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Membrane lipids regulate glyco sphingolipid catabolism, their enzymes and lipid binding proteins

Cholesterol and sphingolipids (SLs) are stabilizing compounds of eukaryotic plasma membranes. Together with phospholipids (PLs) they reach luminal vesicles of the endolysosomal compartment as platforms for membrane degradation. A maturation process removes lipids inhibiting lysosomal catabolism from the luminal vesicles. Sphingomyelin (SM) is hydrolyzed by acid sphingomyelinase, facilitating cholesterol export to the cytosol by NPC2 and NPC1. SM and cholesterol poor luminal vesicles then serve as platforms for glycosphingolipid degradation in the lysosomes employing soluble hydrolases, SAPs (sphingolipid activator proteins) and anionic PLs as stimulators. We reconstituted the catabolic proteins on liposomal surfaces, mimicking luminal vesicles of the lysosomes as platforms for SL degradation. Liposomes without anionic PLs and with no net surface charge generated only negligible and physiologically irrelevant catabolic rates even at lysosomal pH values. Incorporation of anionic PLs into the SL-carrying liposomes, however, stimulated the catabolic rate by up to more than an order of magnitude. We now found, that the incorporation of cholesterol or SM into the SL carrying liposomal membranes generated a strong inhibition of ganglioside GM2 hydrolysis and the transfer of membrane lipids between liposomal vesicles by SAPs, even in the presence of anionic phospholipids. 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 phospholipids.

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 lysosomal (glyco-) sphingolipid storage diseases, structure and function of lysosomal 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 Glyco conjugate Organization Award (2005).

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