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MDR efflux transporters - New drug targets for HIV drug delivery

Statement of the Problem: HIV is now considered a global pandemic affecting millions of people. Sexual transmission is the major mode of HIV infection in healthy humans. None of the vaginal microbicides and/or oral therapies has yet resulted in a complete protection from sexual transmission of HIV. Attachment of HIV to the human CD4+ T-cells, incorporation of viral enzymes and genetic material constitute the first steps of HIV sexual transmission. The purpose of the study is to screen the primary human CD4+ T-cells and transfected vaginal epithelial cells (VK2) for the presence of prominent ABCC class of drug efflux transporters: Multi Drug Resistance Associated Proteins (MRPs), P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP).

Methodology & Theoretical Orientation: Molecular screening was performed by RT-PCR gene expression followed by sequencing analysis. Functional screening was performed by 3H-Tenofovir uptake in the presence of specific MRP inhibitor (MK571), P-gp inhibitor (Pgp-4008) and BCRP inhibitor (Fumitrimorgin-C). Intracellular radio labeled drug concentrations were analyzed by liquid scintillation counter.

Findings: Single specific PCR gene products corresponding to GAPDH, MRPs1-7, MRP9, BCRP and P-gp were observed in primary human T cells. Single distinct bands for MRPs 1-9, BCRP and Pgp were observed in VK2 cells. Relative % drug uptake of tenofovir in primary human T cells in the presence of 50 μ M MK571 was 173.9 \pm 5.8%), 100 μ M MK571 (205.7 \pm 10.6%), 50 μ M Pgp4008 (215.4 \pm 9.2%) and 50 μ M Fumitrimorgin (192.1 \pm 18.38%) compared to control (100 \pm 6.65%).

Conclusion & Significance: The results, for the first time demonstrated the molecular and functional expression of multiple ABCC drug efflux transporters in primary human T cells and VK2 cells. Further, functional uptake studies revealed that the prominent drug efflux pumps (MRPs, Pgp and BCRP) are functionally active in unactivated human T-cells leading to decreased intracellular tenofovir concentrations.

Biography

Pradeep K Karla currently works as an Associate Professor in the Department of Pharmaceutical Sciences. He completed Bachelor's in Pharmacy with distinction from Nagarjuna University, India and interdisciplinary PhD in Pharmaceutical Sciences from University of Missouri in Kansas City. He is the recipient of NIH funded KL2 grant and worked as NIH K Grant research fellow and Principal Investigator. He has been the recipient of AACP New Investigator Grant, Ecobiotix Industrial Grant and Bridge Research Grant. He was the recipient of teaching with technology award at Howard University. His research on drug efflux transporters was cited as one of the eight promising research findings by American Association of Colleges of Pharmacy.

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