Koichi Kato

Profile

Koichi Kato received his Ph.D. in 1991 at Graduate School of Pharmaceutical Sciences, the University of Tokyo (Prof. Yoji Arata), and continued his research as an Assistant Professor and then as a Lecturer in the same group. In 2000, he received the Award for Young Scientists of the Pharmaceutical Society of Japan and moved as a Professor to Nagoya City University. Since 2005, he has been a Director of GLYENCE, a company to exploit glycotechnology of his group. Since 2006, he has also been a Visiting Professor at the Glycoscience Institute, Ochanomizu University. Since 2008, He has been a Professor at Okazaki Institute for Integrative Bioscience, National Institutes of Natural Sciences, holding the Professorship concurrently at Nagoya City University. In 2011, he received the Award for Divisional Scientific Promotions of the Pharmaceutical Society of Japan and the 48th Baelz Prize. His research interests include development and application of structural glycomics methods for characterizing conformations, dynamics, and interactions of glycoconjugates.

Conformational dynamics and interactions of glycoconjugates of therapeutic interest

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The sugar chains covalently modifying proteins and lipids are involved in a variety of molecular recognition events, thereby mediating a broad range of physiological and pathological processes on cell surfaces as well as in cells. Therefore, these carbohydrate-protein interaction systems could be potential therapeutic targets for various diseases, including viral infections, autoimmune diseases and neurodegenerative disorders[1]. In addition, protein glycosylation is currently considered to be one of the most important factors in the design and development of biopharmaceuticals typified by antibody medicines because the carbohydrate moieties affect the physical and biological properties of proteins, e.g. solubility, thermostability, serum half-life, and functional protein-protein interactions.

To facilitate the design of drugs targeting carbohydrate recognition systems, deeper insights into the structural basis of carbohydrate-protein interactions are essential. We have developed a systematic method for characterizing structures, dynamics, and interactions of glycoconjugates at atomic level [2)3)]. Our methodology is constituted by 1) GALAXY-based glycosylation profiling, 2) comprehensive analysis of lectin-sugar interactions using a sugar library, and 3) structural analyses by stable-isotope-assisted NMR spectroscopy in conjunction with X-ray crystallography. In this presentation, I will illustrate several examples of our structural studies of the carbohydrate-protein interaction systems as potential therapeutic targets (Figure 1).

1. *N*-glycan-dependent determination of glycoprotein fates in cells

N-linked oligosaccharides operate as tags for protein quality control, consigning glycoproteins to different fates, i.e. folding in the endoplasmic reticulum (ER), vesicular transport between the ER and the Golgi complex, and ER-associated degradation of glycoproteins, by interacting with a panel of intracellular lectins in the early secretory pathway [4]. Our frontal affinity chromatography data demonstrated that the intracellular lectins exhibit distinct sugar-binding specificity profiles [5)6)]. The glycotopes recognized by these lectins as fate determinants are embedded in the triantennary structures of the high-mannose-type oligosaccharides and are exposed upon trimming of the outer glucose and mannose residues during the *N*-glycan processing pathway. Furthermore, structural basis has been provided for the functional interplay between the L-type lectin ERGIC-53 and the EF-hand Ca^{2+}-binding protein MCFD2 in the intracellular transport of the coagulation factors V and VIII [7)].

2. *N*-glycan-dependent effector functions of immunoglobulin G

The effector functions of immunoglobulin G (IgG) critically depend on *N*-glycosylation of its Fc region. It is well known that removal of the fucose residue from the *N*-glycans of the Fc portion of IgG results in a dramatic enhancement of antibody-dependent cellular cytotoxicity (ADCC) through improved affinity for Fcγ receptor IIIa (FcγRIIIa). Recently, we determined the crystal structure of the complex formed between non-fucosylated IgG1-Fc and a soluble form of FcγRIIIa (sFcγRIIIa) having two *N*-glycosylation sites [8)]. The crystal structure demonstrates that one of the two *N*-glycans of sFcγRIIIa mediates the interaction with the *N*-glycan of non-fucosylated Fc, thereby stabilizing the complex. However, fucosylation of the Fc *N*-glycans impairs this interaction because of steric hindrance. On the other hand, our NMR data demonstrated that Tyr296 of the non-fucosylated Fc glycoform exhibits conformational multiplicity in its uncomplexed state, suggesting that conformational selection is governed by the presence or absence of the fucose residue of the Fc *N*-glycan. Fucose depletion increases the incidence of the active conformation of this tyrosine residue, and thereby accelerates the formation of the high-affinity complex. These findings offer a structural basis for improvement in ADCC of therapeutic antibodies by defucosylation.

3. Ganglioside clusters as platforms for pathological molecular events

Gangliosides are known to play a variety of physiological and pathological roles at the cell surface. For instance, GM1 ganglioside acts as a target of cholera toxin, polyoma virus, growth-regulatory galectin-1 and autoantibodies associated with Guillain-Barré syndrome. Recently, growing evidence has indicated that gangliosides interact with amyloid β (Aβ) and promote its assembly, which is considered to be a crucial step in Alzheime's disease. To better understand the underlying mechanisms of this pathological molecular event, it is highly desirable to obtain detailed structural information of these interaction systems. Our NMR data indicate that the ganglioside clusters provide a unique platform at their hydrophobic/hydrophilic interface for binding coupled with conformational transition of Aβ molecules, rendering their spatial rearrangements restricted to promote specific intermolecular interactions leading to the formation of their pathogenic aggregates [9)10)]. In addition, by NMR approach using mixed micelle system, we successfully identified the atomic contact of the carbohydrate-carbohydrate interaction between the GD1a and GD1b gangliosides, providing clues to the structural basis of epitope recognition by the autoantibodies in Guillain-Barré syndrome.

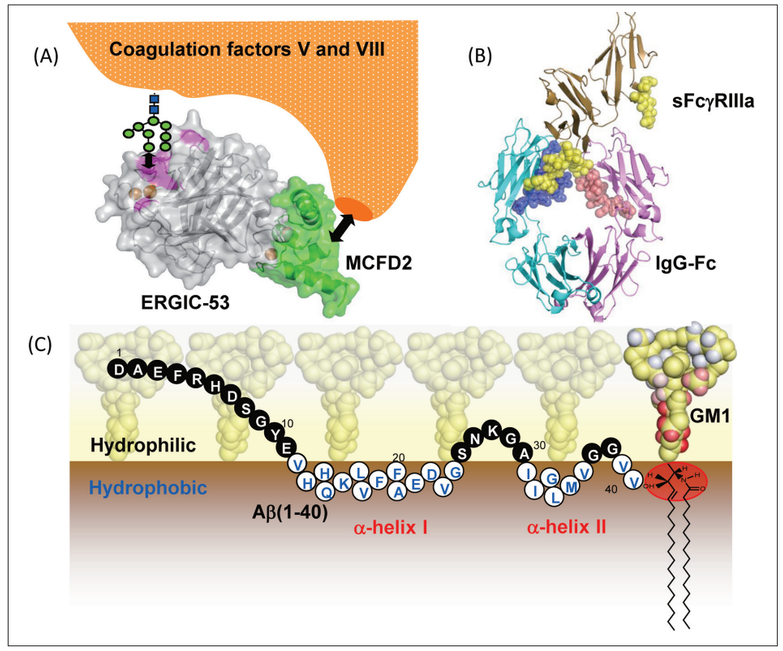

Figure 1. Structural basis for the molecular recognition events involving the glycoconjugate of therapeutic interest.
(A) Functional coordination between ERGIC-53 and MCFD forming a cargo receptor complex that transports coagulation factors V and VIII.
(B) Interaction between the non-fucosylated glycoform of human IgG1-Fc and bis-glycosylated sFcγRIIIa.
(C) Aβ(1-40) accommodated on the hydrophilic/hydrophobic interface of GM1 cluster.

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