The Cryo-EM structure of human fucosidase FucA1 opens new avenues for the treatment of fucosidosis

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Enzymatic hydrolysis of α-L-fucose from fucosylated glycoconjugates is consequential in bacterial infections and the neurodegenerative lysosomal storage disorder fucosidosis. Understanding human α-L-fucosidase catalysis, in an effort toward drug design, has been hindered by the absence of three-dimensional structural data for any animal fucosidase. Here, we have used cryoelectron microscopy (cryo-EM) to determine the structure of human lysosomal α-L-fucosidase (FucA1) in both an unliganded state and in complex with the inhibitor deoxyfuconojirimycin. These structures, determined at 2.49 Å resolution, reveal the homotetrameric structure of FucA1, the architecture of the catalytic center, and the location of both natural population variations and disease-causing mutations. Furthermore, this work has conclusively identified the hitherto contentious identity of the catalytic acid/base, representing a shift from both the canonical glutamate acid/base residue and a previously proposed glutamate residue. These findings have furthered our understanding of how FucA1 functions in both health and disease.

Bibliographic references:

Armstrong Z., Meek R.W., Wu L., Blaza J.N., Davies G.J. (2022) Cryo-EM structures of human fucosidase FucA1 reveal insight into substrate recognition and catalysis. Structure, 30, 1-9