angiogenesis, growth, progression and metastasis (Fig. 2) [10,29,30]. To date, several families of lectins, galectins and some nonspecific receptors have been investigated for cancer therapy.

Lectin receptors for glycosylation

Almost all kinds of cells express membrane lectins, serving as targets for different carbohydrates. These membrane lectins could agglutinate relevant cells and/or precipitate specific glycoconjugates, whereas certain other lectins could recognize galactose residues expressed on the surface of mammalian liver cells. The pivotal effects of lectins on the immune system are also widely studied [31]. For instance, mannose-binding lectin (MBL) can liaise with the first line of the host defense against several microorganisms in the immune system [32]. Furthermore, other lectins are probably involved in nonself- and self-discrimination and modulate autoreactive and inflammatory processes. Intelectins, a type of soluble galactofuranose-binding lectin, were also shown to bind microbial glycans and can affect the innate immune system as well [33].

Lectin–carbohydrate interactions have been proven to play many key parts in various biological processes of the human body [34]. Because lectin–carbohydrate interactions are characteristically weak, presenting multivalent ligands, such as glycans that are Toll-like receptors (TLRs), ligands that are important for dendritic cell (DC) targeting and activation have been leveraged to enhance binding affinity [35–37]. For instance, a structurally homologous carbohydrate-recognition domain (CRD) was applied to improve the binding capacity of C-type lectin receptors (CLRs) to glycan structures through a Ca^{2+}-dependent manner [38]. Lectin receptors also indicate the importance in mediating the endocytosis of bound ligands in liver. The major strategy so far has been focused on the asialoglycoprotein receptor (ASGPR), a type II transmembrane protein highly expressed on the surface of liver cells that regulates the homeostasis of serum glycoprotein levels by binding and uptaking glycoproteins [39,40]. Therefore, hepatocyte-specific targeting and imaging could be achieved by various carbohydrate-functionalized materials, such as galactosylated *N*-2-hydroxypropyl methacrylamide-b-*N*-3-guanidinopropyl methacrylamide [41], galactosylated poly(ethylene glycol)-chitosan-graft-polyethylenimines [42], as well as some other polymeric

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