SAMMA, a mandelic acid condensation polymer, inhibits dendritic cell-mediated HIV transmission

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Abstract SAMMA, a mandelic acid condensation polymer, exhibits a broad antimicrobial activity against several sexually transmitted pathogens including human immunodeficiency virus (HIV). Here we demonstrated that SAMMA suppressed HIV transmission by dendritic cells (DCs), one of the first target cells for primary infection. The greatest inhibitory effect was achieved when SAMMA was present during the co-culture with target cells. The inhibitory effect of SAMMA on DC-mediated HIV transmission was not due to cytotoxicity. Analysis of the level of DC-associated HIV p24 antigen revealed that SAMMA prevented HIV internalization by DCs when the virus was pre-incubated with the compound. In contrast, pre-incubation of DCs with SAMMA followed by wash-off did not affect the amount of cell-associated HIV p24 antigen. In addition, SAMMA blocked HIV glycoprotein-mediated cell–cell fusion. This study suggests that SAMMA prevents HIV infection through multiple mechanisms.

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1. Introduction

Sexual transmission is the most common route of acquiring human immunodeficiency virus (HIV). Women account for nearly half of those infected worldwide and more than 70% in sub-Saharan Africa (UNAIDS report 2006). Women are more susceptible to HIV because of a higher prevalence of sexual transmitted infections (STIs) in addition to hormone changes [1,2]. As an effective vaccine against HIV infection is unlikely to be available in the near future, development of a safe and effective topical microbicide to prevent sexual transmission of HIV as well as other STIs becomes an urgent need. Indeed, studies in rhesus macaques support the concept that topical microbicides can prevent vaginal virus transmission [3–5].

Dendritic cells (DCs) present in the vaginal epithelium and lamina propria, are one of the first target cells for primary infection with simian immunodeficiency virus (SIV) and HIV [6–8]. DCs can capture HIV and present it to CD4\textsuperscript{+} T cells efficiently in vitro, suggesting that genital mucosa DCs may uptake and transmit HIV to the surrounding CD4\textsuperscript{+} T cells or to the draining lymph nodes [6–11]. HIV can establish infection by binding to CD4, mannose-binding C-type lectin receptor (MCLR), other MCLR like mannose receptor, and non-MCLRs on the surface of different subsets of DCs [12–16]. Therefore, it would be an important feature for an ideal topical microbicide to block DC-mediated HIV transmission.

SAMMA, a mandelic acid condensation polymer, has been shown to be a potential candidate as topical microbicide. SAMMA, a non-sulfonated polyanion, differs from N-9 (a detergent) or cellular sulfate (sulfonated polyanion), two microbicide candidates in clinical trials that not only failed to prevent but also enhanced HIV transmission in women ([17–19] and aidsinfo.nih.gov). It exhibits potent anti-HIV activity in vitro by interacting with HIV gp120 at a high affinity and subsequently blocking HIV entry [20,21]. Importantly, it also inhibits other sexually transmitted pathogens including herpes simplex viruses (HSV) 1 and 2, Chlamydia trachomatis, and Neisseria gonorrhoeae [20,22] that are associated with HIV enhancement [23–27]. In addition, SAMMA does not cause cytotoxicity in mammalian cells or affect the growth of commensal bacteria such as lactobacilli [22].

Here we evaluated the effect of SAMMA on DC-mediated HIV transmission. We demonstrated that SAMMA inhibited HIV capture and transfer by DCs as well as HIV glycoprotein-mediated cell–cell fusion. This study demonstrates that SAMMA can block HIV infection by interfering with HIV interaction with not only CD4 but also other receptors on various target cells, suggesting utilization of multiple mechanisms for HIV prevention.

2. Materials and methods

2.1. DC preparation and cell culture

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll-Hypaque gradient centrifugation. CD14\textsuperscript{+} monocytes were positively selected from PBMCs using CD14\textsuperscript{+} magnetic beads from Miltenyi Biotec, Inc. (Auburn, CA). Monocyte derived dendritic cells (MDDCs) were obtained by culturing CD14\textsuperscript{+} monocytes in the pres-
ence of IL-4 (100 U/ml, R&D Systems) and GM-CSF (1000 U/ml, R&D systems) for 6–7 days and cytokines were added every other day. This DC population has a CD14−, CD11c+, HLA-DR+, CD3−, and CD83+ phenotype. Autologous CD4+ T cells were treated with phytohemagglutinin (PHA) at 5 μg/ml for 48–72 h and subsequently cultured in complete RPMI with 10% fetal bovine serum (FBS) and supplemented with IL-2 at a concentration of 20–50 U/ml.

2.2. DC-mediated HIV transmission

To study DC-mediated HIV transmission, DCs were exposed to R5 strain HIVBaL or pseudotyped HIVJR-FL luciferase reporter virus in the presence or absence of SAMMA. Pseudotyped HIVJR-FL luciferase reporter virus was prepared as described previously [28]. After washing off, DCs were co-cultured with susceptible cells including PHA-activated primary CD4+ cells or HeLa-CD4 CCR5 cells. HIV p24 levels in the media were measured by ELISA (SAIC-Frederick Inc.) for a multiple-round infection assay, whereas luciferase activity in target cells was determined by a single-infection assay as described previously [29].

2.3. Cytotoxicity assay

DCs, activated primary CD4+ cells, or TZM-bl cells at 2–5 × 10^5 in a 96-well plate were treated with SAMMA at indicated concentrations for 2 h or three days at 37 °C. Cytotoxicity was determined by measuring the number of viable cells by the MTS assay (CellTiter 96 AQueous Non-Radioactive Cell Proliferation Assay, Promega, Inc.) according to manufacture’s instructions. MTS substrate was added to cells and cells were incubated at 37 °C for 1 h. The conversion of MTS into soluble formazan by dehydrogenase enzymes found in metabolically active cells was measured by quantifying of formazan products using absorbance at 490 nm in a microplate reader.

2.4. HIV capture

HIV-1 capture assay was performed as described elsewhere with modifications [30]. MDDCs were seeded at 2 × 10^5 per well in 96-well flat-bottom plates. HIV-1BaL (3 ng per well) was pre-incubated in the absence or presence of SAMMA for 1 h at 37 °C. DCs were then incubated with virus for 2 h at 4 °C for binding or 37 °C (for binding and internalization). Cells were washed four times to remove unbound virus and SAMMA and lysed with 1% Triton X-100. Cell-associated HIV p24 antigen was measured by p24 ELISA (NCI, Frederick).

To determine whether SAMMA interacted with cellular receptors on DCs and subsequently affected HIV capture, DCs were pre-incubated with SAMMA at 37 °C for 2 h before HIV exposure at 4 °C or 37 °C for 2 h. Cells were washed four times and the level of cell-associated HIV p24 antigen was measured by ELISA.

2.5. HIV glycoprotein-mediated cell–cell fusion

HeLa cells expressing Tat protein (HeLa-Tat) were transfected with the HIVJR-FL envelope plasmid (gift of D. Littman, New York University) for 48 h. HeLa-Tat cells at 5 × 10^5 expressing HIV glycoproteins were treated with SAMMA or T-20 (from ARRRP) at 37 °C for 1 h before addition to TZM-bl indicator cells (from ARRRP; gift of Drs. J.C. Kappes, and X. Wu), which express CD4, CXCR4 and CCR5 co-receptors. TZM-bl cells, seeded at 5 × 10^6 per well in a 48-well plate, contain HIV long terminal repeat (LTR)-driven beta galactosidase and luciferase reporter genes. When cell-cell fusion occurs, Tat proteins activate these reporter genes. After incubation for 8–24 h at 37 °C, TZM-bl cells were treated with lysis buffer (Promega Corp.) and luciferase activity (in relative light units [RLU]) was measured using Perkin-Elmer 1420 Luminometer.

3. Results

3.1. SAMMA blocked HIV transmission by DCs

Both intraepithelial and submucosal DCs and CD4+ T cells are the primary target cell populations for SIV and HIV-1 (reviewed in [6,8]). It has been shown that SAMMA at 100 μg/ml inhibits HIV infection (greater than 90%) in primary CD4+ T cells [20]. Here we investigated the effect of SAMMA on HIV-1 transmission by DCs. Human monocyte derived DCs (MDDCs) were exposed to replication-competent R5 virus HIVBaL at the presence or absence of SAMMA at 100 μg/ml for 2 h. An HIV-1 R5 strain was used as these strains are preferentially transmitted in primary infection [31]. DCs were washed and then co-cultured with autologous PHA-activated primary CD4+ T cells in the presence or absence of SAMMA at 100 μg/ml. HIV-1 infection was monitored by measuring the level of HIV p24 antigen in the media by ELISA. DCs in the absence of CD4+ T cells produced little virus (~7 ng/ml at days 9 and 14 after infection, data not shown) in comparison to DC-T cell co-culture that produced 800–1200 ng/ml (Fig. 1a, control). SAMMA blocked DC-mediated HIV transmission by greater than 99% when it was present during the all co-culture period (Fig. 1a).

Once immature DCs capture HIV in the vaginal mucosa, they can transfer virus to neighboring CD4+ T cells or migrate to other lymphoid organs. To determine whether SAMMA interacted with cellular receptors on DCs and subsequently affected HIV capture, DCs were pre-incubated with SAMMA at 37 °C for 2 h, washed four times with PBS before HIV exposure at 4 °C or 37 °C for 2 h. Cells were washed four times and the level of cell-associated HIV p24 antigen was measured by ELISA.

![Graphs](Fig. 1). SAMMA inhibits HIV transmission by DCs. (a) MDDCs (1.25–2 × 10^5 per well) were exposed to replication-competent R5 virus HIVBaL at MOI of 0.002 in the presence or absence of SAMMA at 100 μg/ml at 37 °C for 2 h. Cells were washed and co-cultured with autologous activated primary CD4+ T cells (1 × 10^5) in complete media in the presence or absence of SAMMA at 100 μg/ml. (b) HIVBaL was pre-incubated without (control) or with SAMMA at 37 °C for 1 h followed by addition to DCs (2 × 10^5) for 2 h in the absence or presence of the inhibitor. After washing four times with media, DCs (1.25 × 10^5) were incubated with activated primary CD4+ T cells (1 × 10^5) in the absence of SAMMA. HIV released into media was monitored by measuring the level of HIV p24 antigen at day 0, 5, 7, 9, 14 after infection. Data in (a) are means ± SD of duplicated samples and represent two independent experiments. In the wash-off setting (panel b), results from two different donors are shown.
to lymphatic tissue followed by HIV transmission to CD4+ T cells. An experiment was set up to simulate a possible in vivo scenario when SAMMA would be present only during HIV capture by DCs but absent during HIV transfer to CD4+ T cells in draining lymph nodes. HIV-1BaL was first exposed to SAMMA for 1 h followed by incubation with DCs for 2 h to allow HIV capture. DCs were then washed extensively before co-culturing with activated primary CD4+ T cells. In wash-off settings, SAMMA at 100 μg/ml inhibited HIV transmission by ∼50–90% at day 9 after infection depending on the donors (Fig. 1b). In addition, we observed the lack of increase in the level of p24 at day 14 after infection, suggesting residual SAMMA and or persistent effect of SAMMA on the cell after washing off. Taken together, results in Fig. 1 suggest that SAMMA can block HIV transmission in vaginal/cervical mucosa but its maximal effect is when it is present both for DC capture and T cell transfer.

To determine the effect of SAMMA on HIV transmission in trans, we used a replication-defective R5 strain HIVJR-FL pseudotyped virus containing a luciferase reporter gene to measure HIV transfer by DCs to target cells. Expression of luciferase provides a quantitative measure of a single-round of HIV infection [32]. MDDCs, capturing HIV primarily through MCLRs [33], were incubated with SAMMA, anti-DC-SIGN antibody, or mannose receptor ligand mannan, which blocks gp120 binding to C-type lectins [34], for 1 h followed by exposure to viruses for 2 h in the absence or presence of inhibitors or antibodies (Fig. 2a). Although CD4 is not the predominant receptor on MDDCs for the binding of HIV gp120 [33], DCs were also treated with anti-CD4 antibody in comparison to SAMMA (Fig. 2b). After 2 h incubation with HIV, DCs were extensively washed then added to HeLa cells expressing CD4 and CCR5, which provided a better luciferase read-out in comparison to primary CD4+ T cells. After incubation for 48 h, HIV transfer to HeLa-CD4. CCR5 cells was determined by measuring luciferase activity in the cells. SAMMA at 100 μg/ml effectively inhibited HIV transmission by DCs when it was present only during exposure of DCs to virus in a single-cycle infection assay (Fig. 2a and b). As expected, mannan inhibited the ability of DCs to transmit HIV. In agreement with previous reports [30,33,35], anti-DC-SIGN antibody partially blocked HIV transmission by DCs, although it completely blocked HIV transmission by a cell line expressing DC-SIGN by greater than 95% (data not shown). No effect was observed in samples treated with isotype control antibodies (Fig. 2b). Anti-CD4 antibody (Leu3a) at 10 μg/ml, which inhibited HIV infection in activated primary CD4+ T cells (data not shown), did not block DC-mediated HIV transmission when it was present during HIV capture by DCs (Fig. 2b).

We then assessed whether SAMMA could inhibit HIV transmission when added after DCs were exposed to HIV. MDDCs were exposed to HIV followed by incubation with SAMMA. The inhibitor was washed away before co-culture of DCs with target cells. SAMMA blocked HIV transmission in the wash-off setting (Fig. 2c). The inhibitory effect of SAMMA on HIV transmission by HIV-exposed DCs was similar when the inhibitor was present during the co-culture (add back) in a single-cycle infection assay.

3.2. SAMMA is not cytotoxic to DCs

To ensure that the inhibitory effect of SAMMA on DC-mediated HIV transmission was not due to cytotoxicity, we examined viability of DCs and CD4+ T cells in the presence of SAMMA by MTS assay. SAMMA had no effect on the viability of DCs or CD4+ T cells when present in the culture for three days at the dose up to 500 μg/ml, indicating that inhibition of DC-mediated HIV transmission was not associated with cytotoxicity (Fig. 3).

3.3. SAMMA blocked DC-mediated HIV capture

The ability of SAMMA to block DC-mediated HIV transmission when it was present only during the initial exposure of DCs to HIV suggests that SAMMA may interfere with HIV capture by DCs. To determine the effect of SAMMA...
on HIV capture by DCs, HIV-1 BaL was incubated in the absence (control) or presence of SAMMA at 100 μg/ml for 1 h at 37 °C before exposure to DCs for 2 h at 37 °C (for viral binding and internalization, Fig. 4a) or 4 °C (viral binding only, Fig. 4b). DCs were then washed extensively, lysed and cell-associated HIV p24 antigen was measured. SAMMA at 100 μg/ml blocked DC-mediated HIV capture by ~58–99% depending on the DC donors (Fig. 4a), which correlated with the effect of SAMMA on DC-mediated HIV transmission when SAMMA was only present during HIV capture (Fig. 1b). When DCs were exposed to HIV-1 BaL at 4 °C in the absence and presence of SAMMA, no significant difference was detected, indicating that SAMMA did not affect HIV binding to DCs (Fig. 4b). Thus, results in Fig. 4a and b suggest that SAMMA interfered with internalization of HIV by DCs.

To delineate whether SAMMA blocked DC-mediated HIV capture by acting on the cell, DCs were pre-incubated with SAMMA for 1 h at 37 °C and washed four times before exposure to HIV-1 BaL for 2 h at 4 °C (for binding) or 37 °C (for binding and internalization). DCs were then washed four times with PBS and lysed. Cell-associated HIV p24 antigen was measured by ELISA. When DCs were pre-treated with SAMMA and washed before HIV exposure, SAMMA did not block HIV binding or binding/internalization by DCs (data not shown and Fig. 4c), suggesting that inhibition of DC-mediated HIV capture is primarily due to the effect on the virus.

Fig. 3. SAMMA does not cause cytotoxicity in DCs and primary CD4+ T cells. DCs or activated primary CD4+ T cells (5 x 10⁵) were treated with SAMMA at 10, 100, 500 μg/ml for three days at 37 °C. Cytotoxicity was determined by measuring the number of viable cells by the MTS assay (Promega). MTS substrate was added to cells for 1 h at 37 °C. Data are means ± SD of triplicated samples and represent two independent experiments.

Fig. 4. SAMMA inhibits HIV capture by DCs. MDDC were seeded at 2 x 10⁵ per well in 96-well flat-bottom plates. HIV-1 BaL (3 ng per well) was pre-incubated in the absence (control) or presence of SAMMA for 1 h at 37 °C. DCs were then incubated with virus for 2 h at 37 °C (a) or 4 °C (b) in the absence (control) or presence of the inhibitor. Cells were washed four times to remove unbound virus and SAMMA and lysed with 1% Triton X-100. Cell-associated HIV p24 antigens were measured by p24 ELISA (NCI, Frederick). Data are means ± SD of duplicated samples. In (a), results from two donors are shown. In (b), results represent two independent experiments from two DC different donors. (c) DCs were treated without (control) or with SAMMA at 100 μg/ml at 37 °C for 1 h and washed four times with PBS followed HIV exposure for 2 h. HIV-exposed DCs were washed and lysed. Cell-associated HIV p24 antigen was measured by ELISA. Results represent two independent experiments from two donors.
3.4. SAMMA blocks HIV glycoprotein-mediated cell–cell fusion

SAMMA effectively blocked DC-mediated HIV transmission when the inhibitor was present during the co-culture. DC-mediated HIV transmission to CD4+ cells occurs at a cell–cell junction referred to as the infectious synapse [36–38]. The potent anti-HIV activity of SAMMA during the co-culture led us to investigate the effect of SAMMA on HIV glycoprotein-mediated cell–cell fusion. HeLa cells stably expressing Tat protein (HeLa-Tat cells) were transiently transfected with a vector expressing HIVJR-FL envelope glycoprotein for 48 h. HeLa-Tat cells expressing HIV glycoproteins were then incubated with SAMMA at 10, 100, and 1000 μg/ml for 1 h at 37 °C before addition to TZM cells, indicator cells that express CD4 and CXCR4 and CCR5 co-receptors and contain an HIV LTR-driven reporter gene. HIV Tat proteins synthesized in cells expressing HIV glycoproteins activate the HIV LTR in the indicator cells after cell–cell fusion occurs. The fusion inhibitor, T-20, at 100 nM was included to ensure the specificity of this assay. As expected, T-20, which blocks HIV trans infection of target cells by HIV-exposed MDDCs [39], inhibited HIV glycoprotein-mediated cell–cell fusion. SAMMA at 10 μg/ml inhibited HIV glycoprotein-mediated cell–cell fusion by 47%. A greater inhibitory effect was achieved with SAMMA at 100 μg/ml (>98%) and 1000 μg/ml (>99%) (Fig. 5a). SAMMA also blocked cell–cell fusion when the donor cells expressed HIV X4 envelope proteins (data not shown).

To ensure inhibition of HIV glycoprotein-mediated cell–cell fusion by SAMMA was not due to cytotoxicity, HeLa-Tat or TZM-bl cells were treated with SAMMA at various concentrations for 24 h. Cell viability was determined by MTS assay. No significant difference in cell viability between cells in the absence or presence of SAMMA at up to 1000 μg/ml (Fig. 5b and data not shown), indicating that the inhibitory effect on cell–cell fusion in Fig. 5a was not due to cytotoxicity.

4. Discussion

SAMMA has been shown to be a potential candidate for topical microbicides because of its broad antimicrobial and antiviral activities against C. trachomatis, N. gonorrhoeae, HIV and HSV [20–22]. Importantly, it does not cause cytotoxicity in many cell lines and primary cells including human CD4+ T cells and macrophages (Fig. 3, [20]). Here we investigated the effect of SAMMA on DC-mediated HIV transmission, which is an important initial step in sexual transmission of HIV. SAMMA is not cytotoxic for DCs and primary activated CD4+ T cells when present in the culture for 3 days. SAMMA effectively blocked HIV transmission by DCs when present during co-culture period. In addition, SAMMA blocked HIV transmission when it was incubated with HIV-exposed DCs followed by wash-off before co-culture with target cells, suggesting its inhibitory effect persists. The observation that SAMMA suppressed HIV glycoprotein-mediated cell–cell fusion by greater than 95% suggests one possible mechanism by which this compound inhibits HIV transfer when present during the co-culture period. SAMMA is likely to inhibit glycoprotein-mediated cell–cell fusion through interfering with the interaction between HIV glycoprotein and CD4 receptors, although it remains to be determined whether SAMMA can block the step of viral fusion.

We demonstrated that SAMMA blocked DC-mediated HIV-1 transmission by preventing HIV capture by DCs (Fig. 4). Specifically, SAMMA affected the step of HIV internalization [8]. Further studies using specific inhibitors targeting specific steps such as endocytosis or fusion are required to dissect in detail the mechanism by which SAMMA inhibits DC-mediated HIV capture. We demonstrated that SAMMA has a similar inhibitory profile to mannan and greater than anti-DC-SIGN or anti-CD4 antibodies (Fig. 2a and b), suggesting that inhibition of capture followed by transfer may be mediated by blocking HIV interactions with other MCLRs rather than DC-SIGN or CD4. Macrophage mannosе-receptors and an unidentified trypsin-resistant CLR have been reported to contribute to gp120 binding in MDDCs [33]. It remains to be determined whether SAMMA interferes with HIV capture by these receptors on the surface of DCs. In addition, the varying abundance of specific receptors among different donors may contribute to differential inhibitory effects of SAMMA on DC-mediated HIV capture and transmission in wash-off settings (Fig. 1b and 4a). The incomplete block of

Fig. 5. SAMMA inhibits HIV glycoprotein-mediated cell–cell fusion. HeLa-Tat cells were transfected HIVJR-FL envelope plasmid for 48 h. Cells were then treated with a fusion inhibitor T-20 or SAMMA at 37 °C for 1 h before addition to TZM cells, indicator cells expressing CD4, CXCR4 and CCR5 and containing a luciferase reporter gene driven by HIV LTR. After incubation at 37 °C for 24 h, luciferase activity was measured. Data are means ± SD of duplicated samples and represent three independent experiments. (b) Viability of TZM-bl cells in the presence of SAMMA at various concentrations for 48 h was determined by MTS assay as described in Fig. 3.
trans infection when SAMMA is present only during DC incubation as well as variation in effectiveness with different donor DCs supports the use of SAMMA in combination rather than alone. Nevertheless, our study and previous reports suggest that several mechanisms are involved in the anti-HIV effect of SAMMA [20,21].

SAMMA also inhibited HIV transfer from HIV-exposed DCs to the indicator cells when added following HIV capture and washed off before co-culture. The sustained effect on HIV transfer from HIV-exposed DCs after washing off has been reported previously with the inhibitors such as CD4-IgG2 and antimicrobial peptides, although the mechanism is not clear [39,40]. It is of note that PRO2000, a sulfonated anionic polymer in phase III clinical trials for topical microbicides against HIV, exhibits a similar inhibitory effect on HIV transmission from HIV-exposed DCs in the wash-off setting (Natalia Teleshova, manuscript submitted). Like CD4-IgG2, PRO2000 and SAMMA bind to HIV gp120 [21]. Presumably, residual SAMMA and or persistent effects of SAMMA on HIV-exposed cells inactivates HIV or alters the formation of virological synapse [37,38], resulting in the inhibition of HIV transmission.

In conclusion, our study demonstrates that SAMMA inhibited DC-mediated HIV transmission through blocking DC-mediated HIV capture and subsequent transfer. SAMMA also efficiently inhibited HIV glycoprotein-mediated cell-cell fusion, supporting its potential as an anti-HIV topical microbicide in combination with other inhibitors.

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