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A key enzyme in the biogenesis of lysosomes is a protease that regulates cholesterol metabolism

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Abstract: Mucolipidosis II is a severe lysosomal storage disorder caused by defects in the α and β subunits of the hexameric N-acetylglucosamine-1-phosphotransferase complex essential for the formation of the mannose 6-phosphate targeting signal on lysosomal enzymes. Cleavage of the membrane-bound α/β-subunit precursor by an unknown protease is required for catalytic activity. Here we found that the α/β-subunit precursor is cleaved by the site-1 protease (S1P) that activates sterol regulatory element-binding proteins in response to cholesterol deprivation. S1P-deficient cells failed to activate the α/β-subunit precursor and exhibited a mucolipidosis II-like phenotype. Thus, S1P functions in the biogenesis of lysosomes, and lipid-independent phenotypes of S1P deficiency may be caused by lysosomal dysfunction.

Statement: Mucolipidosis II (MLII) is a severe inherited lysosomal storage disorder affecting several organs. The disease is caused by mutations in the phosphotransferase complex involved in the formation of a mannose 6-phosphate targeting signal on lysosomal proteins. Biochemically ML II is characterized by missorting of multiple lysosomal enzymes, dysfunctional lysosomes and accumulation of nondegraded material in lysosomes. In the present study we have identified a protease, site-1-protease (S1P), that cleaves the phosphotransferase precursor protein required for activation of the phosphotransferase. Cells deficient of S1P exhibit identical biochemical properties as phosphotransferase defective cells. S1P plays a crucial role in regulating lipid metabolism, cholesterol homeostasis, and viral pathogenesis. Thus, our findings are important for current therapy approaches for cardiovascular diseases and viral infections based on S1P inhibition.

This work was performed at the Department of Biochemistry, Children´s Hospital in the group of Thomas Braulke in collaboration with Michaela Schweizer of the Center for Molecular Neurobiology. The study was part of the PhD thesis of Katrin Marschner supervised by Sandra Pohl and was supported by the DFG (GRK1459 and SFB877). Thomas Braulke's group is interested in the biogenesis and function of lysosomes, and inherited lysosomal storage diseases.