{Alpha}1Proteinase inhibitor regulates CD4+ lymphocyte levels and is rate limiting in HIV-1 disease.

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Abstract

BACKGROUND:

The regulation of adult stem cell migration through human hematopoietic tissue involves the chemokine CXCL12 (SDF-1) and its receptor CXCR4 (CD184). In addition, human leukocyte elastase (HLE) plays a key role. When HLE is located on the cell surface (HLE(CS)), it acts not as a proteinase, but as a receptor for {Alpha}(1)proteinase inhibitor ({Alpha}(1)PI, {Alpha}(1)antitrypsin, SerpinA1). Binding of {Alpha}(1)PI to HLE(CS) forms a motogenic complex. We previously demonstrated that {Alpha}(1)PI deficiency attends HIV-1 disease and that {Alpha}(1)PI augmentation produces increased numbers of immunocompetent circulating CD4(+) lymphocytes. Herein we investigated the mechanism underlying the {Alpha}(1)PI deficiency that attends HIV-1 infection.

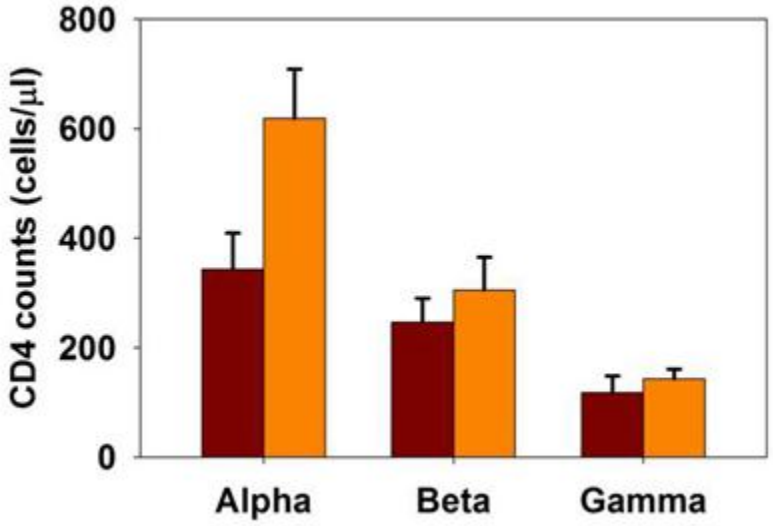
METHODS AND FINDINGS:

Active {Alpha}(1)PI in HIV-1 subjects (median 17 μM, n=35) was significantly below normal (median 36 μM, p<0.001, n=30). In HIV-1 uninfected subjects, CD4(+) lymphocytes were correlated with the combined factors {Alpha}(1)PI, HLE(CS) (+) lymphocytes, and CXCR4(+) lymphocytes (r(2)=0.91, p<0.001, n=30), but not CXCL12. In contrast, in HIV-1 subjects with >220 CD4 cells/μl, CD4(+) lymphocytes were correlated solely with active {Alpha}(1)PI (r(2)=0.93, p<0.0001, n=26). The monoclonal anti-HIV-1 gp120 antibody 3F5 present in HIV-1 patient blood is shown to bind and inactivate human {Alpha}(1)PI. Chimpanzee {Alpha}(1)PI differs from human {Alpha}(1)PI by a single amino acid within the 3F5-binding epitope. Unlike human {Alpha}(1)PI, chimpanzee {Alpha}(1)PI did not bind 3F5 or become depleted following HIV-1 challenge, consistent with the normal CD4(+) lymphocyte levels and benign syndrome of HIV-1 infected chimpanzees. The presence of IgG-{Alpha}(1)PI immune complexes correlated with decreased CD4(+) lymphocytes in HIV-1 subjects.

CONCLUSIONS:

This report identifies an autoimmune component of HIV-1 disease that can be overcome therapeutically. Importantly, results identify an achievable vaccine modification with the novel objective to protect against AIDS as opposed to the current objective to protect against HIV-1 infection.

Figure 1. Improvement in CD4 counts in HIV-1 patients following weekly infusions with {Alpha}1PI.
Average CD4 counts before a_1PI augmentation therapy (**red bars**) were determined in 3 HIV-1 patients Alpha**,** Beta,and Gamma to be 344±66 (n=4), 247±44 (n=10), and 118±31 (n=9) cells/ml, respectively. All patients were at different stages of HIV-1 disease progression and were on antiretroviral medication with adequate suppression of virus. Patients were administered weekly infusions of a_1PI augmentation therapy (120 mg/kg) for 12 weeks (Alpha) or 8 weeks (Beta and Gamma). The average CD4 counts following 2 wks of a_1PI augmentation therapy (**orange bars**) in patients Alpha, Beta, and Gamma were 618±90 (n=11), 305±60 (n=7), 143±18 (n=7), respectively. Improvement in CD4 counts was 80%, 24%, and 21%, respectively. Patient Alpha (47 yrs old) had been infected for 5 yrs and had exhibited below normal CD4 counts for more than 1 yr. Patient Beta (53 yrs old) had not exhibited CD4 counts in the normal range for more than 20 years. Patient Gamma (70 yrs old) had been unaware that he was infected for many yrs and had lost the capacity to respond to antigen (positive PPD followed by negative PPD). For additional information about this clinical trial (ClinicalTrials.gov NCT01370018) please refer to open-access eBook chapter Bristow, C.L., et al. {Alpha}$_1$Antitrypsin therapy increases $CD4^+$ lymphocytes to normal values in HIV-1 patients. In: M. Alfano, eds. Soluble factors mediating innate immune responses to HIV infection. Bentham Science Publishers.2010: 102-110.


800
600
400
200
0
CD4 counts (cells/μl)
Alpha
Beta
Gamma