

PK BLOOD GROUP ANTIGEN: A NATURAL RESISTANCE FACTOR TO HIV INFECTION

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Background: Many blood group antigens belong to a class of lipid-sugar conjugate molecules known as glycosphingolipids (GSLs), including ABH, Lewis and the P blood group systems. GSLs have been implicated in HIV-host cell fusion, and several bind to HIV outer envelope gp120 in vitro. In addition, inhibiting GSL glycolipid biosynthesis has been shown to prevent HIV membrane fusion. Interestingly, reconstitution with the Pk blood group antigen has been shown to restore fusion in these in vitro models. However; the exact role of Pk in HIV infection has not been established. We have recently shown a soluble Pk analogue, a highly effective gp120 ligand, inhibits HIV fusion and infection irrespective of the viral tropism. Our studies on patients with Fabry disease, a genetic defect causing Pk accumulation, indicated Pk over-production may provide significant resistance to HIV-1 infection.

Aims: We hypothesize Pk influences susceptibility to HIV infection at the level of membrane fusion and viral entry. Presently, we investigated the effects of differentially expressed Pk, as presented in P1k and p blood groups, on HIV-1 infection. In addition, we have determined the effects of exogenously introduced Pk on HIV susceptibility.

Methods: The effects of differential Pk expression on R5 HIV-1 or X4 HIV-1 infection were considered. Activated peripheral blood-derived mononuclear cells (PBMCs) with Pk over-expression (from P1k blood group individuals), or lacking Pk (from p blood group individuals) were used as targets. Exogenous Pk was introduced in Jurkat T-cells by liposome fusion, and X4 HIV-1 susceptibility determined. Cell surface HIV-1 receptor (CD4), co-receptor (CCR5/CXCR4) and Pk expression, as well as cell viability via AnnexinV-FITC/PI staining, were measured by flow cytometry. Overall expression of Pk was also confirmed by thin layer chromatography (TLC).

Results: PBMCs over-expressing Pk (P1k) showed resistance to productive R5 and X4 HIV-1 infection (one R5 and one X4 strain tested). Conversely, PBMCs lacking Pk (p) were hypersensitive to R5 and X4 HIV-1 infection (three R5 and two X4 strains tested). Pk cell surface expression on normal PBMC controls was almost undetectable, while PBMCs over-expressing Pk (P1k) showed higher cell surface expression, correlating directly with resistance to HIV-1 infection. Higher expression of total Pk levels in PBMCs over-expressing Pk (P1k) was also confirmed by TLC. Differences in CD4 or CCR5/CXCR4 expression on PBMCs with Pk over-expression (P1k) could not account for the observed resistance. Interestingly, PBMCs lacking Pk (p) highly expressed R5 HIV-1 co-receptor, CCR5, potentially contributing to the higher susceptibility. Jurkat T-cells were shown to express Pk following exogenous Pk fusion, and 30% was cell surface expressed. Exogenous Pk fusion in Jurkat T-cells reduced productive X4 HIV-1 infection by 50%, without affecting cell viability or HIV receptor and co-receptor expression.

Conclusions: Overall, HIV infection is inhibited when Pk is highly expressed on the cell surface, while its absence enhances infection. Furthermore, exogenously introduced Pk seems to mimic natural Pk over-expression (P1k). These findings support a protective role for Pk in providing natural resistance to HIV-1 infection. nicole.lund@utoronto.ca