Efficient synthetic methodology for pseudo-glycans with C-glycoside linkage and their biological pot

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Our research group has been developing glycoconjugate analogs with the aim of contributing to glycobiology and drug discovery research. Our interest is to develop glycoconjugate analogues (pseudo-glycoconjugates or pseudo-glycans) with enhanced or different biological functions, while preserving their structures as much as possible. In this talk we will present the development of pseudo-glycans with a C-glycosidic linkage that are not degraded by glycoside hydrolases in cells.

Most carbohydrates exist as glycans or glycoconjugates and regulate biological events by interacting with various biomolecules in cells. However, the exact function of carbohydrates remains poorly understood and their biological potency is usually moderate. These drawbacks are partly attributed to the hydrolytic cleavage of carbohydrate or glycoconjugate structures by enzymes in cells. The C-glycoside analogues of native O-glycosides are expected to be useful molecular tools as glycoside hydrolase-resistant carbohydrate analogues. We have previously developed the sialidase-resistant ganglioside GM3 analogues with C-sialoside linkage.[1)] In this case, the simple replacement of an O-sialoside linkage with a CH_2-linkage proved to be non-ideal, and we proposed the introduction of a fluorine atom into the C-sialoside linkage, namely CHF-glycoside analogues. In fact, the (*S*)-CHF-linked GM3 analogue has shown the potent biological activity compared to native, CH_2-linked, CF_2-linked, or (*R*)-CHF-linked analogues. Therefore, we are currently investigating the application of this molecular design concept to other glycans and glycoconjugates.

Although various synthetic methods of C-glycosides have been reported, reports on the synthesis of glycan or glycoconjugate analogues with the C-glycoside linkage are still limited due to the complexity of their synthesis. We believe that, as with standard O-glycosylation, a C-glycosylation reaction capable of directly linking stable donor and acceptor building blocks (direct C-glycosylation) would facilitate the preparation of a variety of glycoconjugate analogs that would be useful in biological studies. In this context, we have recently established an efficient method to stereoselectively obtain C-glycoside analogues by controlling anomeric radical species generated by a photoredox catalytic system.[2,3)] In this talk, we will present the detail of this methodologies, their application to the synthesis of glycan or glycolipid analogues with the CH_2- or CHF-glycoside linkage, and their biological activities.

Bibliographic references:

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3) Takahiro Moriyama, Makoto Yoritate, Go Hirai et al. To be submitted.