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Cholesterol masking of carbohydrate tumour antigens blocks tumour immune recognition and sheds new light on statin-based antineoplastic benefit

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Glycosphingolipids (GSLs) are ceramide-carbohydrate conjugates important in differentiation, growth and intercellular interactions. GSL metabolism is abnormal in cancer, and 'tumour-associated GSL antigens', often associated with embryonic development, can be cancer stem cell markers. GSLs and cholesterol accumulate in plasma membrane 'lipid rafts'- transmembrane signaling platforms which are increased in tumour cells.

We have recently shown that the molecular interaction of GSLs with cholesterol can alter the conformation of the GSL carbohydrate, such that the sugar is changed from a membrane perpendicular to parallel format, which is largely unavailable for extracellular ligand binding ("invisible GSLs"). Since cholesterol metabolism is abnormal in cancer, we have investigated the efficacy of cholesterol depletion (via methylßcyclodextrin extraction) of primary human tumor biopsy sections to unmask previously undetectable tumour associated GSL antigens as an index of GSL masking in primary cancer tissues. For all cancers tested (ovarian, prostate, breast, Leydig, pheochromocytoma, neuroblastoma) cholesterol depletion induces immunostaining of previously undetectable tumour-associated GSLs. Such cholesterol mediated masking of GSL antigens may prevent effective tumour immunosurveillance to contribute to the extent of neoplastic disease.

Since many clinical studies show antineoplastic benefit of statin therapy to lower serum cholesterol, we suggest that statin treatment may lower tumour cell membrane cholesterol levels to diminish tumour GSL masking and promote a more effective antitumour immune response. In a small sample of sera from prostate cancer patients who were, or were not, on statin therapy, immune-reactivity against prostate tumour GSLs was detected only in sera from statin treated patients.

Biography

Dr Lingwood obtained his Ph.D at the age of 24 years from University of London, UK and carried out postdoctoral studies both at the University of Washington and University of Toronto. He has published 188 peer review publications and is a leading figure in glycolipid biology and biochemistry. He has patented the use of Verotoxin (Shiga toxin) as a novel antineoplastic agent due to the upregulation of Gb3 glycolipid (the verotoxin receptor) in many human neoplasias and neovascular endothelial cells.

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