Self Antigen Prognostic for Human Immunodeficiency Virus Disease Progression

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We have recently found that an extracellular protein, α₁ proteinase inhibitor (α₁PI; α₁ antitrypsin), is required for in vitro human immunodeficiency virus (HIV) infectivity outcome. We show here in a study of HIV-seropositive patients that decreased viral load is significantly correlated with decreased circulating α₁PI. In the asymptomatic category of HIV disease, 100% of patients manifest deficient levels of active α₁PI, a condition known to lead to degenerative lung diseases and a dramatically reduced life span. Further, HIV-associated α₁PI deficiency is correlated with circulating anti-α₁PI immunoglobulin G. These results suggest that preventing HIV-associated α₁PI deficiency may provide a strategic target for preventing HIV-associated pathophysiology.

In general, proteinase inhibitors are inhibitory for a single class of proteinases, often resulting in mutual inactivation. On the other hand, proteinases may inactivate many classes of inhibitors without being inactivated themselves and, in the process, may produce bioactive fragments, e.g., complement fragments. The proteinase inhibitor in serum exhibiting the greatest concentration is α₁PI, and the proteinase inhibitor encompassing the broadest spectrum is α₂ macroglobulin (α₂M). Multiple molecular conformations of active and inactive α₁PI are known to exist and to be receptor recognized. For example, active α₁PI has been found to react with surface-associated human leukocyte elastase (HLE), and inactive α₁PI has been found to react with the well-characterized scavenger receptor, α₂M receptor—low-density-lipoprotein receptor-related protein (α₂MR-LRP) (2, 21). The highly conserved α₁M uniquely inhibits all four classes of proteinases and exhibits a receptor-recognized conformation involved in signaling as well as an α₂MR-LRP-recognized conformation (17). A significant body of evidence suggests that receptor recognition of the multiple forms of circulating proteinase inhibitors results in activation of discrete cellular subsets of the mononuclear phagocyte system (27).

Whereas α₁PI covalently inhibits the catalytic site of HLE, it has been shown that in certain situations the association of HLE with α₂M in plasma is favored (6). When proteinases are complexed with α₂M, proteolysis of low-molecular-weight peptides and cytokines can persist. The balance between available HLE activity, the inhibitor α₁PI, and the substrate-restricting α₂M represents a tightly regulated mechanism for discrete targeting of proteolytic activity in tissues. It has been shown that inter-α-trypsin inhibitor (IαI) uniquely acts as a shuttle by transferring HLE to α₁PI or α₂M (25). It is the active site of IαI which is identical with the principle HIV-neutralizing determinant in the V3 loop, and it is this region of the V3 loop which has been shown to reversibly inhibit proteinases (1). This suggests the possibility that HIV envelope proteins themselves may disrupt the homeostasis between proteinases and proteinase inhibitors.

The importance of maintaining a balance in proteinase inhibitor ratios was dramatically demonstrated more than two decades ago. Ohlsson and Laurell injected two volunteers intravenously with α₁PI or α₂M less than half saturated with radiolabeled HLE or trypsin (20). Rapid clearance of α₂M complexes and α₁PI complexes was shown to be mediated by the mononuclear phagocyte system and to be accompanied by transient circulatory changes in some circumstances. Intravenous injection in dogs resulted in shock and death whenever the concentration of active proteinase exceeded that of α₂M, even though circulating α₁PI was less than half saturated with proteinase (19). The concept that HLE and α₁PI might impact HIV infectivity originated following the observations that gp120 exhibits a proteinase-inhibiting domain (1) and that CD4, the T-lymphocyte antigen receptor, elastase, and α₁PI are functionally associated during antigen-specific lymphocyte activation (8). Evidence that α₁PI and cell surface HLE participate during HIV infectivity (7) (C. L. Bristow, unpublished data) suggested the hypothesis that α₁PI or α₂M concentrations might be altered during HIV disease.

MATERIALS AND METHODS

**Serum specimens.** Sera from healthy volunteers were collected after obtaining informed consent. Sera from HIV-infected patients were excess specimens reserved from previous studies for which informed consent had been obtained. HIV RNA in serum was quantified by PCR using the Amplicor HIV-1 Monitor Test (Roche Diagnostics, Branchburg, N.J.) by the Retrovirology Core Laboratory, University of North Carolina (UNC)—Chapel Hill, using procedures recommended by the manufacturer. Clinical category of disease progression at the time of specimen collection was determined using 1993 Centers for Disease Control and Prevention classification criteria. The clinical parameters examined included HIV RNA, lymphocyte markers, demographic characteristics, known infectious diseases, and antiretroviral therapy. In this study, 44% category A1-A2, 57% category B1-B2, and 58% AIDS patients had or were receiving azidothymidine therapy, and none were receiving HIV-specific protease inhibitors. Characteristics not presented herein were found not to contribute significantly to the analysis. All measurements, chart extraction, and data analysis were performed in a blinded fashion. Data were excluded from analysis if the sera had not been maintained at −80°C prior to analysis, the patient charts could not be located, or the patient charts indicated no evidence of HIV infection.

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Quantitation of α1M and α1PI and T-cell markers. Methods for quantitating active α1M and α1PI by determination of elastase inhibitory capacity have been described elsewhere (6). Total α1PI was determined by enzyme-linked immunosorbent assay (ELISA). Inactive α1PI was expressed as the ratio of total α1PI and active α1PI. Measurements of CD4+, CD8+, and CD3+ cells were performed by the Flow Cytometry Laboratory, UNC Hospitals. Normal values were determined from 100 healthy donors (Janet Mantell and Cindy Evoy, unpublished results). Data were not normally distributed, and all comparisons were made using nonparametric methods. Medians among clinical categories were compared by using Kruskal-Wallis one-way analysis of variance. Comparison of medians between pairs of clinical categories was done by using the Mann-Whitney rank sum test. Correlation was measured using the Pearson product moment correlation, and linear regression was measured by computer-fit least-squares analysis.

RESULTS

α1PI levels in clinical category of HIV disease. The α1PI and α1M levels were quantitated in the sera from 68 HIV-seropositive patients and 30 seronegative volunteers (Table 1). None were being treated with HIV-specific protease inhibitors at the time of blood collection. In the normal subjects studied here, the mean value for total α1PI was 36.0 ± 13.9 μM and ranged from 18 to 53 μM between the 5th and 95th percentiles (Fig. 1). The mean α1M concentration in the present study was 3.36 ± 1.82 μM and ranged from 1.26 to 5.57 μM between the 5th and 95th percentiles. Values for α1PI and α1M determined here are consistent with previous studies (5, 12).

The total concentration of α1PI in an individual serum sample represents a unique mixture of active and inactive α1PI. In health, the active concentration has been found to represent 90 to 100% of total α1PI concentration (6). In the normal subjects studied here, the mean value for active α1PI was 33.8 ± 12.5 μM and ranged from 18 to 48 μM between the 5th and 95th percentiles. The mean value for inactive α1PI was 2.3 ± 7.2 μM and ranged from 0 to 11 μM between the 5th and 95th percentiles. Consistent with previous studies, population values were found not to be normally distributed, necessitating statistical comparisons using medians (5). Comparison of normally healthy subjects, asymptomatic (clinical categories A1 and A2), symptomatic pre-AIDS (clinical categories B1 and B2), and AIDS (clinical categories A3, B3, and C1 to C3) categories of HIV disease revealed significant differences in the concentrations of total (P < 3 × 10−7), active (P < 2 × 10−5), and inactive (P < 3 × 10−9) α1PI in serum. Median values for each clinical category were compared to normal values by using the Mann-Whitney rank sum test. Individual values and medians are depicted in Fig. 1. Values for HIV RNA were normally distributed. Analysis of variance revealed no significant difference in CD8 levels between categories A1, A2, and B1, B2 and significant differences between categories C1, C2, and AIDS (P < 0.01). Analysis of variance revealed no significant differences in HIV RNA between categories A1, A2, and B1, B2 and significant differences between categories A1, A2, and AIDS (P < 0.0001) and B1, B2, and AIDS (P = 0.0008). Values in boldface are significantly different from normal (P < 0.0001). ND, not detectable.

TABLE 1. Parameters of HIV disease progression

| Category (n) | CD4 (cells/μl) | CD8 (cells/μl) | HIV RNA (log_{10} copies/ml) | Active α1PI concn (μM) | Inactive α1PI concn (μM) | Total α1PI concn (μM) | α1M concn (μM) |
|-------------|---------------|---------------|----------------------------|------------------------|--------------------------|-----------------------|---------------|
| Normal (30) | 1,415 ± 307   | 850 ± 203     | ND                         | 33.8 ± 12.5†           | 2.3 ± 7.2                | 36.0 ± 13.9           | 3.36 ± 1.82   |
| A1,A2 (18)  | 549 ± 302     | 927 ± 306     | 3.16 ± 0.64                | 12.2 ± 4.5             | 44.5 ± 40.0              | 56.7 ± 39.5           | 2.91 ± 1.35   |
| B1,B2 (14)  | 274 ± 50      | 848 ± 622     | 3.63 ± 0.65                | 37.7 ± 28.7            | 113.5 ± 89.3             | 151.2 ± 80.5         | 4.13 ± 2.95   |
| AIDS (36)   | 67 ± 63       | 499 ± 317‡    | 4.31 ± 0.78‡               | 26.5 ± 22.6            | 31.3 ± 39.2              | 57.8 ± 39.0           | 4.51 ± 2.75   |

* Data are represented in Fig. 1. Normal values for T-lymphocyte distribution in 100 healthy donors were determined by the Flow Cytometry Laboratory, UNC Hospitals. All other normal values were determined in the sera of 30 healthy donors as described in the text. † Values for α1PI were not normally distributed. A comparison of median values by Kruskal-Wallis analysis of variance on ranks in the normal, asymptomatic, symptomatic pre-AIDS, and AIDS categories of HIV disease revealed significant differences in the concentrations of total (P < 3 × 10−7), active (P < 2 × 10−5), and inactive (P < 3 × 10−9) α1PI in serum. Median values for each clinical category were compared to normal values by using the Mann-Whitney rank sum test. Individual values and medians are depicted in Fig. 1. Values for HIV RNA were normally distributed. Analysis of variance revealed no significant difference in CD8 levels between categories A1, A2, and B1, B2 and significant differences between categories C1, C2, and AIDS (P < 0.01). Analysis of variance revealed no significant differences in HIV RNA between categories A1, A2, and B1, B2 and significant differences between categories A1, A2, and AIDS (P < 0.0001) and B1, B2, and AIDS (P = 0.0008). Values in boldface are significantly different from normal (P < 0.0001). ND, not detectable.
tions of active $\alpha_1$PI of $>20$ $\mu$M, the odds were 11:1 that CD4$^+$ cell counts were $<300$ cells/$\mu$L ($P = 0.01$) in the HIV-seropositive population. As would be expected, active $\alpha_1$PI was elevated in 29% of symptomatic pre-AIDS patients and in 11% of AIDS patients.

In the asymptomatic category of disease, increased HIV RNA was found to be correlated with increased total $\alpha_1$PI ($P < 0.04$) but not with CD4$^+$ levels. Further, HIV RNA was neither correlated with CD4$^+$ levels nor total $\alpha_1$PI in symptomatic and AIDS patients. Increased HIV RNA was found to be correlated with decreased CD4$^+$ levels when all clinical categories were included in the analysis ($P < 0.00005$). These results support previous findings that decreased $\alpha_1$PI is associated with decreased HIV production. Comparison of the sensitivities and specificities of $\alpha_1$PI, CD4, and HIV RNA measurements in determining the clinical category of HIV disease in the patient population represented here suggests that measuring $\alpha_1$PI could potentially provide a significant improvement in defining clinical course (Table 2).

Inactive $\alpha_1$PI was found to be elevated in 78% of asymptomatic, in 86% of symptomatic pre-AIDS, and in 64% of AIDS patients. The etiologic mechanisms of $\alpha_1$PI inactivation might involve proteolytic inactivation, oxygenation, diminished synthesis, and autoimmune reactivity. A state of dysregulated proteolysis has been shown to exist in HIV disease (23), and this results in generalized diminution in circulating competent proteinase inhibitors.

Like $\alpha_1$PI, $\alpha_2$M can be inactivated by proteinase interaction, as well as by oxygenation. In support of uncontrolled proteolysis, among symptomatic pre-AIDS patients 40% were elevated and 30% were deficient in active $\alpha_2$M concentration. However, 80% of asymptomatic patients and 76% of AIDS patients were within the normal limits for $\alpha_2$M, and this reflects a disposition of controlled proteinase activity in these

### TABLE 2. Sensitivities and specificities of $\alpha_1$PI, CD4, and HIV RNA as prognostic indicators for transition between clinical categories in HIV disease

| Test   | Disease progression | Sensitivity (%) | Specificity (%) |
|--------|---------------------|----------------|-----------------|
| Total $\alpha_1$PI | A1,A2 to B1,B2 | 77.8 | 100 |
|        | B1,B2 to AIDS | 100 | 80.6 |
| CD4    | A1,A2 to B1,B2 | 83.3 | 92.9 |
|        | B1,B2 to AIDS | 100 | 97.2 |
| HIV RNA| A1,A2 to B1,B2 | 66.7 | 78.6 |
|        | B1,B2 to AIDS | 85.7 | 69.4 |

*Sensitivities and specificities were determined from the data represented in Fig. 1 using CART (classification and regression tree) analysis by the Biostatistics Core of the UNC Center for AIDS Research."
TABLE 3. Circulating α1PI-specific IgG immune complexes in HIV disease

| Category (n) | Anti-α1PI IgG m405/min ± SD (%)|
|-------------|--------------------------------|
|             | Negative | Positive | Negative and positive |
| A1,A2 (18)  | 13.4 ± 1.5 (11) | 44.5 ± 18.3 (89) | 41.1 ± 20.0 |
| B1,B2 (14)  | 13.5 ± 3.1 (36) | 50.1 ± 23.5 (64) | 37.0 ± 26.0 |
| AIDS (36)   | 8.7 ± 5.7 (50) | 36.8 ± 14.8 (44) | 21.2 ± 17.2 |

*Values were scored as positive if they exceeded 2 standard deviations above the mean value detected in 17 normal control sera at pH 7.8 (11.2 ± 8.4 m405/min) or at pH 3.0 (9.5 ± 6.1 mOD/min).

**Means were normally distributed. Comparison of mean values by analysis of variance revealed significantly lower values in AIDS patients than in asymptomatic (P < 0.0005) or symptomatic pre-AIDS (P < 0.03) patients. Actual m405/min values were correlated with CDs+ cell counts (P < 0.008) and CD8+ cell counts (P < 0.002) in the HIV-seropositive patients and with α1PI deficiency (P < 0.05) in the asymptomatic category. The frequency of patients positive for anti-α1PI IgG in each category was correlated with CDs+ cell counts (r² = 0.999, P < 0.01) but not with CD8+ cell counts (P < 0.2). Data are represented in Fig. 2.

Clinical categories. The α2M concentrations in HIV disease, including all clinical categories, were not significantly different from normal, and this suggests that deficient levels of α1PI could not be completely explained by dysregulated proteolysis or oxygenation. Significantly, in AIDS, but not in other clinical categories of disease, α2M levels were correlated with active α1PI (P < 6 × 10⁻⁴) and with inactive α1PI (P < 0.04), suggesting that mechanisms other than dysregulated proteolysis were involved in producing increased levels of inactive α1PI in the asymptomatic category. Further, the recovery in the circulating active α1PI concentration during the symptomatic stages of disease suggested that the synthesis of α1PI may not be impaired and that alternative processes could be responsible for acquired deficiency. A previous study has demonstrated no difference in α1PI synthesis during AIDS in contrast to an increased synthesis of the acute-phase C-reactive protein (11).

Anti-α1PI in HIV disease. Since autoantibodies recognizing multiple cytokines and cellular proteins are known to occur in HIV disease (14), the potential for an autoimmune process in producing decreased active α1PI was examined. Antibodies recognizing immobilized α1PI were not discernible in serum from this patient population by traditional ELISA (data not shown). However, it was found that α1PI-anti-α1PI immune complexes were detectable by capturing them with immobilized anti-α1PI and detecting them with anti-human IgG. Control sera from 17 normal subjects and 1 subject with inherited α1PI deficiency were found to have background values of 11.2 ± 8.4 milliabsorbance at 405 nm (m405/min) and to range between 0.9 and 26.0. In contrast, 56% of asymptomatic, 57% of symptomatic pre-AIDS, and 31% of AIDS patients exceeded the mean control value by 2 standard deviations (Table 3). The high concentration of α1PI in serum suggested that the appearance of anti-α1PI would rapidly produce immune complexes, precluding detection by this method. It was further considered that immune complex formation might obscure α1PI epitopes, preventing capture using anti-α1PI and resulting in underestimation. We have previously shown in insulin-dependent diabetes mellitus that insulin–anti-insulin immune complexes are obscured in this manner (28). We determined that acidification of serum allows dissociation of immune complexes and that neutralization of acidified serum in the presence of competing radiolabeled ligand allows the detection of insulin–anti-insulin immune complexes. Using a modification of this approach, acidification and neutralization of sera in the presence of immobilized competing anti-α1PI allowed detection of α1PI-anti-α1PI immune complexes in an additional 33% of asymptomatic patients, an additional 7% of symptomatic pre-AIDS, and an additional 14% of AIDS patients. Background values (m405 per minute) in normal control sera were not influenced by acidification and neutralization. Overall, 89% of asymptomatic, 64% of symptomatic pre-AIDS, and 44% of AIDS patients had detectable anti-α1PI IgG, and this decline in anti-α1PI IgG is consistent with the decline in specific antibody response during AIDS. An increased anti-α1PI level was correlated with decreased active α1PI in the asymptomatic category of HIV disease (P < 0.05). Increased anti-α1PI was correlated with increased inactive α1PI in symptomatic (P < 0.03) and AIDS patients (P < 0.03), and this suggests that α1PI autoimmune antibodies are responsible in part for acquired α1PI deficiency. In patients with detectable anti-α1PI IgG immune complexes, the odds were 3.6:1 that active α1PI would be deficient (P < 0.01). Further, in AIDS patients, the mean reactivity (m405 per minute) was significantly lower than in the other clinical categories (P < 0.002, Fig. 2), and this result is consistent with the decline in detectable anti-α1PI. The correlation between α2M and active and inactive α1PI in AIDS suggests that infection-related dysregulated proteolysis also contributes to the deficiency in α1PI detected.
Significantly, as is true for viral RNA, the actual $m_4_{	ext{apo}}$ per minute values for circulating anti-$\alpha_1$PI IgG immune complexes, including all clinical categories, were correlated with CD4+ cell counts ($P < 0.003$) and CD8+ cell counts ($P < 0.03$). The frequency of patients in each clinical category having circulating anti-$\alpha_1$PI IgG immune complexes was inversely related to CD4+ cell counts ($r^2 = 0.999$, $P < 0.01$) but not with CD8+ cell counts ($P < 0.2$; data not shown). These data suggest that in symptomatic pre-AIDS and AIDS, lymphocyte population abnormalities may be responsible in part for the decline in $\alpha_1$PI autoimmunity antibodies.

Evidence that the V3 loop of gp120 contains a domain identical to the active site of InI and inhibits proteolytic activity in certain circumstances (1) suggested that gp120 and $\alpha_1$PI might share antigenic epitopes. To determine the potential for antigenic mimicry, immunoreactivity for $\alpha_1$PI by antibodies specific for gp120 was examined by ELISA. Significant binding to $\alpha_1$PI was detected by antibodies recognizing epitopes near the fusion domain but not epitopes near the V3 loop. Binding of anti-gp120 to $\alpha_1$PI was competitively inhibited by gp120, suggesting that molecular mimicry may explain this epitope specificity. Comparative analysis of the carboxyl terminus amino acid sequence of $\alpha_1$PI and the HIV peptide sequence recognized by the immunoreactive monoclonal antibody revealed considerable homology. Significantly, these sequences are flanked by the hydrophobic chemotactic pentapeptide domain of $\alpha_1$PI (FXFXX, where X = V, L, I, or M) and the hydrophobic the HIV fusion domain (FLGFL). This result suggests that in the HIV-seropositive patient population, antibodies with specificity for gp120 might also recognize $\alpha_1$PI potentially diminishing the active $\alpha_1$PI concentration.

**DISCUSSION**

We unexpectedly found in this study that active $\alpha_1$PI was deficient in all asymptomatic patients. On the other hand, total $\alpha_1$PI was elevated in all symptomatic HIV-positive patients. The strong association between $\alpha_1$PI and disease progression suggested $\alpha_1$PI might be central to the pathophysiology of HIV disease. Combined with CD4+ levels, determining the viral load (plasma viral RNA) is integral to the recommended guidelines for the clinical management of HIV disease. Discordant values for plasma viral RNA and CD4+ cell counts occur in approximately 14% of patients receiving antiretroviral therapy, and this complicates therapeutic decisions. The prognostic value of $\alpha_1$PI concentration for determining clinical category of HIV disease was equivalent to that of CD4, and this finding supports recent evidence that this self antigen acts as an entry cofactor.

More than 75 codominant alleles of human $\alpha_1$PI have been identified that are correlated in mucosal secretions and serum (16). In 1,084 plasma samples representing six species of monkeys (Macaca irus, M. mulatta, M. cyclopis, M. nemestrina, M. speciosa, and M. fascicata), five codominant alleles have been identified (3). These genetic differences might serve as a key to understanding the different pathologic outcomes of HIV infection in humans and chimpanzees. Neither antibodies to $\alpha_1$PI nor deficiency in $\alpha_1$PI were detected in macaques infected with simian/human immunodeficiency virus (SHIV) (data not shown), suggesting that different pathophysiologic outcomes result during HIV disease in humans and SHIV disease in macaques.

The primary source of circulating $\alpha_1$PI is thought to be the liver. Synthesis and secretion of $\alpha_1$PI by lymphocytes, mononuclear phagocytes, cornea, and intestinal Paneth cells in response to interleukin-6, transforming growth factor $\beta$, granulocyte-macrophage colony-stimulating factor, HLE, and lipopolysaccharide from gram-negative bacteria is under the regulation of NF-$\kappa$B (22). Convincing evidence from $\alpha_1$PI phenotype-mismatched patients undergoing bone marrow transplantation suggests that the mononuclear phagocyte system does not contribute to the systemic pool (13). However, it can be speculated that $\alpha_1$PI secreted by the mononuclear phagocyte system might explain the low levels of $\alpha_1$PI in patients homozygous for the PI$_{va}$ phenotype who lack the capacity for hepatocyte secretion of $\alpha_1$PI. It can be further speculated that $\alpha_1$PI secreted by cells of the mononuclear phagocyte system might primarily remain tissue associated, creating a localized gradient.

The distribution of human $\alpha_1$PI phenotypes has been reported to differ between ethnic groups and between groups dichotomized by sexual preference (9). Testosterone can induce a 20-fold increase in $\alpha_1$PI mRNA, and during pregnancy $\alpha_1$PI increases by 100% and $\alpha_1$M increases by 20% (10).

The detection of anti-$\alpha_1$PI IgG in HIV-seropositive patients suggests that autoimmune recognition of $\alpha_1$PI may be one determinant in producing $\alpha_1$PI deficiency. This result further suggests that in the presence of competing anti-$\alpha_1$PI immune complexes, the quantitation of total and inactive $\alpha_1$PI by ELISA in these patients may have been underestimated here. The binding of $\alpha_1$PI by monoclonal antibody-gp120 suggests humoral immunity to gp120 is one potential mechanism for initiating an autoimmune response to $\alpha_1$PI. Comparative alignment of the antibody-recognized gp120 peptide sequence and the carboxyl-terminal amino acids of $\alpha_1$PI supports antigenic mimicry. Further, because of the hydrophobic nature of the $\alpha_1$PI epitope recognized by anti-gp120, these results suggest that neo-epitopes of $\alpha_1$PI may be exposed during HIV disease. It has been suggested that viral proteins interactive with host proteins can induce conformational changes and the exposure of neo-epitopes, thereby initiating autoimmunity (26), and this suggests a potential mechanism for the initiation of autoimmunity to $\alpha_1$PI. Antibodies recognizing the V3 loop have been shown to inhibit the activity of InI (18), and this suggests that the functional activity of InI may also be diminished in the HIV-seropositive population. Deficiency or overexpression of InI has not been described in any disease process (4); however, the active derivative of InI has been reported to localize to affected tissue in Alzheimer-type dementia (29) and to increase during bacterial infection (24). That morbidity and mortality are documented to result from an imbalance in $\alpha_1$PI and $\alpha_1$M ratios (19, 20) suggests that autoimmunity to $\alpha_1$PI may be cardinal to HIV-associated pathophysiology. The HIV-induced autoimmune recognition of $\alpha_1$PI raises an important concern regarding vaccine development. It is not known at this time whether the initiation of immunity to HIV by vaccination also may initiate autoimmunity to $\alpha_1$PI. Of considerable interest is that immune recognition of multiple HIV proteins can be detected in HIV-exposed seronegative individuals; however, neither IgA nor IgG with specificity for gp120 could be de-
ected in these individuals (15). The evidence from this continuing seronegative population for the potential to coexist with HIV suggests, therefore, that protection against AIDS in HIV-infected individuals might arise by preventing autoimmunity to α1PI.

Results presented elsewhere suggest that α1PI deficiency, a condition which exists in the asymptomatic category of HIV disease, may promote increased cellular sensitivity to HIV infectivity (8a). On the other hand, the increasing concentrations of α1PI which occur during bacterial infection may promote increased viral load, conditions known to occur during the symptomatic category of HIV disease. The correlation between HIV RNA and total α1PI in the asymptomatic category supports the hypothesis that changing concentrations of circulating α1PI in response to HIV proteins and in response to attendant infections during HIV disease directly impact HIV pathophysiology. Evidence that plasma membrane-associated HLE has been previously shown to interact with gp120 (17) and recent evidence that neither cell lines nor peripheral blood monocytes during HIV disease.

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