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The pk blood group glycolipid, globotriaosyl ceramide as a resistance factor and therapeutic target against HIV infection

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The role of the glycosphingolipid(GSL) binding domain at the apex of the gp120 V3 loop in HIV-host cell interaction remains enigmatic. Several GSLs -GalCer, sulfoGalCer, GM3 ganglioside and Gb3(pk antigen) are bound. Host cell GSL binding is generally thought to facilitate/mediate the cholesterol/GSL-enriched lipid raft requirement for entry/egress of infectious HIV particles. GSLs, however, are complex in their receptor function due to the marked influence of the lipid moiety and membrane environment on GSL carbohydrate presentation. GalCer may provide a mechanism for the entry of HIV into CD4 negative cells. Under appropriate conditions, Gb3 binding to gp120 is greater than GalCer. The role of GSL binding in CD4 positive cells is unclear; neither GalCer nor Gb3 are expressed in T cells, although a few T cells express Gb3 following IL2/PHA activation. Soluble analogues of GalCer and Gb3 inhibit T cell HIV infection in vitro and adamantylGb3 inhibits HIV-host cell membrane fusion. Blood group polymorphisms show T cells from individuals lacking Gb3 have marked increased HIV susceptibility whereas cells from individuals in which Gb3 accumulates show reduced susceptibility to infection compared to normal controls. Genetic/pharmacological manipulation of cellular Gb3 confirm an inverse relationship between membrane Gb3 concentration and HIV susceptibility, indicating Gb3 does not assist, but rather resists, HIV infection. The V3 GSL binding site overlaps the chemokine receptor binding site and Gb3 binding may prevent chemokine receptor binding to inhibit membrane fusion and HIV infection. The possible epidemiological relevance and therapeutic potential of Gb3/gp120 binding will be considered.

Biography

Dr. Lingwood completed his Ph.D. in Cell Biology at the NIMR Mill Hill London UK in 1975 and underwent postdoctoral training in Dr. Hakomori's lab in Seattle and Dr. Schachter's lab in Toronto. He has been a research scientist working on glycosphingolipids at the Hospital for Sick Children for 30 years and published >170 peer-reviewed papers in leading journals in this field. Dr. Branch obtained his Ph.D. in 1992 in Immunology at the University of Alberta, and obtained postdoctoral training in Dr. Gordon Mill's lab in Toronto. He has been a member of the University of Toronto and Canadian Blood Services for the last 20 years and has published 116 peer-reviewed papers focused on cell signaling and HIV infection.