Chapter 8
Alpha-1 Antitrypsin as a Therapeutic Agent for Conditions not Associated with Alpha-1 Antitrypsin Deficiency

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Introduction

For many years, alpha-1 antitrypsin has been used as augmentation therapy in patients with COPD associated with alpha-1 antitrypsin deficiency. The primary goal of the treatment has been to raise circulating and tissue levels of alpha-1 antitrypsin thereby counteracting unopposed serine protease activity, notably neutrophil elastase, a putative factor in the pathogenesis of COPD. In the United States, regulatory approval by the Food and Drug Administration was obtained only for intravenous alpha-1 antitrypsin and only for lung disease associated with severe alpha-1 antitrypsin deficiency allele combinations; thus, the therapy has been restricted to a single condition.

Over the past 15 years, there has been a growing recognition of alpha-1 antitrypsin's broader anti-inflammatory actions beyond serine protease inhibition including immunomodulatory and anti-apoptotic effects. It has been shown that alpha-1 antitrypsin that has been modified to lose its antiprotease activity retains potent anti-inflammatory and immunomodulatory effects on human monocytes and in a mouse model of lung inflammation [1, 2]. Additional data have supported this concept by showing that alpha-1 antitrypsin is an endogenous inhibitor of cytokine production in whole human blood [3], that alpha-1 antitrypsin can activate phosphatases to abrogate inflammatory responses in the lung [4], and that alpha-1 antitrypsin inhibits IL-8 and neutrophil chemotaxis in the lung [5–7]. Of equal importance have been observations on alpha-1 antitrypsin's anti-apoptotic activity, likely owing to the inhibition of caspases, notably caspase-3 [8–11]. Antiangiogenic and antimicrobial effects have also been reported [12–14].

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Table 8.1 Alpha-1 antitrypsin-replete conditions under consideration for alpha-1 antitrypsin treatment

Type 1 diabetes mellitus[a]
Viral infections[a]
Graft-versus-host disease[a]
Cystic fibrosis[a]
Chronic obstructive pulmonary disease
Inflammatory bowel disease
Arthritis
Ischemic heart disease

[a]Including investigations that include early human trials

Given alpha-1 antitrypsin's diverse modes of action, it is not surprising that interest arose in using this protein to treat conditions such as inflammatory bowel disease [15], arthritis [16–18], ischemic heart disease [19], organ and cell transplant rejection, graft-versus-host disease, alpha-1 antitrypsin-replete chronic obstructive lung diseases, type 1 diabetes mellitus, and viral infection. The latter application is based on the role of serine proteases involved in viral entry into cells.

Most information has been obtained in type 1 diabetes mellitus, graft-versus-host disease, viral infection, and alpha-1 antitrypsin-replete lung disease, notably COPD and cystic fibrosis (Table 8.1). Furthermore, some of the related studies have not been limited to in vitro or animal observations but have also involved experiments in humans. In this chapter, we therefore will focus the discussion on the latter conditions.

If alpha-1 antitrypsin is administered to patients with normal serum alpha-1 antitrypsin levels, why should a therapeutic effect be expected? Why should supranormal circulating and presumably tissue alpha-1 antitrypsin concentrations be beneficial? In the absence of pharmacokinetic investigations in alpha-1 antitrypsin-replete humans receiving alpha-1 antitrypsin by intravenous infusion or inhalation, the question cannot be answered with confidence. However, in patients with alpha-1 antitrypsin deficiency, intravenously administered alpha-1 antitrypsin at a dose of 60 mg kg^{-1} has been shown to increase serum alpha-1 antitrypsin levels by ~120 mg dl^{-1} from ~60 mg dl^{-1} to a peak of ~180 mg dl^{-1}, with a gradual return to baseline within 7 days [20]. It is not known if similar increases would be seen in people with normal baseline serum alpha-1 antitrypsin levels, but assuming an increase in the same range would raise the levels from ~180 mg dl^{-1} to a peak of 300 mg dl^{-1}, with levels remaining above normal for a week. Alpha-1 antitrypsin is a positive acute phase reactant, and the above levels are well within the range of serum alpha-1 antitrypsin levels seen in conditions of stress such as acute coronary syndrome, abdominal surgery, and open-heart surgery [21–23] (Fig. 8.1).

Pro-inflammatory cytokines, especially interleukin-6, are thought to be involved in the acute phase response by inducing secretory acute phase proteins including alpha-1 antitrypsin in hepatocytes [24]. Inasmuch as the presumed role of alpha-1 antitrypsin in the acute phase response is to modulate the biological effects of acute inflammation, one could argue that maintaining serum alpha-1 antitrypsin levels elevated over longer periods of time by the administration of alpha-1 antitrypsin

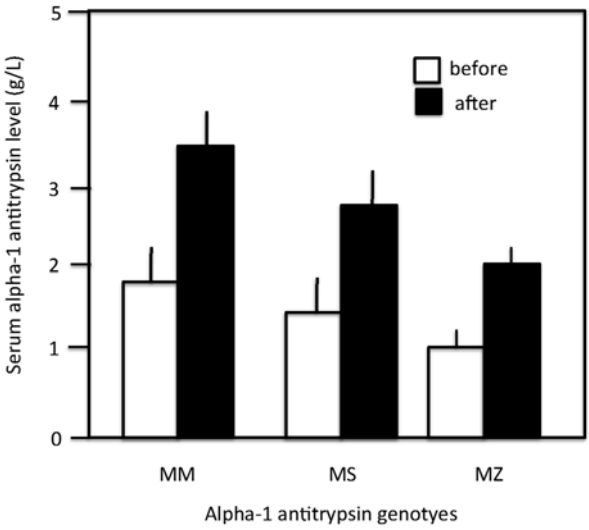

Fig. 8.1 Acute phase response in serum alpha-1 antitrypsin levels in patients before and 4–5 days after open-heart surgery. Means ± SD. Alpha-1 antitrypsin genotypes: MM ($n = 193$), MS ($n = 10$), MZ ($n = 5$). Note that the levels increased by about 100 % in all three groups. Graph constructed with data from Sandford et al., Am J Resp Crit Care Med 1999; 159:1624–1628

might be beneficial in chronic conditions involving inflammatory processes that may or may not include serine proteases.

Currently, only human plasma-derived alpha-1 antitrypsin is available for clinical use. The supply of this product is limited but apparently sufficient to meet the need in patients with an orphan condition such as severe alpha-1 antitrypsin deficiency, the only approved indication for alpha-1 antitrypsin therapy at the present time. Future research could identify new therapeutic target conditions for this protein; some of them may not be rare. Therefore, alternate sources and formulations of alpha-1 antitrypsin may have to be developed to meet the greater demand. Inhaled human plasma-derived alpha-1 antitrypsin has been experimentally administered as an aerosol to patients with alpha-1 antitrypsin-replete lung disease [25–27]. This mode of administration would reduce the amount of protein needed to treat the lung disease of alpha-1 antitrypsin-deficient and alpha-1 antitrypsin-replete patients. However, alternate sources of alpha-1 antitrypsin have been explored in an attempt to replace the human plasma-derived product. Several companies have used transgenic and recombinant approaches. A major challenge has been the requirement of mimicking the glycosylation pattern of native human alpha-1 antitrypsin to ensure adequate tissue penetration and acceptable plasma half-life values. Further studies are warranted to demonstrate the safety and efficacy of such products.

Finally, new formulations and applications of alpha-1 antitrypsin will require regulatory approval. For product licensing, low or lack of immunogenicity, efficacy, and safety will have to be demonstrated in the new target populations, and the trials will have to involve clinically meaningful, not just surrogate endpoints [28]. Meeting these requirements will have a major role in bringing the new alpha-1 antitrypsin products to the market and obtaining regulatory approval for them.

Type 1 Diabetes Mellitus

As an autoimmune condition, type 1 diabetes mellitus involves inflammation-related injury to beta cells in the pancreas, leading to fluctuating blood glucose levels. Alpha-1 antitrypsin is an endogenous anti-inflammatory molecule that could correct altered immunoregulatory pathways and modulate the inflammation associated with type 1 diabetes thereby improving blood glucose control [29]. This concept is strengthened by the fact that alpha-1 antitrypsin is locally manufactured in the pancreas under normal circumstances in various species including man. For example, the porcine pancreas contains alpha-1 antitrypsin as assessed by proteomic analysis, especially during development [30]. In humans, alpha-1 antitrypsin expression and secretion by islet cells has been investigated by immunofluorescence, Western blotting, and ELISA [31]. It was shown that alpha and delta cells are the primary source of synthesis and presumably secretion. Given the proximity of these cells to beta cells, this suggests the presence of a locally mediated biological function of alpha-1 antitrypsin by modulating immunologic and inflammatory processes that could be involved in type 1 diabetes. Furthermore, it has been reported that circulating alpha-1 antitrypsin is less active in diabetic individuals, possibly due to high glucose levels in hepatocytes where alpha-1 antitrypsin therefore is excessively glycated [32, 33]. Alpha-1 antitrypsin glycation also could occur in other alpha-1 antitrypsin-generating tissues, including the islet of the pancreas. So far, this has not been investigated.

Based on these considerations, there has been a considerable interest in studying the effects of exogenous alpha-1 antitrypsin or alpha-1 antitrypsin overexpression in the pancreas on glucose control in animal models of type 1 diabetes and in early human experiments. Underlying these studies is the expectation that above-normal levels of alpha-1 antitrypsin would rebalance immunoregulation in the pancreas. In support of this premise, it has been shown that a beta cell line stably transfected with human alpha-1 antitrypsin resists cytotoxic, T-cell-mediated apoptosis and inflammatory cytokine production [5].

Diabetic mice have been the most popular animal models of type 1 diabetes and have provided important information on the processes underlying the phenotype and their response to alpha-1 antitrypsin. The primary outcomes have been blood glucose levels and survival and function of beta cells transplanted into diabetic mice (antirejection action of alpha-1 antitrypsin). In a 4-week-old nonobese diabetic mouse strain, gene therapy with human alpha-1 antitrypsin using an adeno-associated viral vector prevented the development of diabetes [34, 35]. This was associated with an altered T-cell repertoire in spleen cells, suggesting a possible mechanism for the alpha-1 antitrypsin effect in the pancreas. A complementary study showed that in nonobese diabetic mice with early type 1 diabetes, alpha-1 antitrypsin therapy restored euglycemia and promoted beta cell expansion; again the effect was attributed to alpha-1 antitrypsin's broad anti-inflammatory actions [36]. In another murine model of streptozotocin-induced type 1 diabetes, an Fc-fused recombinant alpha-1 antitrypsin protein lacking anti-elastase activity prevented

hyperglycemia [32]. At least in this model, the anti-inflammatory action of alpha-1 antitrypsin could not be attributed to its anti-elastase activity, pointing to other immunomodulatory and anti-inflammatory actions. In particular, alpha-1 antitrypsin's known caspase-3 inhibitory and anti-apoptotic actions may have a role as shown in vitro and in vivo [37]. In that investigation, alpha-1 antitrypsin inhibited caspase-3 activity and prevented tumor necrosis factor alpha-induced apoptosis in a murine insulinoma cell line and reduced beta cell apoptosis as assessed by a TUNEL assay in streptozotocin-treated diabetic mice.

These results show that alpha-1 antitrypsin improves beta cell function and normalizes blood glucose levels in two different mouse models of type 1 diabetes and suggest that type 1 diabetes in humans could be a target for alpha-1 antitrypsin therapy. To date, a proof-of-concept study has raised the possibility that at least some patients could benefit from such treatment [5]. In 12 patients with type 1 diabetes and detectable blood C-peptide levels, the effect of 80 mg/kg alpha-1 antitrypsin, administered by intravenous infusion weekly for 8 weeks, on the C-peptide response to a mixed meal challenge was investigated. The C-peptide response (expressed as area under the curve) increased at 3 months in only five patients (Fig. 8.2), but there was an inverse relationship between the frequency of IL-1 beta-producing monocytes and the C-peptide response, indicating that specific inflammatory pathways sensitize patients to the effects of alpha-1 antitrypsin on beta cell

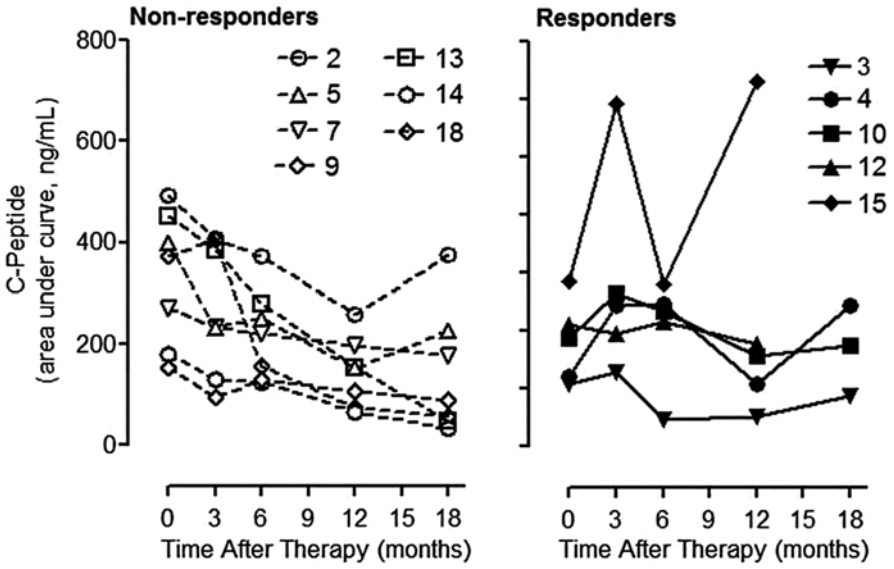

Fig. 8.2 C-peptide responses to a mixed meal tolerance test in 12 patients with type 1 diabetes and detectable blood C-peptide levels, before and at different times after 8 weekly infusions of 80 mg/kg alpha-1 antitrypsin. Note that in five patients, the response increased at 3 months irrespective of responder/nonresponder designation. Interestingly, there was an inverse relationship between the C-peptide response and the frequency of IL-1 beta-producing blood monocytes among all patients. With permission from Gottlieb et al., J Clin Endocrinol Metab 2014; 99: E 1418–1426

function. Three human trials using intravenous alpha-1 antitrypsin in patients with recently diagnosed type 1 diabetes have successfully been initiated; the primary outcomes are glycemic control or C-peptide response. Two trials are ongoing while one has been completed; as of November 2014, no results had yet been reported.

Alpha-1 antitrypsin also has been investigated in islet cell transplantation to treat type 1 diabetes. Essentially all reported studies in animal models have shown a beneficial effect of alpha-1 antitrypsin on beta cell survival and function. To our knowledge, alpha-1 antitrypsin thus far has not been administered to patients who have undergone islet transplantation for the treatment of type 1 diabetes.

Most studies have involved mice and were based on the hypothesis that alpha-1 antitrypsin would exert its effect by suppressing autoimmunity and protecting against graft rejection [38]. For example, islet allograft survival and euglycemia was extended by alpha-1 antitrypsin treatment in diabetic mice in one study; this was associated with a diminished release of tumor necrosis factor alpha from stimulated islet cells [39]. In a similar investigation, islet graft survival was improved by alpha-1 antitrypsin treatment in a syngeneic non-autoimmune mouse model of diabetes, again accompanied by a downregulation of tumor necrosis factor alpha [40]. In yet another study, single-dose T-cell depletion combined with alpha-1 antitrypsin treatment prolonged rat-to-mouse islet xenograft survival [41].

Other mechanisms implicated in limited graft survival also have been examined including deficient graft vascularization. For example, alpha-1 antitrypsin has been reported to stimulate vascular endothelial growth factor expression and release and to promote revascularization of islet cell allografts in an explantable compartment of the mouse pancreas [42]. Graft survival also could be limited due to graft injury by pancreatic proteases as pancreatic acinar cells have been shown to contaminate islet cell preparations and be co-transplanted with them. Acinar cell protease activity could then injure islet cells and shorten their survival. Supporting this possibility, it has been shown that the more impure the islet preparations, the greater their proteolytic activity, islet cell loss, and insulin depletion [43]. Incubation with alpha-1 antitrypsin protected the preparation from these changes, presumably by its protease inhibitory action.

The effect of alpha-1 antitrypsin on islet graft survival and function has also been investigated in a nonhuman primate, bringing the observation closer to the human condition. In subtotally pancreatectomized, streptozotocin-treated monkeys with autologous islet cell transplantation, treatment with alpha-1 antitrypsin during the peri-transplant period leads to functional islet mass expansion and improved graft function [44].

Viral Infection

The influenza A virus, coronaviruses, and the human immunodeficiency virus type 1 (HIV-1) use host serine proteases for cell entry and subsequent infection [45, 46]. The mechanism whereby serine proteases are involved in the initial steps of viral

entry has been clarified for the influenza virus A. Viral hemagglutinin activates hemagglutinin receptors expressed on the host cell membrane thereby activating host serine proteases that through their effect on the virus facilitate its entry into the cell [47]. Alpha-1 antitrypsin theoretically could suppress influenza A infection owing to its serine protease inhibitory action.

To date, the prophylactic or therapeutic effect of alpha-1 antitrypsin therapy in alpha-1 antitrypsin-deficient or alpha-1 antitrypsin-replete humans with influenza-A infection has not been examined. Yet the potential for alpha-1 antitrypsin's anti-influenza action deserves further exploration, especially with inhaled formulations. In this regard, it is noteworthy that influenza pneumonia in mice that overexpress human alpha-1 antitrypsin has been reported to be associated with a better survival than in wild-type control mice [28].

More information is available on the role of alpha-1 antitrypsin in HIV-1 infection. It has been shown that HIV-1 does not replicate in alpha-1 antitrypsin-replete whole blood but replicates well in alpha-1 antitrypsin-deficient blood [46]. Furthermore, alpha-1 antitrypsin has been reported to suppress HIV-1 production in chronically infected monocytes, to inhibit HIV-1 entry into a cell line designed to detect viral entry, and to reduce HIV-1 replication in human peripheral mononuclear cells [46, 48]. A 20-residue virus inhibitory peptide corresponding to the C-terminal region of alpha-1 antitrypsin has been shown to inhibit viral entry and may explain the anti-HIV action of alpha-1 antitrypsin [49].

These in vitro observations have been substantiated by an in vivo study involving human subjects. A 10-day infusion of the virus inhibitory peptide in treatment-naïve patients with HIV infection reduced the viral load by a factor of 12 [32] (Fig. 8.3). Conversely, an association has been reported to exist between HIV infection and reduced serum alpha-1 antitrypsin levels [50, 51]. Taken together, the currently available information provides a basis for future clinical investigations into the therapeutic potential of alpha-1 antitrypsin in HIV-1 infection. In contrast to influenza, HIV infection is of a chronic nature and as such provides a better target for interventional studies with alpha-1 antitrypsin.

Graft-Versus-Host Disease

Allogenic hematopoietic stem cell or bone marrow transplantation, while in clinical use for the treatment of leukemia, can lead to graft-versus-host disease [52]. Standard immunosuppressive therapy administered to attenuate the immunologically mediated attack of the graft against the host increases the risk of opportunistic infections and impairs the graft's antileukemia effect (graft-versus-leukemia response).

In search of agents that would suppress the immunological response of the graft against the host (graft-versus-host disease) without compromising its antileukemia effect (graft versus leukemia), several groups have investigated alpha-1 antitrypsin, a molecule with known anti-inflammatory and immunomodulatory profiles and

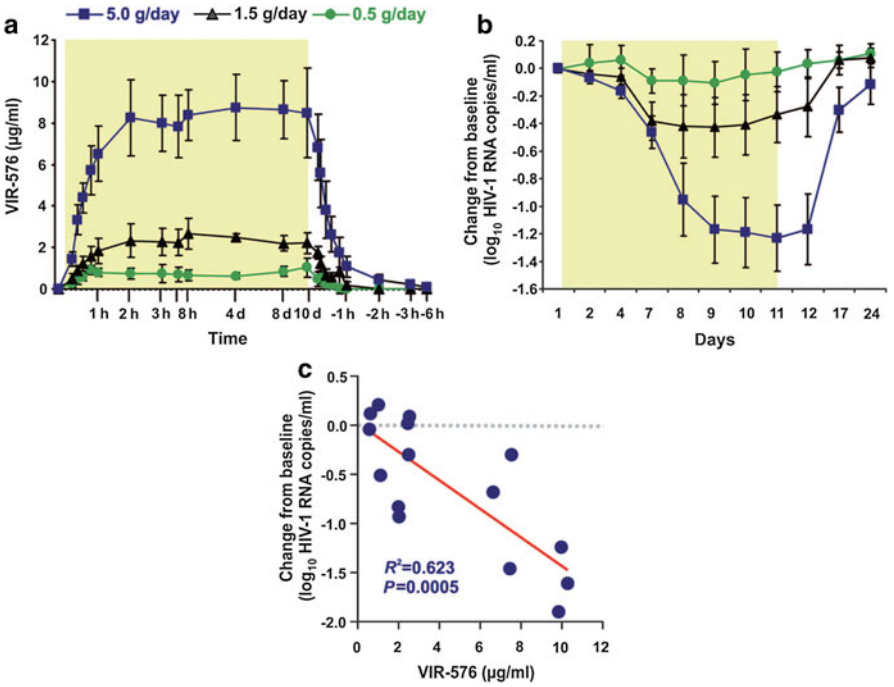

Fig. 8.3 Effect of short-term intravenous monotherapy with a natural 20-residue fragment of human a1-antitrypsin in HIV-infected patients ($N=15$). Values shown as mean (±SEM). (**a**) Quantities of the fragment (VIR-576) detected in the plasma of patients treated with three different doses. (**b**) Changes in $\log_{10}$ plasma viral load over time in the three dosing groups. (**c**) Correlation between the induced change in viral load and achieved VIR-576 plasma levels in all patients. With permission from Forssmann et al., Sci Transl Med 2010; 2: 63–70

excellent safety record. Again, the mouse served as the preferred model for this purpose. It has been reported that the administration of alpha-1 antitrypsin to mice undergoing allogenic bone marrow transplantation blunted graft-versus-host disease and prolonged graft survival [53]. The effect was attributed to inhibition of IL-32 activity. Other cytokines are likely to be involved as well as shown in three murine models of graft-versus-host disease in which the early administration of alpha-1 antitrypsin decreased mortality, an effect associated with a suppressed secretion of tumor necrosis factor alpha and IL-1 beta and upregulation of IL-10 [54]. Another study assessed the effect of alpha-1 antitrypsin on different T-cell populations and cytokines in a mouse model of graft-versus-host disease in which alpha-1 antitrypsin was introduced in the form of alpha-1 antitrypsin-modified donor cells [55]. The graft-versus-leukemia effect was not compromised in this model.

Human studies thus far have not been reported, but it has been shown that in patients who have undergone bone marrow transplantation, mRNA levels of IL-32 in blood leukocytes were higher in recipients with graft-versus-host disease than in those without [53]. As mentioned above, alpha-1 antitrypsin was found to inhibit

IL-32 activity in a murine model of graft-versus-host disease [53]. The time seems to be ripe for examining the effect of alpha-1 antitrypsin on graft-versus-host disease and graft-versus-leukemia responses in patients receiving bone marrow transplantation for the treatment of leukemia.

Alpha-1 Antitrypsin-Replete Obstructive Lung Diseases

Cystic fibrosis (CF) and COPD in patients without alpha-1 antitrypsin deficiency (common COPD) have been the primary targets for alpha-1 antitrypsin therapy where the goal is not to replace the protein but to raise its level beyond normal. There are at least two reasons for considering such therapy in these conditions. First, neutrophil elastase has been clearly shown to have a critical role in the pathogenesis of CF and common COPD [56, 57]. Alpha-1 antitrypsin is the most potent inhibitor of neutrophil elastase and, by suppressing neutrophil elastase activity, would be expected to ameliorate the disease process and prevent or slow progressive lung remodeling and functional impairment. Second, owing to alpha-1 antitrypsin's broader anti-inflammatory and anti-apoptotic actions, additional benefits might be seen in both conditions. Mechanistic investigations and phase 2 trials using aerosol alpha-1 antitrypsin carried out to date have provided a solid basis for further interventional studies using alpha-1 antitrypsin therapeutically in CF and common COPD.

Cystic Fibrosis

The lung disease of CF involves neutrophil elastase and its effects on mucus secretion, proteolytic destruction of airway and lung tissue, and facilitation of bacterial infection, notably by *Pseudomonas aeruginosa* [58, 59]. Neutrophils are recruited to lung tissue primarily by interleukin 8 (IL-8). Neutrophil elastase is released from neutrophils during migration, upon immune complex stimulation, and when they undergo necrosis or apoptosis [60]. In addition, IL-8 and tumor necrosis factor alpha promote neutrophil elastase release from neutrophils [63]. Alpha-1 antitrypsin is the most potent known inhibitor of neutrophil elastase, has other antiprotease activity relevant to CF, and is anti-apoptotic [8, 59]. However, its concentration in airway and lung tissue, even if above normal due to a presumably increased secretion by the liver, may not be sufficient to counteract the markedly augmented neutrophil elastase activity in the CF lung [56]. Given the importance of proteolytic activity in the inflammatory process associated with CF-related lung disease, it is not surprising that alpha-1 antitrypsin has been thought of as a therapeutic for this disease. Over 20 years ago, McElvaney et al. [58] administered aerosolized human plasma-derived alpha-1 antitrypsin to 12 patients with CF for 1 week. The authors showed that the treatment reduced neutrophil elastase activity in epithelial surface liquid (bronchoalveolar lavage fluid) with a critical alpha-1 antitrypsin

concentration of 8 μM; treatment also stimulated *Pseudomonas aeruginosa* killing by bronchoalveolar lavage fluid in vitro. Since then, major advances have been made in aerosol delivery technology with devices that can now deliver up to 70 % of the filling dose to the lungs [26, 27, 62]. In addition, high-purity liquid alpha-1 antitrypsin formulations are now available, and so far short-term aerosol alpha-1 antitrypsin treatment for up to 28 days has been found to be safe [26, 27, 50, 62].

Using the advanced aerosol delivery technology, two phase 2 studies have interrogated the effects of short-term aerosol therapy with alpha-1 antitrypsin in patients with stable CF. In a placebo-controlled investigation using between 125 and 500 mg alpha-1 antitrypsin daily for 4 weeks, there was a trend toward decreased neutrophil elastase activity in sputum as assessed by IL-8, myeloperoxidase, and neutrophil elastase-alpha-1 antitrypsin complexes [63]. In another interventional study, which was not placebo controlled, 52 CF patients were treated with 25 mg aerosolized alpha-1 antitrypsin daily for 4 weeks [64]. There were significant decreases in sputum neutrophil counts and IL-8 and unopposed neutrophil elastase activity from before to after the treatment. There were no concomitant changes in FEV_1.

These investigations have established the biochemical efficacy of inhaled alpha-1 antitrypsin in CF but thus far have not shown any clinical benefits. However, they provide a solid basis for phase 3 trials of longer treatment duration which will be needed to detect changes in clinical outcomes.

Common COPD

Although alpha-1 antitrypsin has broad immunomodulatory, anti-inflammatory, proteostatic, and anti-apoptotic actions [45], which theoretically could benefit patients with alpha-1 antitrypsin-replete COPD, no human studies with intravenous or inhaled alpha-1 antitrypsin have been reported in such patients to date. Yet, several in vitro observations and in vivo investigations in animals have shown that alpha-1 antitrypsin administration can attenuate experimental emphysema. Pemberton et al. [65] reported that a 6-month treatment with inhaled recombinant alpha-1 antitrypsin reduced airspace enlargement by 70 % in cigarette smoke-induced emphysema in mice. Additional experiments have shown that alpha-1 antitrypsin's anti-apoptotic activity could have a major role in this protective effect. Thus, in a murine emphysema model in which airspace enlargement was induced by pharmacologic inhibition of vascular growth factor receptors, mice overexpressing human MM alpha-1 antitrypsin were protected from the airspace enlargement; the protection was attributed to caspase-3 inhibition by alpha-1 antitrypsin [66]. A possible link between this observation and human cigarette smoke-induced COPD can be gleaned from an in vitro experiment in which alpha-1 antitrypsin purified from blood exhibited different anti-caspase activity in smokers and nonsmokers [7]. Alpha-1 antitrypsin derived from smokers inhibited executioner caspases (caspase-3, caspase-6, caspase-7) significantly less than alpha-1 antitrypsin from nonsmokers.

Neutrophil-dependent and neutrophil-independent inflammation and lung cell apoptosis are important players in the pathogenesis of CF and common COPD. In CF, phase 2 clinical trials have already been carried out and the prospect of phase 3 trials with inhaled alpha-1 antitrypsin in the future. In contrast, even early human studies with inhaled alpha-1 antitrypsin currently are lacking although the rationale for such treatment seems to be equally strong for both conditions. Awaiting the results of inhaled therapy with alpha-1 antitrypsin in patients with alpha-1 antitrypsin deficiency-associated COPD before investigating the effects of inhaled alpha-1 antitrypsin in alpha-1 antitrypsin-replete COPD may not be an optimal approach as raising alpha-1 antitrypsin levels toward or to normal may not be sufficient to modify the spectrum of inflammatory processes involved in common COPD. After all, alpha-1 antitrypsin is a positive acute phase reactant whose circulating level is increased above normal to modulate inflammation.

Conclusions

The data reviewed in this chapter lead to several conclusions about the prospect of administering alpha-1 antitrypsin to persons suffering from conditions not caused by alpha-1 antitrypsin deficiency. Promising are the results of investigations using animal models of human diseases such as type 1 diabetes, viral infection, graft-versus-host disease, cystic fibrosis, and alpha-1 antitrypsin-replete COPD. While other conditions including ischemic heart disease, inflammatory bowel disease, and arthritis have also been considered for alpha-1 antitrypsin therapy, the research addressing them may not have reached the same level of maturity.

There are at least two major reasons why these diseases have been considered for alpha-1 antitrypsin treatment. First, they involve immunologic and chronic inflammatory processes for which alpha-1 antitrypsin, owing to its broad immunomodulatory and anti-inflammatory activity, could clinically be beneficial. Second, alpha-1 antitrypsin is a positive acute phase reactant capable of modulating pro-inflammatory pathways; therefore, raising serum alpha-1 antitrypsin levels above normal in patients who are not alpha-1 antitrypsin deficient could mimic the natural anti-inflammatory actions of alpha-1 antitrypsin during inflammatory stress.

Early human studies have been conducted in type 1 diabetes, HIV infection, graft-versus-host disease, and cystic fibrosis. Although these investigations have established the feasibility, safety, and in some instances biological effectiveness of alpha-1 antitrypsin treatment, further trials are clearly needed to demonstrate its clinical utility.

With respect to new alpha-1 antitrypsin formulations, aerosol alpha-1 antitrypsin is the closest to becoming clinically available for patients with alpha-1 antitrypsin deficiency and potentially cystic fibrosis and alpha-1 antitrypsin-replete COPD. Significant challenges remain for the development of recombinant or transgenic alpha-1 antitrypsin as a substitute for human plasma-derived alpha-1 antitrypsin. However, both new applications and formulations of alpha-1 antitrypsin likely will continue to be explored and ultimately lead to a broader use of this protein in clinical medicine.

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