Usage Report for Fiscal Year 2017

Project Title:

Structural basis of CD22-sialic acid interaction by structural biology and computational chemistry

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1. Background and purpose of the project, relationship of the project with other projects

Drugs targeting Siglec-2 (CD22) are an alternative approach for treatment for autoimmune disease and non-Hodgkin's lymphoma (among 10 most common cancers). Siglec-2 interacts specifically with the substituents of sialic acid, and all the known inhibitors are the result of chemical modification in the sialic acid NeuAc or NeuGc. Understanding the structural basis of sialic acid interactions with Siglec-2 and its known inhibitors is of great interest not only for the design of glycan-based therapeutics but also for developing theoretical approaches to understand protein-glycan interactions in general. The other similar projects were also focused on exploring the structure and function of glycans, glycan binding proteins and protein-glycan complexes using molecular modeling. We also studied structural complexity of large N-glycans and their interaction with Orysata and Calsepa lectins.

2. Specific usage status of the system and calculation method

Since the 3D structure of CD22 was initially not known, we used homology modeling and classical MD simulations to model CD22 structures. After the crystal structure was published, we applied extensive MD simulations (using GPUs code of AMBER14) on CD22/sialic-acid complexes to understand the molecular basis of sialic acid recognition. In addition to CD22, we also perform extensive MD of Orysata and Calsepa complexed with N-glycans to understand *N*-glycan binding modes and their molecular recognition. We further perform MM/GBSA biding free-energy calculation on these complexes to rationalize their glycan recognition capabilities. Binding free-energy calculation by other PMF based approaches were performed in BigWaterfall MPC cluster using software Amber16. The Multistate Bennett Acceptance Ratio (MBAR) and Thermodynamic Integration (TI) based binding energy calculations were performed using SireMole software in GreatWave ACSG (using GPUs).

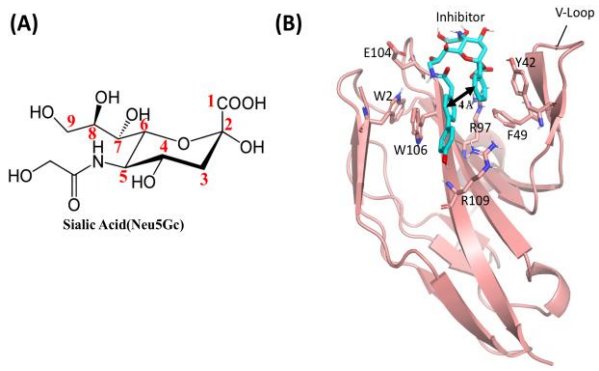

Figure 1: (A) The Sialic acid substituent sites (A) and biding mode of C2, C9 substituent inhibitor in human CD22.

3. Result

Changes in binding energy upon modifications at C2, C4, C5 and C9 positions of the sialic-acid were predicted computationally. The MBAR and TI can reproduce the experimental binding preference data for Sig-2 binding to sialic-acid analogs. This helped us to understand the crucial residues involved in sialic-acid binding to CD22. We also preformed molecular dynamics simulation and MM/GBSA based binding free-energy calculation on branched N-glycans binding to lectins Orysata and Calsepa.

The MD and binding energies helped us to explain the dual binding modes of N-glycans. Branched N-glycans show two modes of binding where each N-glycan can bind two lectin molecules at a time.

4. Conclusion

We successfully explored the protein-glycan interaction in CD22. We also elucidated the nature of branched N-glycans binding to lectins. This helps us to understand the structure and function of various protein-glycan complexes currently being studied in our laboratory. These results are crucial for further glycan-based drug discovery.

5. Schedule and prospect for the future

In this financial year, we are moving out of RIKEN. Thus, we do not request for extension of this project.

Fiscal Year 2017 List of Publications Resulting from the Use of the supercomputer

[Publication]

1. Masamichi Nagae[||], Sushil K. Mishra[||], Shinya Hanashima, Hiroaki Tateno and Yoshiki Yamaguchi (2017) Distinct roles for each N-glycan branch interacting with mannose-binding type Jacalin-related lectins Orysata and Calsepa. *Glycobiology* 1;27(12):1120-1133.

[Proceedings, etc.]

1. Sushil K. Mishra, Jaroslav Koča and Yoshiki Yamaguchi. Binding Free Energy Calculation of Protein-Carbohydrate Complexes: Learnings so far. *Biophysical Journal, Volume 114, Issue 3, 57a*

Note: Including acknowledgment was not allowed in the abstract. We have included acknowledgement in the poster.

[Oral presentation at an international symposium]

1. Sushil K. Mishra and Yoshiki Yamaguchi. Structure-Guided Design of Glycan-Based Compounds for Immunoglycotherapy. The grant research meeting of the Tokyo Biochemical Foundation, Tokyo, Japan. March 02. 2017

[Others (Press release, Science lecture for the public)]

Poster Presentation:

1. Sushil K. Mishra, Jaroslav Koča and Yoshiki Yamaguchi. Understanding Lectin-Glycan Recognition by Molecular Modeling: assumptions, challenges and future direction. RIKEN International Symposium on Systems Glycobiology and Beyond. November 16-17, 2017, RIKEN, Tokyo, JAPAN.