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Alpha-1 antitrypsin: Associated diseases and therapeutic uses

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1. Introduction

Alpha-1 antitrypsin (AAT) is a 52 kDa glycoprotein, also called alpha-1 proteinase inhibitor. AAT is synthesized primarily in the liver but also in neutrophils, monocytes, macrophages, alveolar macrophages, intestinal epithelial cells, carcinoma cells, and the cornea [1,2].

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Table 1
The table outlines levels of AAT, frequency and risk of emphysema in various phenotypes.

Phenotype	Average concentration/levels of AAT (g/L)	Frequency	Risk of emphysema
Pi*MM	2	86	No
Pi*MS	1.6	9	No
Pi*MZ	1.2	3	No
Pi*SS	1.2	0.25	No
Pi*SZ	0.8	0.2	Yes
Pi*ZZ	0.4	0.03	Yes

Inhibition of neutrophil elastase (NE) and proteinase 3 is considered the key function of AAT, but it also regulates inflammation, proteostasis, and possibly cellular senescence independently of elastase inhibition. It is encoded by the proteinase inhibitor (Pi) locus on chromosome 14q321, SERPINA I (12.2 kb) (Table 1). Mutations in SERPINA I lead to the M, S, or Z forms of AAT. The presence of the Pi*MM allele in an individual results in normal levels and function of AAT, while the Pi*ZZ and Pi*SZ alleles are associated with disease. The levels of AAT, frequency and risk of pathology such as emphysema vary with the different phenotypes (Table 2). The misfolded Z-AT form accumulates in hepatocytes and is associated with mitochondrial injury as well as apoptosis signaling through cytochrome C release [2]. The accumulated Z-AT further polymerizes within hepatocytes, overwhelming the degradative processes and inducing cellular stress and repair. In a subset of ZZ-AT homozygotes, this can lead to neonatal hepatitis, cirrhosis (Fig. 1), and hepatoma [3–7]. An insufficient AAT level in the lung causes dysregulation of neutrophil elastase activity and emphysema (Fig. 1) which may progress to COPD.

2. History of AAT

Alpha-1 antitrypsin deficiency (AATD) was described by Laurell and Eriksson in 1963 as resulting from loss of an alpha1 protein band in 5 of 1500 patient serum protein samples submitted to his laboratory for electrophoretic analysis [8]. This protein was called antitrypsin because of its ability to inhibit the serum protease trypsin. Three of the five patients lacking this protein had been diagnosed with emphysema at a young age and one had a family history of emphysema. The initial clinical features of AATD were thus defined to be absence of the AAT protein in serum with early onset of emphysema [9,10].

The next clinical landmark was detected by Sharp et al. [11] who found that AATD was related to cirrhosis. In 2004, they reported that children from six families affected by cirrhosis had decreased serum alpha 1-globulin and low trypsin inhibitory capacity. In the following years, the structure of the AAT protein, the mechanism of its binding to neutrophil elastase, and its relation to intrahepatic fat accumulation were resolved. Gaps in our understanding of AATD still persist, such as the risk factors for liver disease, the determinants of emphysema other than cigarette smoking and occupational risk, the role of other genes in AATD, and the criteria for optimal therapy [12]. Because of the strong correlation between AATD and emphysema in children, tests of family members of these index cases often result in detection of additional cases of AATD. Animal experiments by senior and colleagues revealed that removing controls on neutrophil elastase or other lung serine proteases reproduced the features of human emphysema. These clarifications led to the protease/antiprotease theory of the mechanism of emphysema, in which proteolytic demolition of the lung interstitium modifies alveolar structure leading to emphysema.

Table 2
The table outlines the list of few proteinase inhibitors and their plasma range.

Protease inhibitor	Family/class	Concentration (mg/dL)
α1-Antichymotrypsin	Serpin	42–56
α2-Antiplasmin	Serpin	6–8
α1-Antitrypsin	Serpin	215–365
C1-Esterase inhibitor	Serpin	21–27
Antithrombin III	Non Serpin	22–26
Inter-α-Trypsin Inhibitor	Non Serpin	50
α2-Macroglobulin	Non Serpin	190–330

2.1. . AAT deficiency

AAT deficiency (AATD) is a hereditary condition that typically predisposes individuals to emphysema, COPD, cirrhosis, systemic vasculitis, panniculitis, and other inflammatory or neoplastic diseases [9,13]. In addition, several clinical studies have shown that patients with AATD have an increased risk of developing malignant lymphomas [14] including hepatocellular carcinomas [15,16], lung cancer [17–20], asbestosis [21], neoplasms of the urinary bladder [22,23], gallbladder [24,25], and colon cancers [26,27]. In addition, AAT acts as a biomarker for asbestosis and sarcoidosis. Persons with Pi*Z and Pi*S polymorphisms that trap AAT are at increased risk of these diseases [21] as well as those of the liver and the lower respiratory tract [28,29]. Sarcoidosis is characterized by influx of IL2-secreting T lymphocytes and it has been reported that AAT accelerates delayed hypersensitivity responses in *in vivo* studies and macrophage-mediated enhancement of T cell proliferation in *in vitro* studies [30,31].

2.2. Molecular mechanism of AATD

A point mutation alters the folding of Z-AAT protein and increases the likelihood that the protein polymerizes within the ER of liver cells [32] and is retained there [33,34]. Z-AAT undergoes polymerization in a concentration-dependent and time-dependent fashion (Fig. 2) [35–37]. The unfolded protein response (UPR) is one of the stress responses exhibited by cells in which proteins are accumulated. A rise in the concentration of unfolded proteins in the ER initiates a signal transduction cascade for the synthesis of (*a*) chaperones that help to fold aberrant proteins, (*b*) factors that are helpful in destruction of the unfolded proteins, (*c*) enzymes that expand the volume of the ER decreasing the concentration of misfolded proteins, and (*d*) an alternate degradation pathway activator (Fig. 3). Accumulation of ZZ-AAT does not directly induce the UPR [38] but indirectly alters the ZZ-AAT degradation by other UPR-induced genes. UPR has been implicated in a number of liver diseases like non-alcoholic fatty liver disease and steatohepatitis. Furthermore, UPR induction also attenuates global protein synthesis by phosphorylation and inactivation of eukaryotic initiation factor 2alpha (eIF2α). However, eIF2α phosphorylation enhances the translation of specific proteins, including ATF4, which induces the expression of the "CCAAT/enhancer-binding protein homologous protein" (CHOP) transcription factor. CHOP then activates the synthesis of proapoptotic genes as well as GADD34, which stimulates the protein phosphatase-1 (PP1)-mediated dephosphorylation of eIF2α. Dephosphorylation of eIF2 α turns off ATF4 synthesis and dampens the UPR [39]. *In vitro* and *in vivo* studies showed that CHOP acts as a homeostatic sensor in dictating the cellular consequences of ER stress which increases CHOP levels and can lead to apoptosis (Fig. 3). But during times of continued stress, it is important that eIF2 α remains phosphorylated and that ATF4 is active [40].