REVIEW

The Role of α_1-Antitrypsin Deficiency in the Pathogenesis of Immune Disorders

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The association between α_1-antitrypsin (α1-AT) deficiency and a number of immune mediated diseases including rheumatoid arthritis, anterior uveitis, systemic lupus erythematosus, and asthma suggests that α1-AT may be important not only as an anti-inflammatory protein but also as an immune regulator. That the relationship between decreased amounts of this inhibitor and these diseases is causal is suggested by both some of its physical properties and evidence indicating it is able to modulate immune function. α_1-Antitrypsin has a high plasma concentration, very broad range of inhibitory activity and is an acute phase reactant. Among other things, it is able to modulate lymphocyte proliferation and cytotoxicity, and monocyte and neutrophil function. Additionally, some of these changes are demonstrable *in vivo* in patients with severe α_1-antitrypsin deficiency. This paper reviews the important physicochemical characteristics of this protein, the association of its presence in decreased amounts with immune disorders, and finally the important mechanism that may underlie this disease association.

INTRODUCTION

Since the original report of Laurell and Eriksson (1) in 1963 linking severe (α1-AT) deficiency with emphysema, associations of mild degrees of α1-AT deficiency with a large number of other disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), uveitis, and asthma have been discovered. A common feature of the pathogenesis of most of these diseases has been immune abnormalities and a strong inflammatory component. This paper reviews the basic characteristics of α1-AT then explores its association with immune disorders and the role its deficiency may play in their pathogenesis.

GENETICS

α1-AT is coded for by a pair of codominant alleles which influence many of its properties including plasma levels, response as an acute phase reactant, amino

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[2] Abbreviations used: α1-AT, α_1-antitrypsin; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; AS, ankylosing spondylitis; AAU, acute anterior uveitis; CH50, total hemolytic complement activity; PH50, total alternative-pathway-derived hemolytic complement activity.

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ders. A number of groups have noted an increased incidence of deficient phenotypes PiMS and PiMZ in asthma (25–30). Studies in infantile asthma have shown an overall incidence in 298 children of 22.5% with as many as 46.2% of the nonatopic group have a deficient phenotype (26). Children with deficient phenotypes PiMS and PiMZ have hyperreactive airways from an early age (31, 32). Those children that develop asthma express it at an earlier age (26) and need more bronchodilators and steroids (27, 29) indicating a more aggressive disease.

Geddes and co-workers (33) also noted an association of α1-AT deficiency with interstitial pulmonary disease. They found that 14.7% of patients with fibrosing alveolitis were PiMZ (control frequency 3%). Most remarkable however, was their finding that 50% of those patients with both rheumatoid arthritis and interstitial lung disease were α1-AT deficient with increase in both PiMS and PiMZ frequency to about 23%. Karsh and colleagues (34) however found no such increase in patients with pulmonary involvement secondary to Sjogren's syndrome.

Connective Tissue Disease

A number of groups have defined an association between rheumatoid arthritis and α1-AT deficiency (33, 35–39) while two studies have been unable to support such an assertion (34, 40). It is possible that differences in the severity of disease in the populations studied accounts for this difference. As indicated in Table 1 our study (39) noted a frequency of α1-AT-deficient phenotypes (MS plus MZ) of 25% compared with 10% in the control population, with a significant increase in the frequency of both MS and MZ. Although detailed assessment of the severity of RA was not undertaken, there did not appear to be a marked difference in severity between deficient and nondeficient subjects with RA suggesting that α1-AT deficiency may be a factor in the disease predisposition rather than influencing only severity. However, formal studies addressing this issue need to be carried out.

Most of the studies show an increase in the frequency of the *Z* allele as either PiMZ, PiSZ, or PiZZ. the frequency of PiMS is not significantly increased except in our study (39) and one other (33). In the latter investigation of subjects with RA and interstitial pulmonary involvement, both PiMS and PiMZ were increased dramatically to 22.7% suggesting that these phenotypes may predispose to interstitial pulmonary involvement in RA.

In a follow up survey in Sweden which detected 246 PiZZ individuals, a very high frequency of RA of 4.5% was noted (22). This suggests that PiZZ predisposes to RA, quite probably to a greater degree than just a single dose of the *Z* allele, and the low incidence of PiZZ in surveys of RA is simply a reflection of the rarity of this phenotype. It is particularly interesting, that from this same study of samples that were referred predominantly because of emphysema, 0.8% had SLE, 15% had glomerulonephritis, and 0.4% had ankylosing spondylitis. This suggests that the frequency of immune disorders is very high in subjects with the PiZZ phenotype.

Our group was the first to note an association of α1-AT-deficient phenotypes

variant. Brewerton and coworkers (42) found no increase in PiMZ in 30 uncomplicated patients with AS but did find an increase to 30% in AS patients with acute anterior uveitis (AAU). It is not possible to decide from this data if PiMZ predispose just to AAU or also to a lesser degree to AS as well. The only other group to examine this issue (40) found no increase in deficient phenotypes in AS (or psoriatic arthritis) but the number studied is so small as to make a meaningful conclusion impossible.

The only other connective tissue disease to have been studied in detail is scleroderma (43, 44). There was no increase in deficient phenotypes in 46 patients with this disease 28 of whom had diffuse involvement and 18 of which had the CREST syndrome (43). This is similar to our observation in this disorder (44) (Table 1). It is however of some interest that in our study all three subjects with PiMS had diffuse disease and no subject with the CREST variant had a deficient phenotype.

Eye Diseases

Anterior uveitis is a common and important immunologically mediated inflammatory eye disease that is associated with PiMS and PiMZ phenotypes. Brewerton *et al.* (42) found that 25% of 80 patients with this disorder were PiMZ irrespective of whether they were idiopathic or associated with ankylosing spondylitis. No comment was made about other phenotypes. Three other studies (45–47), however, were unable to substantiate these findings. One of these studies, (45) is somewhat suspect in that no patient with PiMZ could be found in 133 subjects. Additionally, none of the four studies gave adequate information on the sorts of anterior uveitis studied. Our results indicate in fact that these differences may well be due to patient selection.

Our results show a significantly increased incidence of α1-AT deficiency (MS and MZ) in patients with anterior uveitis, being most prevalent in those patients with chronic (40%), bilateral (60%), or recurrent (20%) disease (48) (Table 2). By contrast, none of the 36 patients with a solitary episode of anterior uveitis after a 6-month followup period were found to be α1-AT deficient. These results were not influenced by the presence of the HLA B27 antigen, which seemed to function

TABLE 2
α_1-ANTITRYPSIN PHENOTYPES IN INFLAMMATORY EYE DISEASE

	No.	α1-AT phenotype (%)			
		MM	MS	MZ	MS + MZ
Controls	339	89	7	3	10
Anterior uveitis					
Acute	36	100*	0	0	0*
Chronic	10	60*†	40*†	0	40*†
Bilateral	5	40†	40*†	20	60*†
Recurrent	39	80†	15*†	5	20*†
Posterior uveitis	16	77	5	12	17
Retinal vasculitis	19	84	11	3	16

* $P < 0.001$–0.05 compared with controls.
† $P < 0.05$ compared with acute anterior uveitis.

was studied in detail and proved to have IgM, C3, and α1-AT deposited in glomeruli. There have been several other reports of α1-AT deficiency and glomerulonephritis (66–68) including a French series of 39 patients (66). Many but not all cases have been of mesangioproliferative GN frequently associated with cirrhosis and with α1-AT deposition in glomeruli. Although there is no definitive study of α1-AT phenotypes in GN, these reports suggest there may well be a genuine association.

PHYSICOCHEMICAL PROPERTIES OF α1-AT

α1-AT is the major serine protease inhibitor of human plasma with a molecular weight of about 51,000 (69–72). The three common alleles, *M*, *Z*, and *S* are known to differ at one of their 394 amino acids (70, 71) resulting in proteins with slightly differing characteristics such as migration on electrophoresis serum concentration and acute phase reactant properties. α1-AT is known to be synthesized in hepatocytes (73, 74) and macrophages (75, 76) and has a half-life of about 5–6 days (77). Unlike most of the other protease inhibitors α1-AT is an acute phase reactant so that increased amounts are produced at times of extra need.

α1-AT is an inhibitor of serine proteases, which represent the largest group of mammalian enzymes, and are characterized by serine residues at their active sites. This active site is present within a crevice and the serine residue (78) assisted by adjacent histadine and aspartic acid undertake a nucleophilic attack on the substrate's peptide bond. (79). The substrate specificity of the enzyme is conferred by its three-dimensional structure which constrains access to its active site. α1-AT inhibits serin esterases by acting as a competitive substrate, the enzyme cleaving a 4000- to 8000-Da fragment from α1-AT (80). Once attached to the enzyme, α1-AT forms a very stable complex which does not permit the enzyme to interact with other substrates.

α1-AT has an extraordinarily broad range of enzyme inhibitory activity (Table 3) exceeded in this only by α_2-macroglobulin, whose mechanism of action is unique in allowing it to inhibit enzymes irrespective of class. It remains a difficult problem to know which of the interactions of α1-AT is physiologically important and which are purely *in vitro* effects. This situation is made more difficult by the fact that α1-AT is present in such high plasma concentrations that shear quantity

TABLE 3
SPECTRUM OF INHIBITORY ACTIVITY OF α1-AT

Major importance	Uncertain importance	Minor importance
PMN neutral proteases	Plasminogen activator	Thrombin
Elastase	Sperm acrosin	Plasmin
Cathepsin G	Renin	Kallikrein
Collagenase		Hageman factor
Trypsin		
Chymotrypsin		
Factor XIa		
Urokinase		

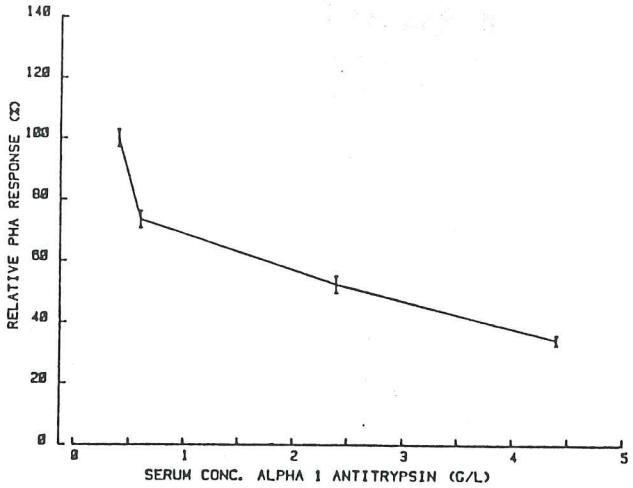

FIG. 1. The effect of α1-AT on the PHA response of lymphocytes cultured in the presence of α1-AT sera. The results are expressed as means ± 1 standard error of 23 experiments and are scaled so that the value obtained without added α1-AT is considered 100%.

terase which is already active prior to the addition of phytohemagglutinin (PHA). The fact that α1-AT does not completely inhibit PHA responsiveness but reduces it by 40–60% indicates that it inhibits the production of a factor or factors from adherent cells that enhance but are not absolutely essential for T-cell proliferation. This would be consistent with an effect on interleukin 1 production. That these *in vitro* findings are of clinical relevance is further supported by *in vivo* studies in which α1-AT deficient subjects exhibited exaggerated cell-mediated immunity, as manifest by marked acceleration of delayed hypersensitivity responses (94). Macrophages secrete a number of factors regulating the growth and differentiation of many other cell types. It seems possible that α1-AT may also inhibit the production of at least some of these factors, which could lead to alteration in growth and regulation of cells other than lymphocytes.

The hepatocyte and the macrophage are the only cells known to synthesize α1-AT (73–76) although one group also noted *de novo* synthesis by the lymphocyte fraction from partially fractionated mononuclear cells (96). The stimulus and control of its synthesis and secretion are not known, but as for many macrophage factors, may well be selective. It would seem self defeating for a cell to simultaneously secrete a protease and its inhibitor so it is likely that some differential secretion of these substances occurs with time. On the other hand, if its function were purely to prevent autolysis of proteases leaking from lysosomes it is difficult to understand why it is secreted into the culture medium in the absence of phagocytic stimuli. If nothing else this provides strong presumptive evidence for a role for α1-AT in macrophage mediated functions, but at this stage, its role and relative importance are uncertain.

Few previous studies concerning the effect of α1-AT on human lymphocyte proliferation have been published. One group could demonstrate no inhibition of the mixed lymphocyte response (97), whilst another showed inhibition of the

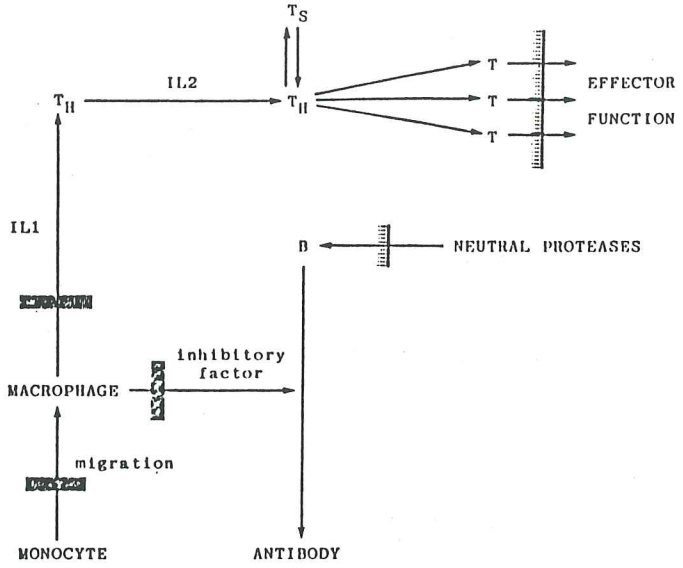

FIG. 2. Possible sites of action of α1-AT on T- and B-cell function.

Inflammatory Abnormalities

While immunoregulatory abnormalities may predispose to immune disorders, inflammatory abnormalities may worsen their expression. Irrespective of the etiology of the disease, no tissue damage results without an inflammatory response in which phagocytic cells and complement plays a major role. There is some evidence of excessive inflammatory responses in α1-AT-deficient subjects.

Studies of the activation of monocytes and neutrophils using zymosan-induced chemiluminescence (CL) have demonstrated enhanced activation of both of these cells in the presence of α1-AT-deficient sera compared with control sera (94). However, using highly purified α1-AT, no suppression of the CL response was demonstrable, indicating that the enhancement noted in α1-AT-deficient sera was due to other secondary factors (111). As the CL assay is dependent on alternative pathway-derived complement and these sera are known to have elevation of the important alternative pathway and attack sequence proteins C3, C5 and factor B (94), it would appear quite possible that the enhancement was due to this factor. This study therefore does not support the hypothesis that α1-AT acts on the cell surface serine esterases that are known to be involved in the activation of phagocytic cells. However, as a number of different receptors and mechanisms exist for activation of these cells, the results do not completely exclude a direct effect of α1-AT or enzymes involved in their activation.

Two studies have investigated the effect of α1-AT on phagocyte motility. In one, α1-AT was found to have a very significant effect on chemokinesis, reducing it by about 35% for monocytes and neutrophils (110). A small (10%) but significant inhibition of casein-induced chemotaxis was probably due to the fact that casein had some chemokinetic as well as chemotactic properties. In 1975, Goetzl (112) reported a rather complex effect of α1-AT on C3a- and C5a-induced neutrophil chemotaxis. He found that cells pulsed with α1-AT for a very short time exhibited

mediated tissue injury. The role of α1-AT in regulating the complement system is probably largely restricted to inhibiting its activation by neutral proteases. While of uncertain significance, we and one other group have demonstrated elevation of alternative pathway and attack sequence proteins, C3, factor B, and C5 in α1-AT-deficient patients, parallelled by an increase in the total alternative-pathway-derived hemolytic activity (PH50) (94). No difference was noted in classical pathway components C1q, C4, or in the total hemolytic complement activity (CH50). We were also not able to demonstrate the interaction of α1-AT with complement components in immune complexes or any direct inhibition by purified α1-AT of functional complement activity using CH50 and PH50 assays (unpublished observation). α1-AT, however, has been shown by one group to bind C3 and inhibit C3-mediated phagocytosis (129, 130). Two other studies have investigated complement profiles in α1-AT deficiency. In a mixed group of α1-AT-deficient subjects Arnaud *et al.* have observed elevated levels of C1q, C3, and C5 and in some groups factor B but normal C4 levels (131). Another group, using functional assays found no variation from normal except for depressed C4 levels (132). These patients however all had severe liver disease known to greatly influence the metabolism of many proteins.

α1-AT also has a role in the inhibition of several mediator pathways. It is the major inhibitor of factor XIa of the coagulation pathway (133), can inhibit factor Xa (134) an has lesser inhibitory activity against thrombin (135). Its activity against factors XIIIa, Xa, and VIIa has not been determined. It also inhibits plasma renin (136), the neutrophil cathepsin G activating angiotensinogen (127), and a skin-derived protease mediating neutrophil infiltration and increased vascular permeability (137). It has no significant effect on activated Hageman factor, kallikrein, or plasmin. It does however inhibit the neutral protease-mediated activation of Hageman factor (138, 139), kininogen (140, 141), and neutrophil-mediated fibrinolysis (142).

The increased severity of some inflammatory diseases in α1-AT-deficient subjects may therefore in part be explained by increased motility and activation of monocytes and neutrophils the former due to the absence of an inhibitor of neutrophil and monocyte locomotion and the latter due to secondary changes in serum resulting in enhanced chemiluminescence. Its inhibition of enzymes of the major mediator pathways is probably not of great significance. However, the capacity to inhibit the many neutral proteases that both cause direct tissue damage and activate many mediator pathways is of great importance.

CONCLUSION

The sum of this evidence suggest that α1-AT deficiency is an important genetic factor in inflammatory and immune diseases. This is mediated through the effect of α1-AT on specific immune responses on the one hand and inflammatory response on the other (Fig. 4). Its deficiency is likely to lead to increased activity of a number of inflammatory pathways leading to excessive inflammatory responses. Additionally, these responses might occur to minimal insults which under normal circumstances would initiate minimal inflammation. Thus, not only would tissue damage occur but a predisposition to autoimmune disease might

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