Retrovirology

Oral presentation

Retrocyclins: Novel Circular Peptides Active Against HIV-1

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Heterosexual transmission through mucosal surfaces is one of the most common routes of HIV-1 spread. Topical microbicides are self-applied prophylactic agents, used to prevent vaginal and other mucosal transmission of HIV-1, which have the advantage of empowering vulnerable receptive partners to take effective measures for their own protection. In a search for candidate topical microbicides we discovered that retrocyclin, a unique θ-defensin synthetically constructed based on sequence data from its pseudogene, can potently prevent infection of CD4+ cells by both X4 and R5 HIV-1. While many studies have utilized simulants of mucosal fluid to test compounds, we are studying how whole human vaginal fluid and its functional components affect the activity and stability of peptide-based microbicides. We explored a novel, physiologically relevant approach to assess the ability of a candidate retrocyclin microbicide, RC-101, to inhibit HIV-1 infection of immunocompetent human cervicovaginal tissue. We revealed that 1) using a novel proteomic approach, human vaginal fluid contained at least 20 different cationic (poly)peptides with purported roles in innate host defense, 2) the cationic polypeptide fraction of vaginal fluid was required for innate anti-HIV-1 activity, 3) RC-101 retained full anti-HIV-1 activity in the presence of whole human vaginal fluid, 4) when applied apically to organotypical cervicovaginal epithelium, RC-101 was retained in the tissue, and 5) RC-101 prevented HIV-1 infection of immunocompetent organotypic cervicovaginal epithelium. Collectively, we have characterized the innate antiviral host defense factors within vaginal fluid, and developed a highly relevant *ex vivo* vaginal model suitable for peptide-based microbicide evaluation.