Background

The shock and kill eradication strategy is based on the hypothesis that latently infected cells can be targeted for elimination by the host immune response or viral cytopathic effects once the latent virus is reactivated. The identification of pharmacological compounds able to activate transcription from latent viruses without inducing cell activation is of utmost importance in order to pursue this approach.

Chromatin plays a pivotal role in the establishment and maintenance of transcriptional latency. By positioning the highly repressive Nuc-1 downstream of the transcriptional start site, the BAF chromatin remodeling complex is a major determinant of transcriptional latency. By positioning the highly repressive Nuc-1 downstream of the transcriptional start site, the BAF chromatin remodeling complex is a major determinant of HIV-1 latency.

Due to its prominent role in establishment and maintenance of latency, BAF is an attractive molecular target in HIV-1 eradication efforts. Here we have tested a panel of BAF inhibitors (BAFi's) for their potential use as latency reversal agents (LRAs).

Small molecule inhibitors of BAF activate latent HIV:

A panel of compounds previously characterized as BAF inhibitors were tested for their ability to activate HIV-1 transcription in a latent cell line.

Two compounds significantly induced HIV transcription without affecting cell viability: A11, or Pyrroth methine (Pyr), is an FDA approved licensed anti-protozoan drug which has been used to control opportunistic infections in HIV-1 infected patients. CD9, or Caffeic acid phenetyl ester (CAPE), is a bioactive compound shown to possess anti-inflammatory and immunomodulatory capacities.

Activation of HIV transcription was associated with the displacement of the BAF complex from the HIV promoter as shown by ChIP experiments.

Methods

- Activation of latent HIV-1 following treatment with BAFi's was determined in cell line models of latency harboring a latent copy of a minimal HIV genome (LTR-TAT-GFP).
- Active compounds were further characterized at the molecular level by Western Blot, chromatin immunoprecipitation (ChIP) and FAIRE assays.
- To determine whether BAFi's synergistically interact with known LRAs, we evaluated activation of transcription in latently infected cell lines following treatment with BAFi's alone or in combination with HDAC inhibitors and PKC activators.
- BAFi's activity was confirmed in primary models of latency and in cells obtained from virally suppressed HIV-1 infected patients.

Results

BAFi's reverse HIV-1 latency in primary infected CD4+ T cells without inducing cell activation:

Transcription from the HIV-1 promoter is activated following treatment with BAFi's in primary CD4 T cells infected in vitro.

Treatment with BAFi's does not induce activation or proliferation of primary CD4 T cells.

Treatment with BAFi's either alone or in combination with Prostratin results in latency reversal in latently infected cells obtained from HIV-1 suppressed patients.

Conclusions

- BAF complex inhibitors (BAFi's) activate latent HIV-1 in cell line models of latency
- BAFi's in combination with HDAC inhibitors and PKC activators synergistically activate latent HIV-1
- PYR and CAPE reverse HIV-1 latency in primary cell models of latency and in cells obtained from HIV-1 patients
- Our data highlight the clinical potential of BAF inhibitors for inclusion in combinatorial therapy to reverse HIV-1 latency.