



Category: Functional Genomics

Full Scholarship Award Winner

SP-D impedes transfer of HIV-1 from multi-layered vaginal epithelium with a distinct gene signature

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Abstract

Surfactant Protein (SP) D is a member of the collectin family of soluble pattern recognition receptors. We have previously shown that a recombinant fragment of SP-D (rhSP-D) inhibits gp120-CD4 interaction and HIV-1 entry in target cells. To potentiate its prophylactic use as a vaginal microbicide, we determined *ex vivo* efficacy using organotypic human vaginal-ectocervical epithelia (VEC-100) that closely resemble the native tissues of origin. VEC-100, stratified human vaginal-ectocervical tissues grown on membrane inserts were treated with rhSP-D followed by a challenge with HIV-1 to assess the transfer of HIV-1 through the VEC-100 tissues to PBMCs in the basal submucosal compartment. Treated VEC tissues were subjected to mRNA Illumina microarray analysis. Levels of transcripts encoding for immune mediators, adhesion and tight junction proteins were also evaluated. Effect of rhSP-D on viability, NFκB activation, cytokine secretion and bacterial colonization of cervical vaginal epithelial cells was determined. rhSP-D significantly inhibited HIV-1 transfer from the multi-layered epithelial tissues to the basal PBMCs as compared to HIV-1 alone. Global gene expression profile of HIV-1 challenged VEC-100 tissues revealed differential regulation of genes and pathways majorly involved in inflammation, cell survival and transcription factors. Levels of Guanylate-binding proteins (GBPs) and interferon-inducible proteins were significantly upregulated suggesting an interferon host defense response. rhSP-D showed an inhibition in the levels of GBPs and rescued the cell adhesion molecules such as Claudin 2, 3, 4, 5 and Occludin, known to be down regulated by HIV-1 in primary vaginal cells. Importantly, rhSP-D conditioned VEC tissue supernatants did not enhance susceptibility of target cells to HIV-1. rhSP-D treated vaginal epithelial cells did not show any significant alteration in viability, NFκB activation and levels of immune mediators like IL-1RA, Elafin, SLPI, TGFβ, GRO-α, MIP-3α and RANTES. Bacterial colonization and direct toxicity assays revealed that rhSP-D did not adversely affect growth of vaginal commensals. Blockade of viral movement within the vaginal epithelium, inhibition of detrimental early gene signature and safety profile of rhSP-D suggests that topical formulation comprising rhSP-D may significantly curb the sexual transmission of HIV-1.

Citation: Pandit, H., Kale, K., Thakur, G., Rokade, S., Yamamoto, H., Kishore, U., Madan, T. and Fichorova, R. SP-D impedes transfer of HIV-1 from multi-layered vaginal epithelium with a distinct gene signature [Abstract]. In: Abstracts of the NGBT conference; Oct 02-04, 2017; Bhubaneswar, Odisha, India: Can J biotech, Volume 1, Special Issue (Supplement), Page 260. <https://doi.org/10.24870/cjb.2017-a244>