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Lysosomal & extracellular GlcCer degradation: Protein & lipid modifiers

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Lysosomal sphingolipid degradation requires the presence of water-soluble hydrolases, SAPs, anionic phospholipids like BMP, and an acidic pH value. Inherited defects of catabolic hydrolases or SAPs cause various sphingolipidoses. SAPs are membraneperturbing proteins which facilitate glycolipid digestion by presenting insoluble lipid molecules to soluble catabolic enzymes. SAPs (the GM2-activator and saposins A-D) bind to lipid bilayers and mobilize lipids out of them at acidic pH values. As demonstrated by plasmon resonance studies for saposins A and B, low cholesterol levels and increasing concentrations of BMP favour lipid extraction and membrane disintegration. Variant saposins as identified in patients with Krabbe disease and metachromatic leukodystrophy, respectively, are deficient in mobilizing membrane lipids. The inherited absence of all four saposins (A-D) causes a severe membrane and sphingolipid storage disease, also disrupting the water permeability barrier of the skin.

Saposins and glucosylceramidase are also involved in the extracellular catabolism of ultralongchain acylglucosylceramides, key components for the generation of the extracellular lipid layers forming the immune and the water permeability barrier in the stratum corneum of the mammalian skin. Their complete functional deficiency causes perinatal fatal diseases of the collodion baby type.

Ongoing *in vitro* studies indicate that PM-stabilizing lipids, i.e. SM and cholesterol, inhibit several steps of lysosomal SL and glycosphingolipid catabolism, and also lipid solubilisation as studied by Surface Plasmon Resonance and intervesicular (glyco-) lipid transfer activities of several SAPs and NPC2, even in the presence of activating anionic PLs.

Biography

Konrad Sandhoff completed his PhD in biochemistry in Munich. After research stays in Munich, Israel and the USA he became a full professor of biochemistry at the University of Bonn in 1979. Since 2007 he is a senior professor at the LIMES institute, Bonn. Major Research Interests: Molecular life sciences: analysis and pathobiochemistry of Iysosomal (glyco-)sphingolipid storage diseases, structure and function of Iysosomal enzymes and lipid binding proteins, topology of endocytosis and glycolipid metabolism, and regulation of glycolipid biosynthesis. He has published more than 480 peer-reviewed papers. Among many other prizes he also received the International Glycoconjugate Organization Award (2005).

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