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The potential role of β-glycosphingolipids in the immune system: Novel secondary messengers

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Oral Immune therapy is an approach to treat autoimmune, infectious, malignant and inflammatory diseases. It is an active process that uses the inherent ability of the GI tract's immune system to control unwanted systemic immune responses by inducing regulatory T cells in an antigen-specific manner. Dendritic cells and Natural Killer T cells play an important role in this interaction. Glycosphingolipids were shown as secondary messengers of the immune system affecting the dendritic cells-natural killer cells interplay thereby underlying the interaction between the innate and the adaptive immune systems and promoting oral immune therapy. Glycosphingolipids were also shown as potent adjuvant in the gut. Preclinical studies supports the role of glycosphingolipids in alleviating immune-mediated colitis, autoimmune hepatitis, type 2 diabetes and fatty liver disease. In addition, they were shown to promote the anti-tumor immunity in animal models of primary liver cancer. Recent clinical trials support a similar effect in humans with immune-meidated disorders. Patients with Gaucher disease, who have elevated levels of glucocerebroside in their serum, were shown to have altered immune response and to have an evolutionary advantage, further supporting the immune modulatory role of the sphingolipids. In summary, balance between various glycosphingolipids is important for immune homeostasis. Gaucher, administration of β-glycosphingolipids, compounds that alter enzymes that increase or decrease sphingolipids levels, skew the immune balance. The effect of β-glycosphingolipids may be associated with promotion of the DC-NKT interaction, Tregs and or via alteration of lipid rafts and intracellular signaling. β-glycosphingolipids can serve as potent adjuvants/immune modulators for immune therapy.

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Chemical assembly of N-glycans by use of modular building blocks

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N-glycans play important roles in biological events such as cell adhesion, cell differentiation, pathogen infection and immune response. Due to the micro-heterogeneity and low abundance of N-glycans on glycoproteins, there are only few N-glycans can be isolated from natural resources. As a result, synthesis particularly chemo-enzymatic synthesis has become an indispensable tool to get access to these compounds. We developed a highly efficient strategy based on the use of oligosaccharylthioether for the convergent installation of branched GlcNAc-terminated antennae to achieve high stereo selectivity with excellent yields. This new approach minimizes synthetic steps and maximizes yield which proceeded very efficiently with less glycosyl donor (1.3 equivalents) and mild conditions (at 0o C). This strategy would allow us to prepare a series of N-glycans with various glycoforms for enzymatic extension.

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