Synthesis of Alkyne-tagged Ribitol-5-phosphate as Metabolic Labelling Tools

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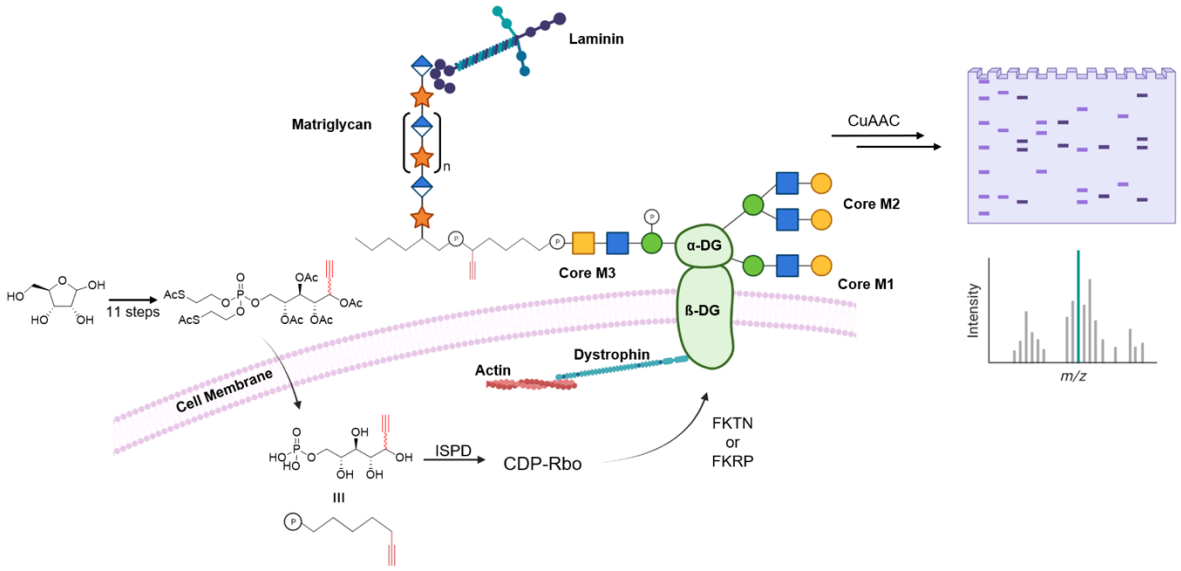
α-Dystrogylcan (α-DG) is a cell surface protein present on the cell membrane in peripheral nerve, skeletal muscle, and brain tissues. α-DG is heavily glycosylated and one of its glycans (core M3) is essential for interactions between the cell and laminins in the extracellular matrix.[1]Failures in the regular biosynthesis of this glycan result in a range of congenital muscular dystrophies, sub categorised as α-dystroglycanopathies.[2]

In 2016, two groups independently elucidated the structure of a linker region consisting of a tandem ribitol-5-phosphate (Rbo5P) responsible for maintaining the extracellular interactions. This was first, and to date only, discovery of Rbo5P in mammalian tissue.[3,4]

This makes Rbo5P a unique target to label α-DG. We therefore aim to build a library of ribitol and Rbo5P derived metabolic labelling tools.

The work presented herein, describes the development of a challenging synthesis towards a range of alkyne-tagged ribitol and Rbo5P derivatives. We employ these derivatives in mammalian cells and use bioorthogonal reactions with azide containing fluorophores or biotin to analyse the glycoprotein. These tools also enable us to potentially identify new Rbo5P containing glycoproteins.

We also report the development of a new methodology for the installation of a cell liable protected phosphotriester without the use of hazardous phosphoramidate intermediates.



Incorporation of an alkyne-Rbo5P probe into α-dystroglycan

Bibliographic references:

1. M. Kanawaga, T. Toda (2017), J. Neuromuscul. Dis. (4) 259-267.
2. T. Endo (2015), J. Biochem. (268) 1-12.
3. I. Gerin, et al., (2016) Nat. Comm., 11534.
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