Poster Presentation

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Structural basis of pharmacological chaperoning for human β-galactosidase

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GM1-gangliosidosis and Morquio B are rare lysosomal storage diseases associated with a neurodegenerative disorder or dwarfism and skeletal abnormalities, respectively. These diseases are caused by deficiencies in the lysosomal enzyme human β-Galactosidase (β-Gal), frequently related to misfolding and subsequent endoplasmic reticulum-associated degradation (ERAD) due to mutations in the β-Gal gene. Pharmacological chaperone (PC) therapy is a newly developed molecular therapeutic approach by using small molecule ligands of the mutant enzyme that are able to promote the correct folding, prevent ERAD and promote trafficking to the lysosome. Here, we present the enzymological properties of wild-type human β-Gal and two representative mutations in GM1 gangliosidosis Japanese patients (R201C and I51T). We have also evaluated the PC effect of two competitive inhibitors of β-Gal. Moreover, we determined the crystal structures of β-Gal in complex with these compouds and two structurally related analogues to elucidate the detailed atomic view of the recognition mechanism. All compounds bind to the active site of β-Gal with the sugar moiety making hydrogen bonds to active site residues. Moreover, the binding affinity, the enzyme selectivity and the PC potential are strongly affected by the mono or bicyclic structure of the core as well as the orientation, the nature and the length of the exocyclic substituent. These results provide understanding on the mechanism of action of β-Gal selective chaperoning by newly developed PC compounds.

Keywords: pharmacological chaperone, lysosomal storage diseases