Molecular mechanism of self-antigen recognition by the ligand binding domain of B cell inhibitory co-receptor CD72

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CD72 is an inhibitory co-receptor that negatively regulates B cell antigen receptor (BCR) signalling. The ligand-binding domain of CD72 at the extracellular region belongs to the C-type lectin-like domain (CTLD) superfamily. We have demonstrated that it recognizes the nuclear autoantigen Sm/RNP composed of proteins and RNA, and suppresses autoimmune diseases such as systemic lupus erythematosus [1]. The crystal structure of the ligand-binding domain of mouse CD72c, a lupus-resistant allele, has been determined at 1.2 Å resolution. Electrostatic potential analysis of the molecular surface of CD72c-CTLD suggest that charge distribution at the putative ligand-binding site may affect the binding affinity between CD72 and Sm/RNP. We have determined the crystal structure of the ligand-binding domain of mouse CD72c, a lupus-susceptible allele with reduced affinity to Sm/RNP. The obtained crystals were large enough for X-ray diffraction experiments of about 200 μm cubic, but clusters of hundreds or thousands of microcrystals (Fig. 1). Development of the micro focus X-ray beam and rapid automated data collection [2] and processing [3] systems at SPring-8 enabled us to obtain a full data set that allowed the successful structure determination and refinement at 2.5 Å resolution (Fig. 2). We took 1,400 of small-wedge (10 degree) data from 14 crystals. The data were classified based on the unit-cell dimensions or correlation coefficient between data and merged to a full data set for structure determination. Analysis of the hierarchical clustering of the small-wedge data shows that the crystal packing varies along with the c-axis direction, but no significant conformational variations were observed among the crystal structures.

The obtained structure reveals that substitutions of amino acids at the ligand-binding site do cause the inversion of the charge distribution of the molecular surface as we hypothesized. Charge repulsion between CD72c-CTLD and strong negative charges of RNA of Sm/RNP would be the molecular mechanism of reduced affinity.


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