Molecular Mechanism of the Interaction of CERT Protein with Lipid Membrane

Ceramide, which is one component of lipid molecules in cell membrane, is biosynthesized in the endoplasmic reticulum and transferred to the Golgi apparatus by CERT, a cytosolic protein. The START domain of CERT is responsible for the transfer of ceramide. We determined the crystal structures of the CERT START domain in complex with ceramide and specific inhibitors. These crystal structures reveal how CERT recognizes ceramide specifically, and how CERT interacts with membrane.

Ceramide is a member of sphingolipids, which are the major lipid molecules in cell membrane. In mammalian cells, ceramide is synthesized in the endoplasmic reticulum (ER) and transferred to the Golgi apparatus for conversion to sphingomyelin, and further metabolized to other complex glycosphingolipids. Ceramides are not only the structural elements in the lipid bilayer, but also the possible mechanisms by which CERT interacts with membranes.

We have determined the crystal structures of the CERT START domain in the apo-form (2.2 Å resolution), and Ceramide and HPA molecules are drawn as filled spheres in which yellow, blue, and red represent C, N, and O atoms, respectively. (a) Superimposed structure of the ceramide-bound (blue) and apo-form (purple) of the CERT START domain. Trp-473 residues are represented as stick models. Hydrogen bond network between the CERT START domain and Ceramide and HPA molecules are shown. The outer surface and cross section of the CERT START domain are drawn in light brown and gray, respectively. The purple dotted line indicates Trp-473, and the black dotted line indicates a small opening of the cavity in the ceramide-bound CERT START domain.

REFERENCES


BEAMLINES

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Figure 1
Crystal structures of the CERT START domain, in the apo-form (a), in complex with Ceramide (b) and with HPA-14 (c). Ceramide and HPA molecules are drawn as filled spheres in which yellow, blue, and red represent C, N, and O atoms, respectively. (d) Superimposed structure of the ceramide-bound (blue) and apo-form (purple) of the CERT START domain. Trp-473 residues are represented as stick models. Hydrogen bond network between the CERT START domain and Ceramide and HPA molecules are shown. The outer surface and cross section of the CERT START domain are drawn in light brown and gray, respectively. The purple dotted line indicates Trp-473, and the black dotted line indicates a small opening of the cavity in the ceramide-bound CERT START domain.

Figure 2
(a) Schematic of the CERT START domain and membrane interaction via Trp-473. Molecular surfaces are drawn in light brown. Ceramide bound (left) and HPA-14 bound (right) structures of the CERT START domain are presented. In the case of the HPA-14-bound structure, Trp-473 exists inside the cavity, while it is exposed to the outside of the protein in the ceramide-bound structure. (b) Trp-473 is drawn as filled spheres. Molecular surfaces of the CERT START domain in complex with Ceramide (b) and HPA-14 (c) cut at the level of the cavity, are shown. The outer surface and cross section of the CERT START domain are drawn in light brown and gray, respectively. The purple dotted line indicates Trp-473, and the black dotted line indicates a small opening of the cavity in the ceramide-bound CERT START domain.