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The SEC Receptor: A Possible Link between Neonatal Hepatitis in α_1-Antitrypsin Deficiency and Alzheimer's Disease[1]

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Homozygous PiZZ α_1-antitrypsin (AT) deficiency is the most common genetic cause of liver disease in children (1). It has also been shown to cause chronic hepatitis, cirrhosis, and hepatocellular carcinoma in adults (2, 3) and predispose adults to premature development of emphysema (4). A single amino acid substitution, lysine for glutamate 342, results in the synthesis of an abnormal protein. Rather than being secreted, this abnormal protein is retained within the endoplasmic reticulum (ER) of liver cells (1). Experiments in transgenic mice have confirmed previous suspicions that the liver injury results from the hepatotoxic effects of the retained mutant α_1-AT Z molecule (5, 6). This means that the pathogenesis of liver injury in this deficiency is distinct from the pathogenesis of lung injury that involves reduction in antiprotease levels in the circulation and in tissues, allowing unregulated proteolytic attack on the lung elastin matrix (4). This also means that the liver disease of α_1-AT deficiency is unlikely to respond to protein or gene replacement therapy, at least the type of replacement therapy in which there is delivery of a normal α_1-AT protein or gene. Cohort studies from a nationwide prospective newborn screening in Sweden have demonstrated that significant liver injury develops in only a subpopulation of α_1-AT–deficient individuals (7, 8).

With these considerations in mind, we have made two predictions: *1*) genetic traits, environmental factors, or both predispose a subpopulation of α_1-AT–deficient individuals to liver injury; and *2*) these putative genetic traits and environmental factors affect the fate of the abnormal α_1-AT Z molecule within the secretory pathway. If, for example, the deficient individual also bears a trait that reduces the efficiency of degradation of the abnormal α_1-AT molecule once it has accumulated in the ER, there will be greater accumulation of the abnormal hepatotoxic protein in the ER, and the individual is more susceptible to liver disease.

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When these predictions are viewed in the context of the principles that govern the folding, assembly, and secretion of proteins in eukaryotic cells, the following conceptual model for liver injury can be developed (Fig. 1). In normal (PiMM) individuals with or without liver disease, α_1-AT is translocated into the lumen of the ER. It may transiently associate with polypeptide chain-binding proteins, most of which are members of the heat shock/stress protein family, or membrane-associated calcium-binding proteins, until it has folded into its translocation-competent, native conformation, allowing it to traverse the remainder of the secretory pathway. A few newly synthesized α_1-AT molecules may ordinarily undergo degradation in the ER. In deficient (PiZZ) individuals, α_1-AT is translocated into the lumen of the ER. It also associates with polypeptide chain-binding proteins, calcium-binding proteins, or both, but because of its single amino acid substitution, the mutant α_1-AT is much less efficient at folding into the translocation-component shape. Only ~15% of the newly synthesized molecules dissociate and exit through the secretory pathway. Most newly synthesized α_1-AT molecules remain bound and ultimately undergo degradation in the ER, or ER-salvage compartment. This model also provides a reasonable explanation for the development of significant liver injury in a subpopulation of deficient PiZZ individuals. Genetic or environmental factors that increase the net

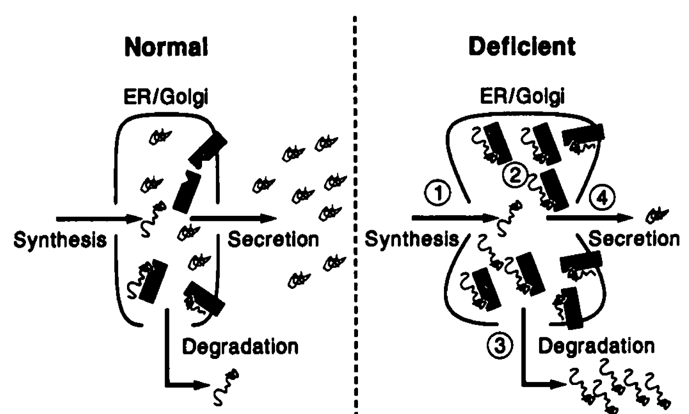

Figure 1. Conceptual model for liver injury in α_1-AT deficiency. See text for description. *PCBP* denotes polypeptide chain-binding protein and *CBP* denotes calcium-binding protein. Modified from reference 1 with permission.

balance of abnormally folded α_1-AT in the ER would predispose the PiZZ individual to liver disease. These other factors could affect the rate of synthesis of α_1-AT (Fig. 1, *right panel, 1*), interaction of α_1-AT with polypeptide chain-binding proteins in ER (Fig. 1, *right panel, 2*), rate of degradation in ER (Fig. 1, *right panel, 3*), or the rate of secretion for the 15% of newly synthesized α_1-AT molecules that are secreted by bulk flow (Fig. 1, *right panel, 4*). For instance, a genetic trait that decreases the efficiency of the putative ER degradative system would lead to higher steady state levels of misfolded α_1-AT in ER and a higher likelihood of hepatotoxicity. Such a genetic trait would be silent in the general population, who are not exposed to a chronic burden of mutant misfolded secretory protein. In another example, PiZZ individuals exposed to higher or more sustained concentrations of environmental factors that enhance synthesis of α_1-AT would be expected to have higher steady state levels of abnormally folded α_1-AT molecules in the ER if the putative ER degradative system is already operating at maximal efficiency.

During the last several years we have tested this conceptual model in two general ways. First, we examined the possibility that there was a reduced rate of ER degradation of α_1-AT Z in a subgroup of deficient PiZZ individuals susceptible to liver disease (9). We transduced skin fibroblasts from PiZZ individuals with liver disease and PiZZ individuals without liver disease with amphotropic recombinant retroviral particles designed to express the mutant Z α_1-AT gene under the direction of a constitutive viral promoter (Fig. 2). Human skin fibroblasts do not express the endogenous α_1-AT gene but presumably express other genes involved in synthesis and postsynthetic processing of secretory proteins. The results show that expression of human α_1-AT gene was conferred on each fibroblast cell line. Compared with the same cell line transduced with the wild-type M α_1-AT gene, there was selective intracellular accumulation of the mutant Z α_1-AT protein in each case (Fig. 3). However, there was a marked delay in degradation of the mutant Z α_1-AT protein after it accumulated in the fibroblasts from ZZ individuals with liver disease

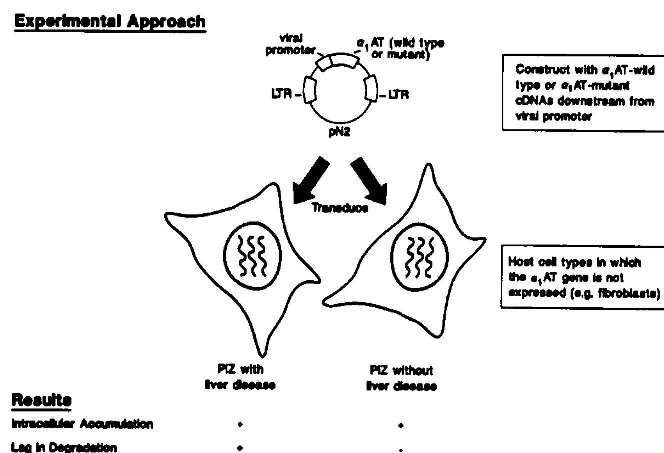

Figure 2. Identification of genetic traits that affect the rate of ER degradation of mutant Z α_1-AT. See text for description. Modified from reference 9 with permission.

("susceptible hosts") compared with that in fibroblasts from ZZ individuals without liver disease ("protected hosts"). Appropriate disease controls showed that the lag in degradation in susceptible hosts is specific for the combination of PiZZ phenotype and liver disease. Biochemical characteristics of α_1-AT Z degradation in the protected hosts were found to be similar to those of a common ER degradation pathway previously described in model experimental cell systems for mutant Z α_1-AT, T-cell receptor-α subunits, asialoglycoprotein receptor subunits, and truncated ribophorin subunits (10–13). These results raise the possibility that the lag in degradation of mutant Z α_1-AT in the susceptible host is a defect in the common ER degradation pathway.

We also examined the possibility that the mutant Z α_1-AT interacts with p88/IP90/calnexin in our transduced skin fibroblast cell lines. Calnexin is an approximately 88-kD calcium-binding ER membrane phosphoprotein that has been shown to interact with retained, incompletely assembled T-cell receptor subunits, membrane Ig chains, and MHC class II heavy-chain subunits in the ER (14–18). In fact, Ou *et al.* (19) have recently shown that the 52-kD precursor of wild-type M α_1-AT in HepG2 cells coprecipitates with calnexin. The results show that calnexin interacts with the 55-kD mutant Z α_1-AT protein that accumulates in the ER of the transduced skin fibroblast cell lines. Even more interesting, however, is evidence that more mutant Z α_1-AT protein coprecipitated with calnexin in the protected host than in the susceptible host. If interaction with calnexin is necessary for initiation of ER degradation of the mutant Z α_1-AT protein or is required for directing the α_1-AT molecule into the ER degradative pathway, then our data would suggest the possibility that there is a structural or functional abnormality in calnexin in at least some susceptible hosts. It is also possible, however, that the failure of mutant α_1-AT protein to interact with calnexin in BWZ cells is a secondary effect, *e.g.* the α_1-AT molecule fails to reach the calnexin-rich subcompartment of the ER because of a more proximal defect.

Taken together, these studies validate our predictions and our conceptual model by showing that a lag in ER degradation of mutant α_1-AT Z correlates with the liver disease phenotype within the α_1-AT-deficient population. Moreover, it provides evidence for a specific mechanism that could serve as the basis for identification of the susceptible subpopulation and for pharmacologic intervention designed for the susceptible subpopulation.

A second general approach has also been used to test the conceptual model for liver injury in α_1-AT deficiency shown in Figure 1: identification of mechanisms by which synthesis of α_1-AT in normal cells is up-regulated and use of these mechanisms to examine the effect of up-regulation of α_1-AT synthesis on the fate of the mutant α_1-AT protein in cells from deficient PiZZ individuals. In this approach, we initially identified three separate mechanisms for up-regulation of α_1-AT synthesis. Bacterial lipopolysaccharide (20), IL-6 (21), and neutrophil elastase (22) each mediated increases in synthesis at α_1-AT in normal

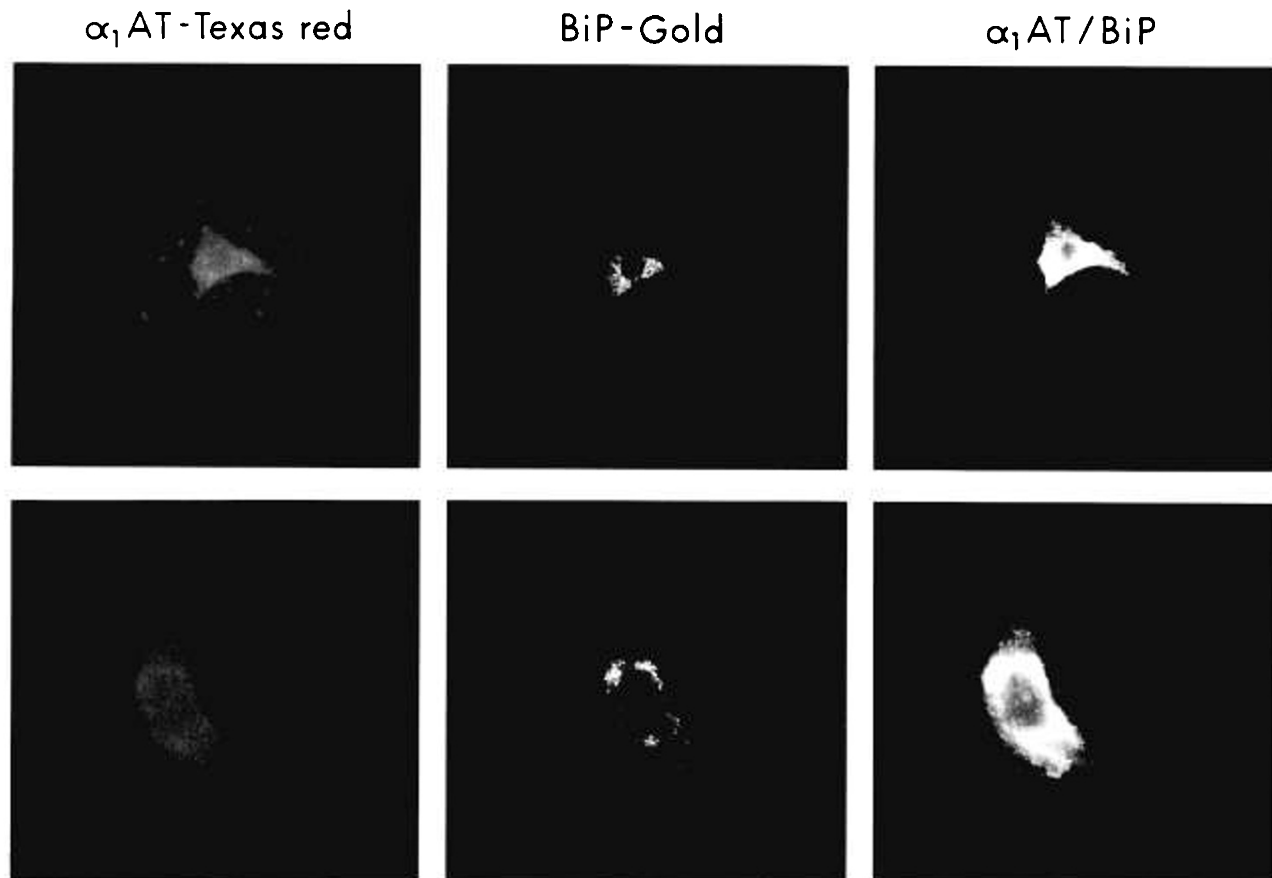

Figure 3. Double-label immunohistochemistry for α_1-AT and BiP in fibroblasts transduced with cDNA for α_1-AT Z. Fibroblasts from a PiZZ individual with liver disease were transduced with cDNA for α_1-AT Z. These cells were first stained with anti-α_1-AT IgG/Texas red-cojugated anti-Ig and viewed under fluorescence microscopy (*left panel*). The cells were then stained with anti-BiP IgG/silver enhanced gold-cojugated anti-Ig and viewed under polarized microscopy (*center panel*). Finally, the same cells were viewed under both polarized and fluorescence microscopy for double labeling (*right panel*). A separate cell is shown in the *top row* and *bottom row*. The results show labeling in a reticular pattern especially prominent in the perinuclear region, colocalizing α_1-AT with the ER protein BiP. Taken from reference 9 with permission.

monocytes. In monocytes from deficient PiZZ individuals, lipopolysaccharide, IL-6, and elastase also mediated increases in synthesis of α_1-AT, but the result was greater net intracellular accumulation of α_1-AT. We have now studied in great detail one of these regulatory mechanisms, the mechanism by which elastase regulates synthesis of its inhibitor, α_1-AT. Because this type of regulatory mechanism potentially allows the integration of α_1-AT production with its functional activity, we believed it would be important in the overall physiologic fate of α_1-AT. We also reasoned that detailed biochemical characterization of this mechanism, such as identification of a cell surface receptor, would allow us to develop pharmacologic antagonists for prevention of at least this type of potentially hepatotoxic phenomenon.

Subsequent experiments had the following results: *1)* neutrophil elastase, in nanomolar concentrations, mediated concentration- and time-dependent increases in steady state levels of α_1-AT mRNA and in the synthesis of α_1-AT in human monocytes and bronchoalveolar macrophages; *2)* the regulatory effect was specific for the effector, elastase, and for the responder, α_1-AT, and required enzymatically active elastase; and *3)* the effect required the formation of a complex of exogenous elastase with endogenous α_1-AT or an exogenous, preformed elastase-α_1-AT complex (22). The last observation suggested that structural rearrangement of the α_1-AT or elastase molecules during formation of an α_1-AT-elastase complex exposed a domain that could be recognized by a specific cell-surface receptor or receptors. To test this hypothesis, we used synthetic peptides based on the sequence of the carboxyl-terminal fragment of α_1-AT as candidate mediators for regulation of α_1-AT synthesis and as candidate ligands for cell-surface binding (23). This region was selected because it had been previously implicated in the chemoattractant properties of α_1-AT-elastase complexes (24, 25) and because crystal structure analysis predicted that a domain within this region was exteriorly exposed after formation of a complex (26, 27). The results indicated that a synthetic peptide (peptide 105Y), based on amino acids 359 to 374 of α_1-AT, mediated a selective increase in α_1-AT synthesis in human monocytes and in human hepatoma HepG2 cells. Radioiodinated peptide 105Y bound specifically and saturably to HepG2 cells, defining a single class of receptors with k_d of ~40 nM at a density of ~4.5×10^5 plasma membrane receptor molecules per cell. Binding of [^{125}I]peptide 105Y was blocked by unlabeled elastase-α_1-AT complexes, and unlabeled peptide 105Y blocked binding of

[^{125}I]α_1-AT-elastase complexes, [^{125}I]elastase-α_1-AT complexes, and [^{125}I]trypsin-α_1-AT complexes. Antisera to keyhole-limpet hemocyanin-coupled peptide 105Y blocked the binding of [^{125}I]α_1-AT-elastase complexes and the increase in synthesis of α_1-AT mediated by α_1-AT-elastase complexes. These results provided confirmatory evidence that at least part of the region corresponding to peptide 105Y represented the receptor-binding domain of α_1-AT-elastase complexes and was capable of transducing a signal to increase synthesis of α_1-AT.

Next, we examined the significance of the high degree of primary sequence homology within this receptor-binding domain of α_1-AT and in the corresponding regions of serpins ATIII, α_1-ACT, and C1 inhibitor. In competitive binding assays, we found that the binding of [^{125}I]peptide 105Y was displaced by ATIII-thrombin, α_1-ACT-cathepsin G, and, to a lesser extent, C1 inhibitor-C1s complexes but not by the corresponding proteins in their native forms. There is also cross-competition for binding to this receptor by serpin-enzyme complexes including α_1-AT elastase, ATIII-thrombin, HCII-thrombin, and α_1-ACT-cathepsin G complexes (28). These data indicated that the receptor that recognizes peptide 105Y and α_1-AT-elastases complexes also recognizes these other serpin-enzyme complexes, so we have called it the serpin-enzyme complex or SEC receptor. In addition, these data showed that the SEC receptor only recognizes the serpin after it has undergone the structural rearrangement that accompanies formation of a complex with its cognate enzyme. Other experimental results showed that the SEC receptor recognizes α_1-AT after it has undergone proteolytic modification at its reactive site by the action of the metalloelastase of *Pseudomonas aeruginosa* or the collaborative action of reactive oxygen intermediates and serine-type elastase (28, 29). In each case, the SEC receptor recognizes a domain within the carboxyl-terminal fragment of α_1-AT that has remained associated with the rest of the α_1-AT molecule by tenacious hydrophobic interactions at the extreme carboxyl terminus and thereby carries to the cell-surface receptor-binding site the larger amino-terminal portion of α_1-AT. The SEC receptor has subsequently been found on a number of different cell types, including hepatoma cells, mononuclear phagocytes, neutrophils, human neutrophilic cell lines U937 and HL-60, human intestinal epithelial cell line Caco2, mouse fibroblast L cells, mouse kidney epithelial cell line Cos, rat neuronal cell line PC12, and human glial cell line U373MG, but it is not present on Chinese hamster ovary cells or HeLa cells.

We have also examined the possibility that the SEC receptor is involved in clearance/catabolism of serpin-enzyme complexes *in vivo* by determining whether it mediated internalization or degradation of these complexes in tissue culture (30). As mentioned earlier, α_1-AT-protease complexes are subject to rapid *in vivo* clearance and are predominantly catabolized in the liver (31, 32). The pathway for clearance/catabolism is shared by other serpin-enzyme complexes, including ATIII-thrombin and α_1-AT-cathepsin G. Our studies showed that α_1-AT-elastase and α_1-AT-trypsin complexes were internalized in Hep G2 cells by SEC receptor–mediated endocytosis and delivered to an acidic compartment, either late endosome or lysosome, for degradation. Thus, these results provide evidence that the characteristics of the SEC receptor in cell culture are similar to those that would be expected for the receptor responsible for *in vivo* clearance/catabolism of at least several serpin-enzyme complexes.

In more recent studies, we have used synthetic peptides to determine the minimal structural requirements for the binding of α_1-AT-elastase complexes by the SEC receptor (33). These studies have shown that a pentapeptide domain within the carboxyl-terminal fragment of α_1-AT (amino acids 370-374, FVFLM) is sufficient for binding to the SEC receptor. A synthetic analog of this pentapeptide (peptide 105C, FVYLI) blocked binding and internalization of [^{125}I]trypsin-α_1-AT complexes by HepG2 cells. [^{125}I]peptide 105C bound specifically and saturably to HepG2 cells, and its binding was blocked by unlabeled trypsin-α_1-AT or elastase-α_1-AT complexes. Alterations of the sequence of the pentapeptide introduced into synthetic peptide (mutations, deletions, or scrambling) demonstrated that recognition by the SEC receptor was sequence specific. Synthetic peptides were also capable of mediating an increase in the synthesis of α_1-AT. As might have been predicted from competitive binding of other serpin-enzyme complexes to the SEC receptor, the SEC receptor–binding pentapeptide neodomain of α_1-AT is highly conserved in the corresponding regions of these other serpins.

Mapping of the SEC receptor–binding domain of α_1-AT led to the serendipitous discovery that there were remarkably similar sequences in other bioactive peptides including substance P, several other tachykinins, bombesin, and the amyloid-β peptide. These peptides have a number of different biologic activities. In many cases, these biologic activities are mediated by specific cell-surface receptors, including tachykinin receptors NK-1 (substance P), NK-2 (substance K), NK-3 (neurokinin B), and several bombesin receptors. Because these cell-surface receptors have only recently been described and because there are only a few highly selective, high-affinity receptor antagonists, it has not yet been possible to attribute all of the biologic activities of these peptides to the known receptors. Furthermore, recent data have suggested that the amyloid-β peptide, the major proteinaceous component of the extracellular deposits found in Alzheimer's disease (AD) and Down's syndrome, has neurotrophic/neurotoxic effects that could be blocked by substance P (34), but a specific cell-surface receptor had not yet been identified. With these considerations in mind, we examined the possibility that the tachykinins, bombesin, and amyloid-β peptide bind to the SEC receptor (35). The results indicated that substance P, several other tachykinins, bombesin, and amyloid-β peptide compete for binding to, and cross-linking of, the SEC receptor. These other ligands also mediated an increase in the synthesis of α_1-AT in monocytes and HepG2 cells. These results were not surprising in

that the two residues within the receptor-binding pentapeptide of α_1-AT that were most affected by mutations, the carboxyl-terminal leucine and methionine residues, are the ones most highly conserved among the tachykinins, bombesin, and amyloid-β peptide.

The SEC receptor was found to be distinct from the substance P receptor by several criteria. There was no substance P receptor mRNA in HepG2 cells or human liver as assessed by ribonuclease protection assays with human substance P receptor complementary RNA as probe. The SEC receptor recognized synthetic peptide ligands with c-terminal, carboxyl-acid or carboxyl-amide moieties with equivalent affinity, whereas the substance P receptor recognized substance P carboxyl-amide with an affinity several orders of magnitude higher than that for substance P carboxyl-acid. The SEC receptor was present in much higher density on receptor-bearing cells and bound its ligands at lower affinity than the substance P receptor. The SEC receptor was much less restricted in the specificity with which it recognized ligands, *i.e.* ligands for the SEC receptor, including peptide 105Y, α_1-AT-protease complexes, bombesin, and amyloid-β peptide did not compete for binding of substance P to a stable transfected cell line expressing the substance P receptor. Several of these criteria also make it highly likely that the SEC receptor is distinct from the substance K, neurokinin B, and bombesin receptors. Partial structural characterization of the SEC receptor also suggests that it is distinct from the tachykinin and bombesin receptors. The ligand-binding subunit of the SEC receptor in HepG2 cells is a single-chain polypeptide of ~80 kD, as determined by covalent photoaffinity cross-linking with a radioiodinated photoreactive derivative of peptide 105Y. Cross-linking of the SEC receptor is highly specific in that it is blocked by unlabeled peptide 105Y, pentapeptide 105C, substance P, bombesin, amyloid-β peptide, and α_1-AT-protease complexes but not by negative-control peptides, mutant peptides, deleted pentapeptides, a substance P receptor antagonist, or native α_1-AT. The SEC receptor has also been purified to homogeneity as an ~80-kD polypeptide from HepG2 cell membranes by ligand-affinity chromatography with α_1-AT-elastase complexes. Amino-terminal amino acid sequence analysis clearly demonstrates that it is distinct from the tachykinin and bombesin receptors.

We have recently examined the possibility that the SEC receptor mediates the neutrophil chemotactic effects of α_1-AT-elastase complexes (36). Previous studies have shown that α_1-AT-elastase complexes and proteolytically modified α_1-AT are chemotactic for neutrophils and that the carboxyl-terminal fragment of α_1-AT possessed all of this biologic activity. First, receptor-binding studies with [^{125}I]peptide 105Y showed that there was a single class of receptors with a k_d (~43 nM) almost identical with that previously reported for HepG2 cells. Second, chemotactic studies showed that peptide 105Y and pentapeptide 105C mediated neutrophil chemotaxis with maximal stimulation of 10^{-9} M to 10^{-8} M. The magnitude of the effect was comparable to that of the chemotactic peptide fMLP at 10^{-8} M. The specificity of the effect was consistent with its being mediated by the SEC receptor, as shown by negative control peptides. Of more importance, the neutrophil chemotactic effect of α_1-AT-elastase complexes was completely blocked by antiserum to keyhole-limpet hemocyanine-coupled peptide 105Y and antiserum to purified SEC receptor but not by a control antiserum. Other ligands for the SEC receptor, including the amyloid-β-peptide, mediated neutrophil chemotaxis. Finally, preincubation of neutrophils with peptide 105Y completely abrogated the chemotactic effect of amyloid-β peptide by inducing homologous desensitization of the SEC receptor. Thus, the SEC receptor mediates the previously recognized chemotactic effect of α_1-AT-elastase complexes and the previously unrecognized chemotactic effect of amyloid-β peptide. It is also likely to mediate the recently described chemotactic effect of α_1-ACT-cathepsin G complexes (37). One would predict that it mediates the chemotactic effect of HCII-thrombin complexes, although a structurally distinct region in the amino-terminal domain of HCII has been shown to possess neutrophil chemotactic activity (38). Additional studies will be necessary to determine whether two regions of HCII can mediate neutrophil chemotactic effects through two distinct receptors. Although the possibility has not been completely excluded, there is no current evidence to suggest that other regions within the α_1-AT molecule or other serpin molecules contribute to binding to the SEC receptor.

Taken together, these studies define the cellular biochemistry of an interesting and physiologically relevant network for the regulation of α_1-AT activity and, hence, extracellular proteolytic activity (Fig. 4). Formation of covalently stabilized inhibitory complexes with neutrophil elastase, or proteolytic modification by metalloelastases, such as pseudomonas elastase, induces structural rearrangement of α_1-AT and, in so doing, exposes a pentapeptide receptor-binding domain in the carboxyl-terminal fragment of α_1-AT. This domain can, in turn, be recognized by a single class of receptors with a

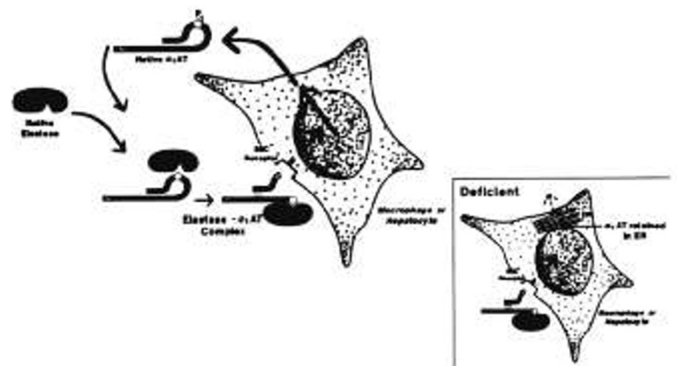

Figure 4. Regulation of α_1-AT synthesis mediated by the SEC receptor. A cell from an α_1-AT-deficient individual is shown in the *inset.* See text for description. Adapted from Perlmutter DH 1993 α1-Antitrypsin: structure, function, physiology. In: Mackiewicz A, Kushner I, Baumann H (eds) Acute phase protein: Molecular biology, Biochemistry, and Clinical Applications. CRC Press, Boca Raton, FL, pp 149–167, with permission.

k_d of ~40 nM and a ligand-binding subunit of ~80 kD. The receptor-binding domain is highly conserved among the serpin family and several serpin-enzyme complexes can be recognized by the same receptor, the SEC receptor. The receptor-binding domain is also conserved among several tachykinins, bombesin, and the amyloid-β peptide. These other ligands are also recognized by the SEC receptor. Once engaged, the SEC receptor is capable of activating a single transduction pathway for increased synthesis of α_1-AT. Thus, the regulatory effect maintains an excess of inhibitor in the extracellular milieu, an effect that is likely to be important for control of limited proteolytic cascade pathways at sites of inflammation, orderly initiation of tissue repair, or prevention of excessive connective tissue destruction around migrating cells and sprouting cell processes. The SEC receptor is also capable of internalizing its ligands and delivering them to an acidic compartment, either late endosome or lysosome, for degradation. On the basis of this property and the similarity of its ligand specificity to the specificity of pathways for *in vivo* clearance/catabolism of serpin-enzyme complexes, the SEC receptor probably mediates *in vivo* clearance/catabolism of certain serpin-enzyme complexes. The SEC receptor also mediates neutrophil chemotactic activities induced by its ligands.

Because activation of the SEC receptor by ligand results in increased synthesis of α_1-AT, it is a mechanism by which more of the mutant, presumably hepatotoxic, α_1-AT Z molecule accumulates within liver cells of PiZZ individuals (Fig. 4, *inset*). According to our conceptual model, therefore, activation of the SEC receptor increases the susceptibility of PiZZ individuals to liver injury. This may be especially relevant in PiZZ individuals with emphysema who receive replacement therapy with purified plasma α_1-AT. This therapy is based on the rationale that the infused α_1-AT will inhibit free neutrophil elastase in body fluids, particularly in the lung. Thus, it is theoretically associated with enhanced levels of α_1-AT-elastase complexes, feedback up-regulation of α_1-AT synthesis by the SEC receptor, and, in turn, increased intracellular accumulation of α_1-AT. Biochemical characterization of the interaction of ligands with the SEC receptor may allow us to develop pharmacologic antagonists for prevention of this type of potentially hepatotoxic mechanism.

Finally, the serendipitous identification of amyloid-β peptide as a ligand for the SEC receptor and the identification of the SEC receptor in cells of neuronal origin raise the possibility that the SEC receptor is involved in neurotrophic/neurotoxic effects that may characterize the neuropathology of AD and presenile dementia in Down's syndrome. The SEC receptor may be involved in the pathophysiologic events that lead to dementia in AD in several other possible ways. First, it is possible that the SEC receptor plays a role in the local inflammatory response associated with amyloid-β deposition. Although it has not been emphasized in the description of AD, an inflammatory response surrounding amyloid plaques has been reported in several studies. In studies of immune-associated antigens in human postmortem samples, several reports show the expression of HLA-DR major histocompatibility antigen on microglial cells adjacent to amyloid plaques (39). Moreover, microglial cell proliferation and scavenging activity, as well as T-cell infiltration, have been observed at plaque sites (40). Because the SEC receptor has been demonstrated on the surfaces of cells of myeloid lineage, including monocytes and neutrophils, and because the SEC receptor has been demonstrated on the surface of human glioblastoma cell lines, it is possible that it is expressed on microglia *in vivo*. Moreover, it becomes a formal possibility that interaction of ligand such as amyloid-β with the SEC receptor plays a role in the directed migration of microglia, as it does for neutrophils, or in the expression of proinflammatory or antiinflammatory products by microglia. Several studies have indicated that molecules that are known ligands for the SEC receptor elicit production of proinflammatory and antiinflammatory cytokines. Kurdowska and Travis (41) showed that α_1-antichymotrypsin-protease complexes and proteolytically modified α_1-antichymotrypsin mediate an increase in production of IL-6 by fibroblasts. Tilg *et al.* (42) have recently shown that peptide 105C (pentapeptide that binds to the SEC receptor) but not peptide 105C-C (tetrapeptide that has a deletion of C-terminal amino acid of peptide 105C and that does not bind to the SEC receptor) mediates induction of IL-1 receptor antagonist and IL-1β in peripheral blood mononuclear cells, with 5- to 10-fold greater induction of IL-1 receptor antagonist than IL-1β. IL-1 receptor antagonist is known to block the biologic activity of IL-1β (43). This may be particularly important in AD in that IL-1β has been shown to mediate increases in synthesis of amyloid precursor protein (44) and therein could increase the tendency toward amyloid-β deposition in a susceptible genetic background. Second, the SEC receptor could play a role in directed migration of neurons or sprouting of neuronal processes toward amyloid plaques. As noted earlier, it is expressed on neuronal cell lines and it mediates directed migration of other cell types, particularly neutrophils. An effect of this type on neurons is potentially very important because ingrowth and degeneration of neurites is considered one of the hallmarks distinguishing mature plaques, associated with dementia, from diffuse plaques, associated with aging. Third, the SEC receptor could play a role in clearance/catabolism of amyloid-β peptide in the CNS. Several recent studies have shown that there is a substantial amount of soluble amyloid-β peptide in brain and spinal fluid (45–48). This soluble amyloid-β peptide is presumably generated by an alternative intracellular processing pathway, the use of which is exaggerated in AD (49–52). The fate of soluble extracellular amyloid-β peptide, the mechanism by which it is converted into aggregates or plaques, and the mechanisms responsible for its catabolism are not known. Fourth, the SEC receptor could play a role in regulating the net proteolytic activity in the extracellular space of the brain, an activity that could contribute to neuronal degeneration (53).

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