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Dual anti-HSV and anti-HIV activity of the lantibiotic Labyrinthopeptin A1

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Background

It has been shown that genital lesions and altered innate mucosal immunity caused by HSV-2 are important cofactors to increase the rate of HIV transmission and infection. Therefore, a product that inhibits HIV and HSV would have potential benefits in the prophylaxis against these sexually transmitted viruses. The labyrinthopeptin A1 (LabyA1) is a prototype peptide of a novel class of carbacyclic lantibiotics. Here, we extensively evaluated LabyA1 for its broad-spectrum activity against HIV and HSV.

Methods

Replication of HIV-1, HIV-2 and drug (e.g. tenofovir, maraviroc, raltegravir, saquinavir)-resistant viruses were evaluated in CD4+ T cell lines and in PBMCs. LabyA1 was also tested against HSV-1 and HSV-2 and HSV-resistant viruses (such as acyclovir). It was tested also in combination with other classes of anti-HIV/HSV drugs. EC50 values and potential synergy levels were calculated using CalcuSyn software. Potential cellular side-effects, cytokine induction, toxicity and growth inhibitions were also investigated.

Results

LabyA1 exhibited a consistent and broad anti-HIV activity (EC50: 0.70-3.3 μM) and anti-HSV activity (EC50: 0.29-2.8 μM). LabyA1 also inhibited viral cell-cell transmission between persistently HIV-infected T cells and uninfected CD4+ T cells (EC50: 2.5 μM) and inhibited the transmission of HIV captured on DC-SIGN to CD4+ T cells (EC50: 4.1 μM). LabyA1 behaves as a novel type of viral entry inhibitor. LabyA1 also demonstrated additive to synergistic effects in its anti-HIV-1 and anti-HSV-2 activity with anti(retro)viral drugs in dual combinations such as tenofovir, acyclovir, saquinavir, raltegravir and enfuvirtide. LabyA1 was equally active against all drug-resistant HIV and HSV strains. It did not induce any inflammatory cytokines/chemokines and did not affect the growth of vaginal Lactobacilli.

Conclusions

LabyA1 has profound dual antiviral activity. Based on the lack of toxicity on the vaginal Lactobacillus strains and its synergistic/additive profile in combination with all approved anti(retro)virals, it deserves further attention as a potential microbicide candidate in the prevention of sexually transmitted (HIV/HSV) diseases.

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