Clifford Lingwood, Biol Syst Open Access 2017, 6:1(Suppl)
DOI: 10.4172/2329-6577-C1-007

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Cholesterol masking of membrane glycosphingolipids provides a means to evade tumor immunosurveillance and the basis of a living cell transistor

Glycosphingolipids (GSLs) and cholesterol accumulate in membrane lipid rafts and play a central role in these foci of signal transduction. However, within the GSL/cholesterol complex, an H-bond network is formed which alters the conformation of the GSL carbohydrate from a membrane perpendicular, to a membrane parallel format. This latter GSL conformation is largely unavailable for exogenous ligand binding-"invisible GSLs". Due to the increased cholesterol levels typical of cancer cells, we studied the prevalence of cholesterol-masked GSLs in human primary tumor biopsies (prostate, neuroblastoma, colon, breast, testicular, pheochromocytoma, ovarian and ganglioneuroma). We found that such 'invisible' GSLs were widely present in these tumor serial cryosections, e.g., SSEA1, SSEA3, SSEA4, Globo-H and Gb3. We propose that such masking can prevent immunosurveillance of tumor–associated GSL antigens and thereby compromise natural tumor immunity to block progression. Moreover, anti GSL Mabs in development or clinical use for treating cancer (F77 for prostate and Unituxin-antiGD2 for pediatric neuroblastoma) were highly subject to such masking, and prior tumor cholesterol extraction with β-methyl-cyclodextrin, resulted in a remarkable increase in anti-GSL tumor staining. This suggests that tumor cholesterol depletion would increase the antineoplastic activity of these therapeutic Mabs. We also found that the order in which the binding ligands were added was of major significance. Prior Gb3 binding promoted ligand-cholesterol binding and vice versa. This provides the means for amplification and/or diversification of GSL-dependent signal transduction and thus is the first example of a native cell based membrane "transistor.

Biography

Clifford Lingwood completed his PhD from the University of London in 1974, and Post-doctoral studies from 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, Research Institute, Hospital for Sick Children, Toronto. His research program concerns 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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