東北医科薬科大学

審査学位論文（博士）要旨

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OGT Regulates β1,4-GlcNAc-branched *N*-glycan Biosynthesis Via the OGT/SLC35A3/GnT-IV Axis

(OGT は OGT/SLC35A3/GnT-IV 軸を介して β1,4-GlcNAc 分岐型 N-グリカンの生合成を制御する)

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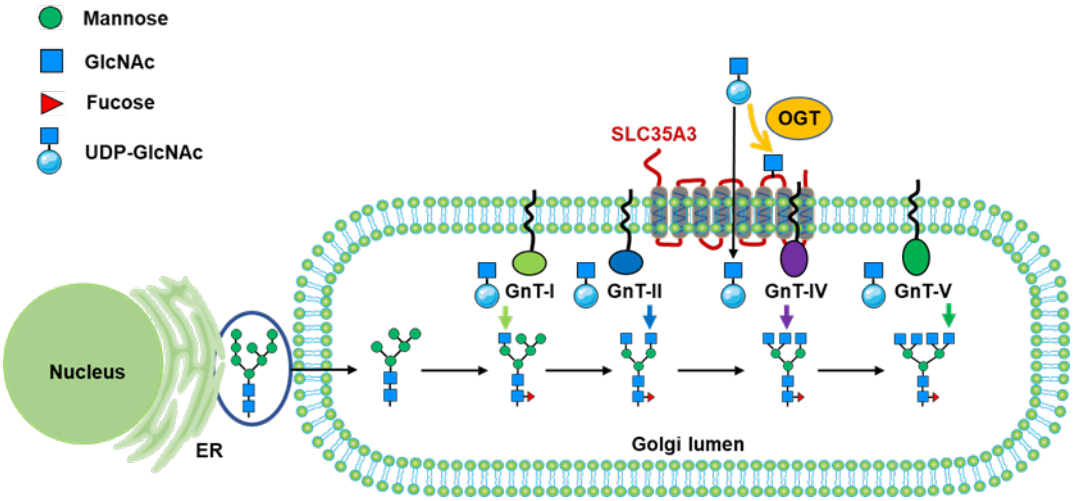
Amongst multiple post-translational modifications (PTMs), protein glycosylation is a common and important process in cells, and altered glycosylation is a hallmark of many diseases including cancers and diabetes. *N*-Linked glycosylation and *O*-linked *N*-acetylglucosamine (*O*-GlcNAc) are important protein PTMs. One of unique features of *N*-glycans is the GlcNAc-branched complex structure that is sequentially synthesized first by *N*-acetylglucosaminyltransferase I (GnT-I) and GnT-II, and then by GnT-III, GnT-IV, or GnT-V to produce functionally diverse *N*-glycosylated proteins. But *O*-GlcNAcylation is a simple protein PTM, where a single moiety of GlcNAc acts on the serine or threonine residue of target proteins without further elongation or modification into more complex structures. Thus far, the relationship between these two types of glycosylation has remained elusive, and it is unclear whether one influences the other via UDP-GlcNAc, which is a common donor substrate. Theoretically, a decrease in *O*-GlcNAcylation may increase the products of GlcNAc-branched *N*-glycans. In this study, we found that the amounts of GlcNAc-branched tri-antennary *N*-glycans catalyzed by *N*-acetylglucosaminyltransferase IV (GnT-IV) and tetra-antennary *N*-glycans were significantly decreased in *O*-GlcNAc transferase knockdown cells (OGT-KD) compared with those in wild type cells. We examined this specific alteration by focusing on SLC35A3, which is a main UDP-GlcNAc transporter in mammals that is believed to modulate GnT-IV activation. It is interesting that a deficiency of SLC35A3 specifically leads to a decrease in the amounts of GlcNAc-branched tri- and tetra-antennary *N*-glycans. Furthermore, we found that SLC35A3 interacts with GnT-IV,

but not with *N*-acetylglucosaminyltransferase V (GnT-V) as shown in following figure. And our experiments have confirmed that OGT modifies SLC35A3 and that *O*-GlcNAcylation contributes to its stability. Furthermore, we found that SLC35A3-KO enhances cell spreading and suppresses both cell migration and cell proliferation, which are similar to the phenomena observed in the OGT-KD cells. Taken together, these data are the first to demonstrate that *O*-GlcNAcylation specifically governs the biosynthesis of tri- and tetra-antennary N-glycans via the OGT-SLC35A3-GnT-IV axis.



Schematic diagram of the proposed molecular mechanism for regulation of the biosynthesis of β1,4-GlcNAc-branched *N*-glycans by OGT.

Reference

Song, W, Isaji, T, Nakano, M, Liang, C, Fukuda, T, Gu, J. O-GlcNAcylation regulates β1,4-GlcNAc-branched N-glycan biosynthesis via the OGT/SLC35A3/GnT-IV axis. FASEB J. 2022; 36:e22149. doi:*10.1096/fj.202101520R*