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DC-SIGN a potential new target for antiretroviral (HTLV/HIV) drug discovery

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Despite the susceptibility of dendritic cells (DCs) to human T-cell lymphotropic virus type 1 (HTLV-1) infection and the defined role of these cells in disease pathogenesis, the mechanisms of viral binding to DCs have not been fully delineated. Recently, a glucose transporter GLUT-1, heparan sulfate proteoglycans (HSPGs), and neuropilin-1 (NRP-1) were demonstrated to facilitate HTLV-1 entry into T cells. DCs express their own array of antigen receptors, the most important being the DC-specific intercellular adhesion molecule-3 (ICAM-3)-grabbing nonintegrin (DC-SIGN) with respect to retrovirus binding. Consequently, the role of DC-SIGN and other HTLV-1 attachment factors was analyzed in viral binding, transmission, and productive infection using monocyte-derived DCs (MDDCs), blood myeloid DCs, and B-cell lines expressing DC-SIGN. The relative expression of DC-SIGN, GLUT-1, HSPGs, and NRP-1 was first examined on both DCs and B-cell lines. Although inhibition of these molecules reduced viral binding, HTLV-1 transmission from DCs to T cells was mediated primarily by DC-SIGN. DC-SIGN was also shown to play a role in the infection of MDDCs as well as model B-cell lines. HTLV-1 infection of MDDCs was also achieved in blood myeloid DCs following the enhancement of virus-induced interleukin-4 production and subsequent DC-SIGN expression in this cell population. This study represents the first comprehensive analysis of potential HTLV-1 receptors on DCs and strongly suggests that DC-SIGN plays a critical role in HTLV-1 binding, transmission, and infection, thereby providing an attractive target for the development of antiretroviral therapeutics and microbicides. In this respect, we have developed both cell-based and cell-free high throughput screening assays in order to identify novel inhibitors of DC-SIGN interaction with HTLV-1 gp46 and HIV-1 gp120 proteins.

Biography

Dr. Khan obtained his Ph.D. degree from the Banaras Hindu University, India. He was a Senior Scientist and Deputy Director in the Central Drug Research Institute- a premier organization of the government of India. He served this institute for over 25 years before immigration to USA. He published extensively in high impact factor journals and obtained numerous patents. For many years Dr. Khan's frontier area of research has been on the microbial pathogenesis and therapy of infectious diseases including retroviruses and opportunistic infections. The current research efforts primarily focus on defining the mechanism of HTLV-1-induced neuroinflammation and demyelination in the central and peripheral nervous system in order to identify potential diagnostic markers and High-throughput targets for therapeutic interventions. Other areas of his research interests are HIV-1 therapeutics and microbicide development. Dr. Khan has developed collaborative INDO-US program with a view to develop a new database on HIV-1 cohorts (HIV clade B & C) for the purpose of genotyping, sequencing and novel therapeutic strategies to overcome HAART resistance in HIV/AIDS patients.

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