Chemical and chemo-enzymatic synthesis of tandem ribitol phosphate scaffolding of matriglycan

Jun-ichi TAMURA [1], Takahiro TAMURA [1], Shunsuke HOSHINO [2], Rieko IMAE [2], Ryuichi KATO [3], Mizuki YOKONO [1], Mao NAGASE [4], Shiho OHNO [4], Noriyoshi MANABE [4], Yoshiki YAMAGUCHI [4], Hiroshi MANYA [2], Tamao ENDO [2]

[1] Tottori University, Tottori, Japan, [2] Tokyo Metropolitan Institute for Geriatrics and Gerontology, Tokyo, Japan, [3] High Energy Accelerator Research Organization, Tsukuba, Japan, [4] Tohoku Medical and Pharmaceutical University, Sendai, Japan

jtamura@tottori-u.ac.jp

The glycosylation of proteins is an important post-translational modification. The core M3 *O*-mannosyl glycan (OMG) of α-dystroglycan was recently shown to play an important role in muscle and brain development. The complete structure of core M3 OMG was elucidated in 2016 [1,2]. The core M3 OMG is responsible for the link between the extracellular matrix and cytoskeleton that stabilizes muscle tissue. However, the underlying molecular mechanisms remain unclear because a sufficient amount of core M3 OMG cannot be purified from natural sources. To overcome this issue, sequentially extended partial structures of the core M3 OMG including a tandem ribitol phosphate (**1**~**6**) were synthesized (Figure 1). Rbo5P-3GalNAcβ with *p*-nitrophenyl at the aglycon (**2**) served as a substrate for ribitol phosphate transferase (FKRP, fukutin-related protein), and its product was glycosylated by the actions of a series of glycosyltransferases, namely, ribitol xylosyltransferase 1 (RXYLT1), β1,4-glucuronyltransferase 1 (B4GAT1), and like-acetyl-glucosaminyltransferase (LARGE). Rbo5P-3GalNAcβ equipped with an alkyne-type aglycon was also active for FKRP. The molecular information obtained on FKRP suggests that Rbo5P-3GalNAcβ derivatives are the minimal units required as the acceptor glycan for Rbo5P transfer and may serve as a precursor for the elongation of the core M3 OMG We propose the therapeutic potential of adopting versatile Rbo5P-3GalNAcβ units as glycan bridges bound to α-dystroglycan for patients with α-dystroglycanopathies, including Fukuyama congenital muscular dystrophy.

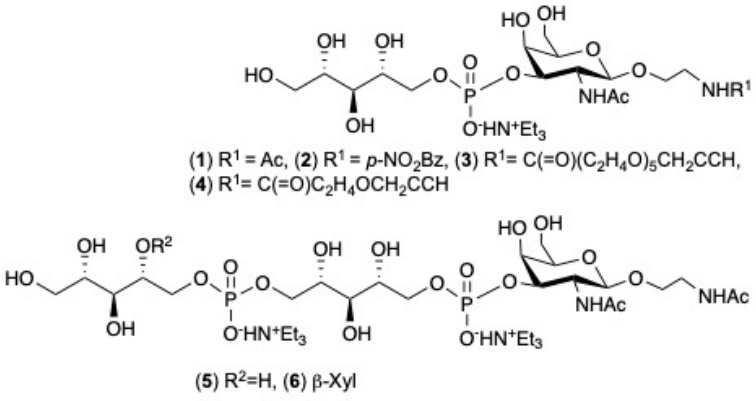

Figure 1

Bibliographic references:
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[2] H. Manya and T. Endo (2017), Biochim. Biophys. Acta Gen. Subj. (1861) 2462-2472.
[3] J. Tamura et al. (2022) ACS Chem. Biol. (17) 1513-1523.