Title

Structure, Function, and Pharmacological Chaperones for Human α-N-Acetylgalactosaminidase

Author

Nathaniel E Clark, *University of Massachusetts - Amherst*

Date of Award

9-2012

Document Type

Campus Access

Degree Name

Doctor of Philosophy (PhD)

Degree Program

Molecular and Cellular Biology

First Advisor

Scott C. Garman

Second Advisor

Peter Chien

Third Advisor

Richard A. Goldsby

Subject Categories

Biochemistry | Biophysics | Cell Biology

Abstract

Human lysosomal α-N-acetylgalactosaminidase (α-NAGAL) is responsible for the break down of glycolipids and glycopeptides that contain a terminal α-linked N-acetylgalactosamine residues. Deficiency of α-NAGAL results in Schindler and Kanzaki diseases. α-NAGAL is closely related to another lysosomal enzyme, α-galactosidase (α-GAL), which breaks down glycolipids and glycopeptides with a terminal α-linked galactose residues. Fabry disease results from a deficiency of α-galactosidase activity. We studied the reaction mechanism of both enzymes using biochemistry and X-ray crystallography, and found that α-GAL and α-NAGAL use an identical reaction mechanism, and differ only in substrate specificity. We solved the first structure of human α-NAGAL, allowing us to examine the disease-causing patient mutations in the context of a high-resolution 3D atomic structure, moving Schindler and Kanzaki disease into the realm of personalized molecular medicine. We then developed the first ever proof-of-principle treatment of Schindler and Kanzaki disease, by developing and characterizing 2 pharmacological chaperones that show promise to treat Schindler and Kanzaki diseases, which currently have no treatment options.

Recommended Citation

Clark, Nathaniel E, "Structure, Function, and Pharmacological Chaperones for Human α-N-Acetylgalactosaminidase" (2012). *Doctoral Dissertations 1896 - February 2014*. 403.
https://scholarworks.umass.edu/dissertations_1/403

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