Title

Pharmacological Chaperoning in Fabry Disease

Authors

Jerome Rogich, *University of Massachusetts Amherst* Follow

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Abstract

Fabry Disease is an X--linked lysosomal storage disorder characterized by a variety of symptoms including hypohydrosis, seizures, cardiac abnormalities, skin lesions, and chronic pain. These symptoms stem from a lack of functional endogenous α-- Galactosidase A (α-GAL), which leads to an accrual of its natural substrate. The severity of the disease symptoms can be directly correlated with the amount of residual enzyme activity. It has been shown that an imino sugar, 1-deoxygalactonojirimycin (DGJ), can increase enzymatic activity and clear excess substrate. This pH--dependent chaperoning phenomenon is believed to arise from the presence of aspartic acid 170 in the active site. This key residue may become protonated at lower pH, preventing a buried salt bridge from being formed. We mutated this residue to an alanine, abolishing activity, and making traditional assays impractical. We have measured the KD of chaperone for this modified active site through crystallography. Previous crystallographic studies on this enzyme have also shown a preliminary second binding site on the surface of α-Galactosidase that prefers the β--Galactose anomer. When β-Galactose binds it buries a greater surface area than when α-Galactose binds to the active site. Binding of this site by a small molecule should stabilize the native state of the enzyme, but would be sterically occluded from inhibiting active site. We have probed this second site by soaking crystals of α-Galactosidase with a small library of compounds.

First Advisor

Scott C Garman

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