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ABC cassette transporters regulate glycosphingolipid biosynthesis

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ABC cassette transporters differentially control GSL synthesis. The precursor for the synthesis of most complex glycosphingolipids (GSLs) is glucosylceramide (GlcCer) made on the outer Golgi membrane. The mechanism by which GlcCer is flipped into the Golgi has remained a mystery for more than 40 years. Based on the use of *MDR1 (ABCB1)* inhibitors, we proposed a role for this multidrug resistance protein. We have now used a newly synthesized photolabile GlcCer cross-linker to identify GlcCer binding proteins in microsomes, using proteomics/mass spectrometry. Three ATP binding ABC cassette transporters were thus identified, *ABCB10, ABCB4* and *ABCA3*. Using SiRNA knockdown, these candidate GlcCer flippases were reduced in DU145 cells. The loss of ABC cassette proteins had a differential effect on selective GSLs. Some were increased e.g., lactosyl ceramide, while others reduced. In each case of ABC cassette knockdown, GalCer was increased. Moreover, *MDR1* siRNA knockdown reduced overall GSL content by greater than 50% according to cell line. These studies provide new insights into the complex regulation of GSL biosynthesis by precursor supply, a new basis for the link between cancer/multidrug resistance and GSL biosynthesis, suggest a new link between GlcCer and GalCer-based GSLs and indicate that multiple ABC transporters can transport GlcCer into the Golgi to generate LacCer pools used for the synthesis of different GSLs. Different LacCer pools could provide a partial basis for the biosynthesis of different GSLs within different Golgi regions.

Biography

Clifford Lingwood has completed his PhD at the University of London in 1974 and Postdoctoral studies at the Universities of Washington and Toronto. He has been a Full Professor at the University of Toronto since 1997 and is a Senior Scientist within the Molecular Medicine program of the Research Institute at the Hospital for Sick Children, Toronto. His research program is concerned with the biochemistry, chemistry, metabolism and function of glycosphingolipids with a view to the therapy of diseases in which they are involved. He has published more than 200 papers in reputed journals.

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