A theoretical study of the interaction between a lectin called Siglec-7 and its glycan ligand in the immune system

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Siglecs (sialic acid-binding immunoglobulin superfamily lectins) are a group of receptors in the immune system, which specifically recognize glycans that contain sialic acids (Neu5Ac). Siglec-7 belonging to CD33-related siglecs was mainly expressed on natural killer cell. More attention has been paid to its potential role in natural killer cells as part of cancer research in addition to its major role in the innate immune system. Siglec-7 has been reported to recognize α(2,8)-disialyl residue (Neu5Acα2-8Neu5Ac) preferentially[1], the mechanism of which, however, has not been elucidated. In order to investigate the specificity of glycan recognition of siglec-7, we analyzed the intermolecular interaction between siglec-7 and its ligand.

We clarified in detail the theoretical features of the interaction between the glycan ligand and Siglec-7 by *ab initio* Fragment Molecular Orbital (FMO) calculations [2] and classical molecular dynamics (MD) simulations. We utilized the X-ray crystal structure of siglec-7 complexed with GT1b analog, α (2,8)-disialyl glycolipid (PDB ID: 2HRL) [3]. By comparing the ligand-Siglec-7 interaction of the wild-type Siglec-7 and those of mutant-Siglec-7s, we herein describe the protein-glycan interaction thoroughly, and provide fundamentals to elucidate ligand-recognition mechanism [4].

The interaction energies obtained by the FMO method were consistent with the experimental ligand-binding results. The glycan ligand preferentially interacted with Siglec-7 via sialic acid residues. The stabilization by the dispersion interaction between the neutral parts of the ligand was also considerable in the binding.

The experimentally observed decrease in ligand binding produced by mutagenesis at residues in non-active site was explained with MD simulations; both Trp85 and Trp74 residues are fundamental in structural stability of the Siglec-7, which is involved in the binding of the glycan ligand (Figure 1).

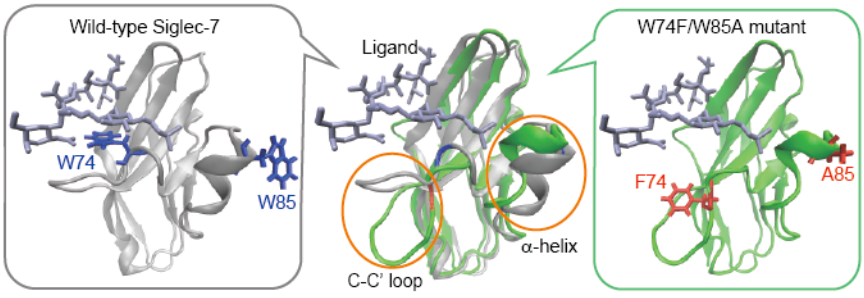

Figure 1 The structure of the double mutant W74F/W85A (depicted in green, the snapshot at 9 ns in the MD simulation) is superposed with the X-ray structure of wild-type Siglec-7 (silver, PDB ID: 2HRL).

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