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Title

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

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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.

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