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STRUCTURAL BIOLOGY AND PHARMACOLOGY OF HUMAN CATHEPSIN A AND NEURAMINIDASE 1

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Abstract
Human cathepsin A (also known as Protective Protein/Cathepsin A, PPCA; E.C. 3.4.16.5) is a lysosomal serine carboxypeptidase. Cathepsin A is also involved in a complex with two other lysosomal enzymes: lysosomal neuraminidase (NEU1, E.C. 3.2.1.18) and β-galactosidase (GLB1, E.C. 3.2.1.23). Deficiency in cathepsin A and NEU1 result in the lysosomal storage diseases, galactosialidosis and sialidosis respectively. Deficiency in GLB1 results in G_{M1} gangliosidosis and Morquio B diseases.

Cathepsin A protease activity is spatially regulated by activation of the inactive precursor form to the mature form in the lysosome. Structural studies on the mature form of cathepsin A were performed to understand

the mechanism of activation. We present X-ray crystallographic, mass spectrometric, amino acid sequencing, and enzymatic data to support a cleavage-only model, involving proteolytic processing of the precursor with no conformational change required. Additionally we show that multiple cleavage sites on the surface of the protein ensure activation of cathepsin A in the lysosome. The structural results presented here point to new avenues for the design of mechanism-based inhibitors of the enzyme.

NEU1 is an exosialidase that cleaves terminal sialic acids from glycoproteins and glycolipids in the lysosome and on the cell surface highlighting its importance in cellular functions such as signal transduction and cancer metastasis pathways. NEU1 activity is deficient in sialidosis and galactosialidosis, and there are no available treatments for both the diseases. Although the molecular basis for sialidosis and galactosialidosis is not fully understood, complex formation is proposed to be important for the activity and stability of NEU1. In the current study we show that cathepsin A directly interacts with NEU1 and this interaction is not required for the catalytic activity of NEU1, instead facilitates stabilization of NEU1. The data presented here provide new insight into the NEU1-cathepsin A complex. We further present a proof-of-concept study for pharmacological chaperone therapy using inhibitors targeting NEU1 for the treatment of sialidosis and galactosialidosis.