Principal Investigator: Yoshiki Yamaguchi
Grant Title: Study on structural dynamics and interaction of branched *N*-glycans
Abstract

Glycans normally exist as a dynamic equilibrium of several conformations. A fundamental question concerns how such molecules bind lectins despite disadvantageous entropic loss upon binding. Bisected glycan, a glycan possessing bisecting *N*-acetylglucosamine (GlcNAc), is potentially a good model for investigating conformational dynamics and glycan-lectin interactions, owing to the unique ability of this sugar residue to alter conformer populations and thus modulate the biological activities. Here we analyzed bisected glycan in complex with two unrelated lectins, Calsepa and PHA-E. The crystal structures of the two complexes show a conspicuous flipped back glycan structure (designated 'back-fold' conformation), and solution NMR analysis also provides evidence of 'back-fold' glycan structure. Indeed, statistical conformational analysis of available bisected and non-bisected glycan structures suggests that bisecting GlcNAc restricts the conformations of branched structures. Restriction of glycan flexibility by certain sugar residues may be more common than previously thought and impinges on the mechanism of glycoform-dependent biological functions.

Now we extend our study toward other lectins including mannose-type Jacalin-related lectins (mJRLs). Although mJRLs share a common β-prism fold with a small mannose-binding pocket, each mJRL shows its own binding specificity toward various branched *N*-glycans. We are currently investigating the structural basis how each mJRL gains unique specificity for branched *N*-glycans. Experimental and theoretical studies are in progress through X-ray crystallography, MD simulations and binding affinity estimation.

glycan 1

glycan 2

Calsepa-glycan 1 complex

PHA-E-glycan 2 complex

In general glycan-protein interaction proceeds under the marginal balance of enthalpy gain and entropy loss. We have experienced the difficulty in interpreting the entropy term in the glycan-protein interactions. Recently we observed the "non-epitopic" carbohydrate region which significantly contribute to the affinity but are not directly involved in the interaction with protein. At this moment we cannot interpret such phenomena from our current knowledge. We do continue to expand our knowledge on glycan-protein interaction and will develop a method to predict binding affinity of glycan-protein interaction in the near future.

Reference:

Nagae M, Kanagawa M, Morita-Matsumoto K, Hanashima S, Kizuka Y, Taniguchi N, Yamaguchi Y.

Atomic visualization of a flipped-back conformation of bisected glycans bound to specific lectins.

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