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Review

Pathobiological implications of mucin glycans in cancer: Sweet poison and novel targets

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ABSTRACT

Mucins are large glycoproteins expressed on the epithelia that provide a protective barrier against harsh insults from toxins and pathogenic microbes. These glycoproteins are classified primarily as being secreted and membrane-bound; both forms are involved in pathophysiological functions including inflammation and cancer. The high molecular weight of mucins is attributed to their large polypeptide backbone that is extensively covered by glycan moieties that modulate the function of mucins and, hence, play an important role in physiological functions. Deregulation of glycosylation machinery during malignant transformation results in altered mucin glycosylation. This review describes the functional implications and pathobiological significance of altered mucin glycosylation in cancer. Further, this review delineates various factors such as glycosyltransferases and tumor microenvironment that contribute to dysregulation of mucin glycosylation during cancer. Finally, this review discusses the scope of mucin glycan epitopes as potential diagnostic and therapeutic targets.

Contents

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1. Introduction

Mucins are a family of glycosylated proteins with high molecular weight and complex molecular organization. So far, 21 mucin genes have been identified. Based on their structural organization, mucins are mainly classified as secreted and membrane-bound forms [1,2]. Both of these mucin classes are involved in epithelial cell homeostasis where they act as a protective shield against severe environmental insults from toxins and pathogenic microbes [3]. MUC2, MUC5AC, MUC5B, MUC6, MUC7, and MUC19 are secreted mucins, which lack transmembrane domains and have a common von Willebrand factor D domain (vWF-D) and C terminus cysteine knot domain that are required for their oligomerization [4]. The other important class of mucins is the transmembrane mucins, which include MUC1, MUC3, MUC4, MUC12, MUC16, and MUC17. These transmembrane mucins are anchored to the cell surface via their transmembrane domains and are involved in various signaling pathways through their short cytoplasmic tails [5].

The structural complexity of these secreted and transmembrane glycoproteins is due to their large polypeptide chain and various post-translational modifications such as glycosylation, sulfation, and phosphorylation [6–8]. Glycosylation is one of the major post-translational modifications that defines these mucins and affects their function. Mucins can be either *O*-glycosylated or *N*-glycosylated. Both forms of glycosylation occur in distinct subcellular compartments. They differ by the amino acid involved and the covalent attachment of carbohydrates [9]. *N*-glycosylation of mucins is initiated in the endoplasmic reticulum (ER) by the action of UDP-GlcNAc phosphotransferases, whereas mucin type *O*-glycosylation occurs in the Golgi apparatus and is mediated by a family of enzymes known as UDP-GalNAc:polypeptide GalNAc-transferases (GalNAc-Ts/GALNTs) [10,11]. Notably, *O*-glycosylation is the major post-translational modification of mucins. It occurs predominantly in the central tandem repeat domain, which is common to all mucins and rich in proline, serine, and threonine (PTS) residues [12].

Carbohydrate structures located on mucin polypeptides dictate their biochemical and biophysical characteristics. These structures also determine the biological functions of mucins. For instance, mucin glycans act as a steric barrier that prevents microorganisms from attacking the underlying epithelium [6,13]. Indeed, some of the glycan structures are also involved in mediating cellular interactions like those with leukocytes [14]. Importantly, this review discusses the pathobiological significance of altered mucin glycosylation in cancer and focuses on the functional implications of oligosaccharide structures displayed by mucins during cancer progression. It also discusses regulation of mucin glycosylation by several factors such as glycosyltransferases and the tumor microenvironment. Finally, the potential involvement of these mucin-associated glycans in diagnostics and therapeutics is discussed.

2. Mucin glycosylation

Glycosylation is the principal post-translational modification and hallmark of mucins. Mucins undergo both *O*- and *N*-linked glycosylation, depending on the amino acid on which glycans are added. In the case of *N*-glycosylation, carbohydrate chains are attached to the amidic nitrogen of asparagine, whereas *O*-glycosylation is defined by the addition of carbohydrate chains to the hydroxyl group of serine or threonine [15,16]. Both forms of glycosylation occur in distinct cellular compartments and contribute to the biochemical, biophysical, and functional properties of mucins [9].

2.1. N-linked glycosylation

Protein *N*-glycosylation is initiated by the transfer of *N*-acetyl glucosamine phosphate (GlcNAc-P) to the polyisoprenol lipid precursor, dolichol phosphate (Dol-P), which results in the formation of dolichol pyrophosphate *N*-acetyl glucosamine (Dol-P-P-GlcNAc) (Fig. 1). This occurs on the cytoplasmic face of the ER and is mediated by the action of UDP-*N*-acetylglucosamine-dolichyl-phosphate *N*-acetylglucosaminephosphotransferase (DAPGT1/GPT). Following this event, another molecule of *N*-acetyl glucosamine (GlcNAc) and five mannose (Man) residues are transferred sequentially by specific glycosyltransferases to generate $Man_5GlcNAc_2$-P-P-Dol. Subsequently, the dolichol-linked glycan precursor translocates to the ER lumen by the action of the enzyme flippase. Further, the transfer of four mannose and three glucose (Glc) glycans from Dol-P-Man and Dol-P-Glc, respectively, completes the synthesis of the *N*-glycan precursor $Glc_3Man_9GlcNAc_2$-P-P-Dol. This structure is then transferred *en bloc* by oligosaccharyl transferase (OST) to the asparagine residue in one of the prominent *N*-glycosylation sites of the nascent protein (Asp-X-Ser/Thr) [15]. A series of enzymatic reactions inside the ER trim this 14 sugar *N*-glycan structure, following which the nascent glycoprotein is transported to the Golgi apparatus by COPII-coated vesicles [17,18]. In *cis* Golgi, further processing involves the removal of mannose residues by means of mannosidases. The processed protein is then transferred to the medial Golgi, where oligomannose (containing high mannose), complex-type (comprising several saccharides including *N*-acetylglucosamine) and hybrid *N*-glycans (mixture of oligomannose and complex *N*-glycans) are synthesized. In Trans Golgi, complex and hybrid *N*-glycan structures are further elongated by the addition of several repeats of *N*-acetyllactosamine (LacNAc-3Galβ1-4GlcNAcβ1). Finally, these elongated structures are capped by the addition of residues like sialic acid, *N*-acetylglucosamine, and fucose [11].

The number of *N*-glycosylation sites varies among mucin family members. For example, MUC1 has five potential *N*-glycosylation sites, whereas MUC4 has more than 10 putative *N*-glycosylation sites [19,20]. *N*-glycosylation sites in different mucins contribute to protein stability, folding, and trafficking. For example, in the secreted mucin