

Abstract:

Cohort studies of female commercial sex workers (CSWs) in Kenya were among the first to identify highly HIV-1-exposed seronegative (HESN) individuals. As natural resistance is usually mediated by innate immune mechanisms, we focused on determining whether expression and function of innate signaling pathways were altered locally in the genital mucosa of HESN CSWs. Our results demonstrated that selected pattern-recognition receptors (PRRs) were significantly reduced in expression in cervical mononuclear cells (CMCs) from HESN compared with the new HIV-negative (HIV-N) and HIV-positive (HIV-P) groups. Although baseline levels of secreted cytokines were reduced in CMCs of HESN, they were highly stimulated following exposure to ssRNA40 *in vitro*. Importantly, cervical epithelial cells from HESN also expressed reduced levels of PRRs, but Toll-like receptor 3 (TLR3) and TLR7 as well as nuclear factor- κ B and activator protein 1 were highly expressed and activated. Lastly, inflammatory cytokines interleukin (IL)-1 β , IL-8, and RANTES (regulated and normal T cell expressed and secreted) were detected at lower levels in cervicovaginal lavage of HESN compared with the HIV-N and HIV-P groups. Overall, our study reveals a local microenvironment of HIV resistance in the genital mucosa consisting of a finely controlled balance of basal immune quiescence with a focused and potent innate anti-viral response critical to resistance to sexual transmission of HIV-1.