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Maneuvering of genital mucosa by HIV for successful transmission

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Genital mucosal transmission is a dominant mode of HIV infections worldwide. However, the primary barrier vaginal/cervical epithelial cells lack HIV receptors and the genital mucosal tissues have low pH and numerous soluble antiviral factors. Therefore, HIV needs to manipulate the mucosal tissue microenvironment for successful infection and spread. We obtained evidence to show that HIV exposure, without productive infection, induced human cervical epithelial cells to produce thymic stromal lymphopoietin (TSLP), an IL-7 like cytokine, which potently and uniquely activated dendritic cells (DC) to cause the recruitment and homeostatic expansion of autologous $CD4^+$ T cells for HIV infection. Blocking TSLP expression in the epithelial cells or its activity with neutralizing antibodies prevented the unique DC activation represented by specific chemokines that are important for the recruitment of CD4+ T cells. We investigated the epithelial cell surface molecule(s) HIV interacts with to induce NFkB-mediated signaling for TSLP expression. Vaginal SIV infection of rhesus macaques showed dramatic increases in TSLP expression concurrent infiltration of DC and $CD4^+$ T cells followed by enhanced SIV replication in the vaginal tissues within the first two weeks. These data suggest that epithelial cells represent the first target for HIV to trigger DC-mediated immune activation that facilitates viral replication in $CD4^+$ T cells during early vaginal HIV infection. Thus, TSLP may be important in acute HIV-1 infection to creating conducive environment for sustaining the small dose of the initial virus inoculum that crosses the mucosal barrier. Therefore, targeting TSLP can be a novel strategy against mucosal HIV-1 transmission.

Biography

Dr. Sastry is a Professor in the Department of immunology in Houston, TX, with joint appointment in the department of Veterinary Sciences, Bastrop, TX, at The University of Texas M. D. Anderson Cancer Center. His research over the past 20+ years supported by NIH and private funding in the broad areas of viral oncology and immunology focuses on understanding the biology, pathology and genetics of HPV-associated cancers and HIV-induced AIDS. The overall goal is to develop procedures and reagents for prediction, treatment and prevention by developing vaccines and therapeutics. He serves on NIH study panels and editorial boards of journals.