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Review

Disease-associated glycans on cell surface proteins

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ABSTRACT

Most of membrane molecules including cell surface receptors and secreted proteins including ligands are glycoproteins and glycolipids. Therefore, identifying the functional significance of glycans is crucial for developing an understanding of cell signaling and subsequent physiological and pathological cellular events. In particular, the function of *N*-glycans associated with cell surface receptors has been extensively studied since they are directly involved in controlling cellular functions. In this review, we focus on the roles of glycosyltransferases that are involved in the modification of *N*-glycans and their target proteins such as epidermal growth factor receptor (EGFR), ErbB3, transforming growth factor β (TGF-β) receptor, T-cell receptors (TCR), β-site APP cleaving enzyme (BACE1), glucose transporter 2 (GLUT2), E-cadherin, and α5β1 integrin in relation to diseases and epithelial–mesenchymal transition (EMT) process. Above of those proteins are subjected to being modified by several glycosyltransferases such as *N*-acetylglucosaminyltransferase III (GnT-III), *N*-acetylglucosaminyltransferase IV (GnT-IV), *N*-acetylglucosaminyltransferase V (GnT-V), α2,6 sialyltransferase 1 (ST6GAL1), and α1,6 fucosyltransferase (Fut8), which are typical *N*-glycan branching enzymes and play pivotal roles in regulating the function of cell surface receptors in pathological cell signaling.

Contents

Abbreviations: BACE1, β-site APP cleaving enzyme, β-secretase; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; Fut8, α1,6 fucosyltransferase; GlcNAc, *N*-acetylglucosamine; GLUT2, glucose transporter 2; GM3, NeuAcα3Galβ4Glcβ1Cer; GnT-III, *N*-acetylglucosaminyltransferase III; GnT-IV, *N*-acetylglucosaminyltransferase IV; GnT-V, *N*-acetylglucosaminyltransferase V; MMP, matrix metalloproteinase; PI3K, phosphoinositide 3-kinase; sEGFR, soluble EGFR; sErbB3, soluble ErbB3; SP-D, surfactant protein D; ST6GAL1, α2,6 sialyltransferase 1; TβRI, transforming growth factor β receptor type I; TβRII, transforming growth factor β receptor type II; TCR, T cell receptors; TGF-β, transforming growth factor β.

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1. Introduction

In eukaryotes, more than 50% of the proteins are glycosylated and there is no doubt that glycosylation is the most abundant post-translational modifications of proteins (Apweiler et al., 1999). Due to the technical difficulties associated with glycoscience research as compared to those of DNA/RNA and proteins, some of the detailed research on glycans in proteins has been disregarded. However, recent advances in glycome studies using mass spectrometry, lectin arrays, and glycosyltransferase gene technology etc., now make it possible for us to characterize glycan structures in relation to their function. Glycans control various kinds of physicochemical properties of proteins such as conformation, flexibility, charge, and hydrophilicity. Investigations of receptor glycans are essential for understanding the cell signaling that occur under pathophysiological conditions (Dube and Bertozzi, 2005; Dwek, 1995; Haltiwanger and Lowe, 2004; Imperiali and O'Connor, 1999; Lau and Dennis, 2008; Ohtsubo and Marth, 2006; Saxon and Bertozzi, 2001; Taniguchi, 2007; Varki, 1993; Zhao et al., 2008). The functional roles of glycans in glycoproteins can be classified into two types: regulation of protein conformations by specific glycan(s), and the regulation of molecular interactions depending on the glycan structure, which are determined by the balance of the activities of glycosyltransferases and glycosidases. There are two types of molecular interactions in which glycans are involved such as protein–carbohydrate interactions and carbohydrate–carbohydrate interactions. For the protein–carbohydrate interactions, lectins or antibodies, and for the carbohydrate-carbohydrate interactions, glycolipids act as carbohydrate recognition molecules, and for both cases, the glycan structure determines the specificity or the interaction. By manipulating the glycosyltransferase genes, it is possible to examine the function of a particular structure of glycans. Moreover, by identifying the target proteins on which glycans are carried, it is possible to characterize the function of the specific glycan(s) on a specific glycoprotein. "Functional glycomics", which aim for a comprehensive understanding of the function of each glycan structure, are a powerful approach for elucidating the true *in vivo* function of a glycan.

In this review, we focus on several cell surface receptors including epidermal growth factor receptor (EGFR), ErbB3, transforming growth factor β (TGF-β) receptor, T-cell receptors (TCR), β-site APP cleaving enzyme (BACE1), glucose transporter 2 (GLUT2), E-cadherin, and α5β1 integrin, and the roles of glycosyltransferases such as *N*-acetylglucosaminyltransferase IIII (GnT-III, MGAT3; EC 2.4.1.144), *N*-acetylglucosaminyltransferase IV (GnT-IV, MGAT4; EC 2.4.1.145), *N*-acetylglucosaminyltransferase V (GnT-V, MGAT5; EC 2.4.1.155), and α1,6 fucosyltransferase (Fut8; EC 2.4.1.68). GnT-III catalyzes the transfer of

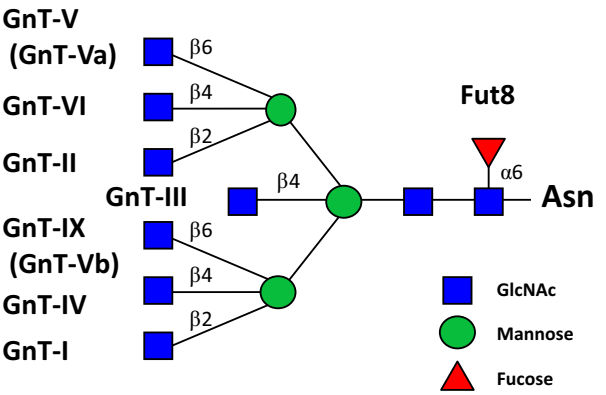

Fig. 1. The activities of GnT-III, GnT-IV, GnT-V, and Fut8.

N-acetylglucosamine (GlcNAc) to the mannose residue at the base of the core structure of *N*-linked oligosaccharides ($Man_3GlcNAc_2$-Asn), to produce a "bisecting GlcNAc" (Ihara et al., 1993; Nishikawa et al., 1992). GnT-IV catalyzes the transfer of GlcNAc to the GlcNAcβ1-2Manα1,3 arm of the *N*-glycan core via a β1-4 linkage (Oguri et al., 1997). GnT-V catalyzes the transfer of GlcNAc to the GlcNAcβ1-2Manα1,3 arm of the *N*-glycan core via a β1-6 linkage (Togayachi et al., 2010). Poly-*N*-acetyllactosamine glycans are extended through the initial action of GnT-V. Fut8 catalyzes the addition of a fucose to the innermost GlcNAc residue of a *N*-glycan, to produce α1,6-fucose, or "core fucose" (Uozumi et al., 1996; Yanagidani et al., 1997). All these glycosyltransferases directly modify the *N*-glycan core (Fig. 1). Thus, we introduce examples of the disease-associated functional regulation of cell surface proteins by *N*-glycans and its involvement of glycosyltransferases.

2. *N*-Glycans of ErbB receptors and receptor functions

The ErbB receptors are type I transmembrane receptor tyrosine kinases and are involved in a variety of cellular events such as proliferation, differentiation, and migration, and the aberrant expression of these receptors has been implicated in the initiation and maintenance of various types of cancer. Therefore, ErbB receptors are considered to be the targets for cancer therapy (Arteaga and Engelman, 2014; Kovacs et al., 2015; Sharma et al., 2007; Yarden and Sliwkowski, 2001; Zhang et al., 2007).

Among the four members of the ErbB family, which include EGFR (ErbB1/HER1), ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4, EGFR is the most studied. EGFR is a 170 kDa protein which consists of 1186 amino acid residues. By binding to a ligand, EGFR forms a homodimer or a heterodimer with ErbB2, ErbB3, and ErbB4, and is