Structural basis of pharmacological chaperoning for human β-galactosidase

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Abstract. G_{M1} gangliosidosis and Morquio B disease are autosomal recessive diseases caused by the defect in the lysosomal β-galactosidase (β-Gal) enzyme, frequently related to misfolding and subsequent endoplasmic reticulum-associated degradation (ERAD). 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. We determined the crystal structure of human β-Gal, which was folded into the TIM barrel domain and two β-domains. We have also evaluated enzymatic properties of recombinant β-Gal, and the PC effect of two competitive inhibitors of β-Gal. Moreover, we provide detailed atomic view of the recognition mechanism of these compounds in comparison with two structurally related analogues. The PC compounds binding were affected by the core structure and exocyclic substituent. This atomic view of β-Gal/PC complex provides understanding PC mechanism.

Keywords: β-D-galactosidase; pharmacological chaperone; lysosomal storage diseases; crystal structure.