α-1 Antitrypsin is a potential target of inflammation and immunomodulation (Review)

TIANTIAN WANG[1*], PEIMENG SHUAI[1*], QINGYU WANG[2], CAIMAO GUO[2], SHUQI HUANG[1], YUANYUAN LI[1], WENYU WU[2] and LAN YI[1,2]

[1]Hengyang Key Laboratory of Cellular Stress Biology, Institute of Cytology and Genetics, Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study, Hengyang Medical School, University of South China, Hengyang, Hunan 421001, P.R. China; [2]Hengyang Key Laboratory of Cellular Stress Biology, Institute of Pharmacy and Pharmacology, Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study, Hengyang Medical School, University of South China, Hengyang, Hunan 421001, P.R. China

Received August 22, 2024; Accepted December 12, 2024

DOI: 10.3892/mmr.2025.13472

Abstract. α-1 Antitrypsin (AAT) is an acute phase protein encoded by the *serine protease inhibitor family A member 1* gene. This multifunctional protein serves several roles, including anti-inflammatory, antibacterial, antiapoptotic and immune regulatory functions. The primary role of AAT is to protect tissues and organs from protease-induced damage due to its function as a serine protease inhibitor. AAT is associated with the development of lung inflammation, liver inflammation and immune-mediated inflammatory diseases, which are influenced by environmental and genetic factors. For instance, AAT acts as an anti-inflammatory protein to prevent and reverse type I diabetes. The present study briefly reviewed the molecular properties and mechanisms of AAT, as well as advances in the study of lung, liver and inflammatory diseases associated with AAT. The potential of AAT as a diagnostic and therapeutic target for inflammatory and immune-mediated inflammatory diseases was reviewed. In addition, the damaging and protective effects of AAT, and its effects on organ function were discussed.

Correspondence to: Professor Lan Yi, Hengyang Key Laboratory of Cellular Stress Biology, Institute of Cytology and Genetics, Hunan Province Cooperative Innovation Center for Molecular Target New Drug Study, Hengyang Medical School, University of South China, 28 Changsheng West Road, Hongxiang Street, Hengyang, Hunan 421001, P.R. China
E-mail: yilan@usc.edu.cn

*Contributed equally

Key words: α-l antitrypsin, serine protease inhibitor, immunomodulator, autoimmune disease, immune-mediated inflammation

Contents

1. Introduction

α-1 Antitrypsin (AAT) is an acute phase glycoprotein with a molecular weight of 52 kDa, belonging to the serine protease inhibitor (SERPIN) superfamily (1,2). It is encoded by the *SERPIN family A member 1* (*SERPINA1*) gene located on the long arm of chromosome 14 (14q31-32.3), which spans 12.2 kb and exhibits structural plasticity (3,4). The structure of AAT comprises three β-folds (A-C) and nine α-helices (A-I), along with a reaction center loop (RCL) that protrudes from the molecule. Plasma AAT is primarily synthesized by hepatocytes, but it is also produced by monocytes, macrophages and epithelial cells (5). During the acute phase response, circulating levels of AAT increase markedly. AAT has anti-inflammatory, immunomodulatory, anti-infective and tissue repair properties (6).

Changes in AAT expression levels are associated with a variety of inflammatory and immune-mediated inflammatory diseases, such as chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis (7-9). In addition, its expression levels are also correlated with environmental exposure factors (10-14), highlighting the role of this protein in diseases associated with environmental exposure. Consequently, elucidating the association between AAT and environmental factors is important to advance AAT-related therapeutic developments. The present study reviews the impact of AAT

on inflammation, immune-mediated inflammatory diseases and other conditions associated with genetic mutations and environmental exposures. Mutations in the AAT gene are implicated in lung inflammation, hepatitis, cirrhosis and liver cancer (7,8,15-17). Furthermore, AAT is discussed as a novel immunomodulator in autoimmune diseases, as it is involved in complex signaling pathways and interactions with multiple cytokines. It is proposed that AAT may serve as a potential therapeutic target for inflammatory diseases.

2. AAT is a multifunctional protein involved in disease development

AAT conformational polymorphisms determine biological function. AAT, as other secreted proteins, requires processing by the endoplasmic reticulum (ER) and Golgi apparatus. The stable conformation of AAT is established through protein folding (18). AAT synthesis is regulated by both ER cargo receptors and biosynthetic quality control systems. The process of AAT monomer extension to polymer secretion is not accomplished in cells with disruption of the ER cargo receptors lectin mannose binding 1 and surfeit protein locus 4. ER cargo receptors modulate the synthesis of AAT within the ER and can influence the accumulation of polymeric AAT by controlling the concentration of precursor monomers and facilitating the secretion of polymers (19). The biosynthetic quality control system first enhances the structural maturation of AAT and subsequently selectively eliminates immature molecules, thereby promoting AAT secretion (20). The transport pathway of AAT is intricate; it is transported to the pulmonary epithelium and interstitium through apical endothelial cells via endocytosis and transcytosis, with secretion occurring at the basolateral surface (21). Additionally, AAT undergoes bidirectional uptake and secretion between lung endothelial cells and alveolar epithelial cells, as well as the air chambers (22). The conformational polymorphisms of the AAT protein contribute to the complexity of its biological functions.

AAT is a unique regulator of inflammatory cytokines. AAT is a multifunctional protein with several key roles, including anti-inflammatory, antibacterial and antiapoptotic functions, as well as the inhibition of serine proteases (23). As a unique endogenous anti-inflammatory agent, AAT inhibits the synthesis and release of inflammatory mediators while suppressing the production of inflammatory cytokines. Its anti-inflammatory activities include NF-κB-dependent mechanisms, such as the induction of the IL-1 receptor antagonist (24). The antibacterial properties of AAT are primarily demonstrated through its inhibition of *Streptococcus pneumoniae* in the lungs of mice. A previous study reveals that lung clearance in untreated mice infected with *S. pneumoniae* is compromised due to the degradation of surfactant proteins A and D (which are important for phagocytic activity) by neutrophil elastase (25). Conversely, AAT was shown to inhibit neutrophil elastase-mediated degradation, thereby alleviating the bacterial infection in the lungs (25). Additionally, AAT exerts antiapoptotic effects on structural lung endothelial cells (26). Previous studies have investigated the role of AAT in disease regulation, particularly in autoimmune diseases, diabetes and cell transplantation (9,27). Furthermore, there is an adaptive immune response to AAT in AAT-deficient lungs (28). In addition, the anti-inflammatory and immunomodulatory properties of AAT remain intact despite its anti-elastase effect (29). AAT therapy can prevent or reverse type 1 diabetes and acute graft-vs.-host disease (GvHD) in preclinical models of autoimmunity and transplantation, in which alterations in cytokine and transcriptional profiles, as well as T cell subset tolerance, are observed (30,31).

AAT may have a role in cellular senescence. Oxidative stress is central to the cellular aging process (32) and the supplementation of exogenous AAT can increase antioxidant levels such as SOD and reduces oxidative stress (33). The balance between oxidants and antioxidants is indirectly restored through the antiapoptotic and anti-inflammatory effects of AAT, although AAT does not directly facilitate the clearance of oxidants. One of the key physiological functions of AAT is to protect lung tissue from serine proteases (34), and AAT specifically inhibits neutrophil elastase, proteinase 3 and proteinase G (35). The identification of AAT as a potent inhibitor of neutrophil elastase led to the proposal of the protease-antiprotease imbalance concept, which links the pulmonary destruction associated with AAT deficiency (AATD) to the unchecked activity of proteases (36). AATD results in the loss of inhibition of neutrophil serine proteases, leading to local tissue damage, as highlighted in the protease-antiprotease hypothesis (37). Furthermore, AATD is associated with the overexpression of inflammatory cytokine, which triggers inflammation in lung cells, resulting in both lung and liver disease.

3. AAT is associated with a variety of diseases

When AAT is expressed *in vivo*, its regulation of processes such as immunity, inflammation, protein stabilization, apoptosis and cellular decay contribute to lung maintenance (6,33,38). AAT has also been associated with hepatitis, cirrhosis and rheumatoid arthritis (9,17).

AAT is involved in the development and progression of lung-related diseases. AATD is an autosomal codominant disorder caused mainly by point mutations in the *SERPINA1* gene that can cause lung related diseases such as emphysema (39). Decreased serum and tissue levels of AAT increase the risk of developing COPD and emphysema (7,8). Compared with healthy individuals, patients with COPD, emphysema or bronchiectasis have an increased susceptibility to AATD (15,16). AAT influences exacerbation patterns in patients with COPD, particularly in those with frequent exacerbations of AATD (40). The levels of AAT protein differ across various lung diseases, including cystic fibrosis, interstitial pneumonia and bronchiectasis. In cystic fibrosis, AAT levels remain normal, but neutrophil elastase levels increase to levels that exceed the protective effect (41). Lower serum AAT levels are prevalent in patients with non-idiopathic interstitial pneumonia compared with patients with idiopathic interstitial pneumonia (42). Reduced AAT levels can also instigate bronchiectasis (43). In contrast to COPD, AATD is associated with an increased abundance and activity of primary granule proteins, including neutrophil elastase, on the cell surface (44).

Table I. AAT is expressed at different levels in lung diseases.

Diseases	Expression of AAT	Associated mechanism	(Refs.)
COPD	Downregulated	Inhibits the invasion and damage of neutrophil proteases	(15,16)
Emphysema	Downregulated	Inhibits the invasion and damage of neutrophil proteases	(15,16)
Cystic fibrosis	Normal	Overreaction of neutrophil elastase overwhelms normal AAT protection	(41)
Interstitial pneumonia	Downregulated	Inhibits excess cytokines and cellular inflammation in the lung	(42)
Bronchiectasis	Downregulated	Inhibits the inflammatory response triggered by serine proteases/matrix metalloproteinases	(41)
Coronavirus disease 19	Downregulated	Inhibits transmembrane serine protease 2	(45,46)
Lung cancer	Upregulated	Resists cell death	(38)
Lung adenocarcinoma	Upregulated	Promotes intercellular adhesion as well as tumor invasion and metastasis	(47)

AAT, α-1 antitrypsin; COPD, chronic obstructive pulmonary disease.

Coronavirus disease 2019 represents a novel challenge with an unprecedented impact on human health and development (45). AAT inhibits severe acute respiratory syndrome coronavirus 2 infection by blocking transmembrane serine protease 2 (46).

In addition to the lung diseases mentioned above, AAT is also associated with a poor prognosis for cancer. In non-small lung cancer cell lines, the presence of exogenous AAT inhibits staurosporine (STS)-induced apoptosis. At the same time, CLU (a pro-tumorigenic gene coding clusterin protein) expression was higher (38). Furthermore, the expression of AAT is associated with the metastasis of lung adenocarcinoma cells, potentially promoting their spread by upregulating fibronectin (47). The upregulation of the expression of AAT enhances the adhesion between lung adenocarcinoma cells and human umbilical vein endothelial cells (47). This adhesion represents a key step in the processes of tumor invasion and metastasis.

In summary, AAT is associated with a variety of lung inflammatory diseases. The expression level of AAT is different in different pulmonary inflammatory diseases. The upregulated expression of AAT can inhibit the inflammatory factors produced by lung inflammation, while the lack of AAT can promote the expression of inflammatory cytokines in the lung (Table I).

Association of AAT with liver-related diseases. AATD is associated with neonatal hepatitis, cirrhosis hepatocellular carcinoma and other liver-related diseases (17). Misfolded AAT accumulates in the ER of hepatocytes, leading to mitochondrial dysfunction (48). Defective AAT results in swelling and damage to hepatocytes, which can progress to cirrhosis and pancreatitis (49,50). Hepatic steatosis can exacerbate acute pancreatitis (51) and panniculitis may be the initial presentation of both AATD and pancreatic disease (52). Hepatic steatosis acute pancreatitis is associated with reduced levels of AAT and these levels associate with increased disease severity (51). A previous study indicates that AAT may be effective in treating acute liver failure and pancreatic disease (53). Furthermore, AATD may predispose patients to panniculitis (50). In addition to being associated with a variety of lung inflammatory diseases, AAT is also associated with liver inflammation. The main manifestation of AATD is that it can cause diseases such as hepatitis, panniculitis, cirrhosis and pancreatitis.

AAT regulates inflammation and immune-mediated autoimmune diseases. AAT exhibits anti-inflammatory and immunomodulatory effects in various lung diseases; however, there is increasing evidence that it also has a role in diseases such as rheumatoid arthritis, systemic lupus erythematosus (9,31,54,55). Autoimmune diseases are characterized by an overactive immune system that attacks the tissues and organs of the host. Numerous mechanisms and factors can trigger these diseases, including the inflammatory response. Consequently, anti-inflammatory therapies hold promise for the treatment of autoimmune diseases. AAT, an anti-inflammatory protein, can prevent and reverse type 1 diabetes and improve conditions such as rheumatoid arthritis and systemic lupus erythematosus (SLE) (9,54). Wegener's granulomatosis (WG), another autoimmune disease, is classified as a necrotizing granulomatous vasculitis. Proteinase 3 is predominant in WG, and AAT acts as the main inhibitor of proteinase 3; thus, AATD may contribute to the pathogenesis of WG (55,56). Furthermore, AAT is hypothesized to be a novel immunomodulator in transplantation (27). Acute graft-vs.-host disease (GvHD) arises from the interaction of donor T cells, host antigen-presenting cells and various proinflammatory cytokines (such as TNF-α and IL-1β). However, exogenous AAT can mitigate clinical manifestations of GvHD (31). Autoimmune diseases are caused by an active immune system that produces a number of antibodies that attack its own tissues, leading to inflammation and tissue damage. In this process, AAT has an important anti-inflammatory role, and AAT has become a potential therapeutic target for immune-mediated inflammation.

AAT has various functions in other diseases. AAT is associated with heart disease and neurodegenerative diseases.

Table II. Other diseases associated with AAT.

Diseases	AAT expression level	Function	(Refs.)
AMI	Low level of AAT	Limits infarct size and reduces Caspase-1 activity in ischemic myocardium	(57,58)
ND	Expression of AAT is upregulated	Downregulation of inflammasome expression level	(60,61)
Diabetes	Change in activity	Protects pancreatic β-cells from cytokine-induced apoptosis	(63)
IDD	Expression of AAT is upregulated	Improving disease progression	(65)
CRC	Upregulation of AAT expression level in plasma	Enhance the resistance of cancer cells to anti-cancer drugs	(70)
GC	Upregulation of AAT expression level in plasma	Biomarkers of stomach-related diseases	(72)

AAT, α-1 antitrypsin; AMI, acute myocardial infarction; IDD, intellectual development disorder; CRC, colorectal cancer; ND, neurodegenerative diseases; GC, gastric carcinoma.

Plasma-derived AAT reduces cardiac infarct size in mice with acute myocardial infarction (57). Furthermore, exogenous AAT decreases caspase-1 activity in the ischemic myocardium, thereby offering myocardial protection (58). A previous study indicated an association between AAT and the regulation of vascular function by lipoproteins (59). Neuroinflammation contributes to the degeneration of nerve cells, which is a hallmark of neurodegenerative diseases. Blocking neuroinflammation by downregulating inflammasome expression levels by altering the expression of AAT may be beneficial in delaying the onset of neurodegenerative diseases, as demonstrated in rd1 mice, a mouse model for retinal degeneration (60,61).

AAT also exhibits therapeutic potential in diabetes, with its activity being altered in both type 1 and type 2 diabetes mellitus (62). Additionally, AAT protects pancreatic β-cells from cytokine-induced apoptosis (63), with these effects potentially being mediated through the cAMP pathway (64). Upregulation of AAT expression levels reduces the extent of intervertebral disc degeneration (65). In addition, there is a positive correlation between AAT levels and different types of cancer, including pancreatic, ovarian, breast and colorectal cancers (66-69). AAT enhances the resistance of non-small cell lung cancer cells to anticancer drug-induced apoptosis and autophagy (70). Additionally, higher concentrations of AAT are observed in the sera of patients with colorectal cancer compared with healthy controls (66). Patients with gastric cancer also have increased AAT levels in the gastric fluid compared with that of healthy individuals and patients with benign gastrointestinal diseases (71); however, the precise mechanism underlying this observation remains unclear and warrants further investigation. Nonetheless, AAT has a potential use as a biomarker for gastric-related diseases (72) (Table II).

4. AAT is involved in multiple mechanisms of action in inflammation and immunomodulation

AAT is expressed at different levels in, and is associated with the mechanisms underlying the pathogenesis of, a range of diseases (38,47,70). The functions of AAT are associated with multiple factors such as genetic polymorphisms of AAT, complex cellular signaling pathways and multiple cytokines (73).

Genetic diversity of AAT. Genetic polymorphisms are associated with disease development and prognosis. The *SERPINA1* gene, which encodes AAT, is polymorphic, with >100 known variants (74). Following gene mutation, plasma AAT can undergo three different fates: Intracellular storage, intracellular degradation or lack of synthesis (75). These alterations result in a compromised defense mechanism in the lungs against serine proteases (73). Wild-type AAT proteins exhibit variable folding patterns. A more stable conformation is achieved when the active central loop is incorporated as the fourth strand in β-sheet A. The formation of these more stable conformations can render AAT susceptible to mutations (76). Severely misfolded mutants trigger the unfolded protein response (UPR), which enhances protein folding. Conversely, if these mutants fail to activate the UPR, they can promote NF-κB-mediated ER overload responses (77). The protease inhibitor (Pi) M homozygotes represents the normal genotype, characterized by normal AAT plasma levels (78). Heterozygotes composed of M-type and other phenotypic (S/Z) alleles exhibit AAT deficiency (78). By contrast, the PiZ, PiS and Null alleles are defective variants, with the PiZ allele most frequently associated with severe defects and disease (79,80). Missense mutations identified in the PiZ variant of AAT (Z-AAT) may accelerate misfolding and/or lead to the formation of aggregates (81), resulting in increased N-glycosylation of Z-AAT.

Several studies have identified and characterized new variants of AAT mutants (79,80,82). One such defective variant, Ala336Pro, demonstrates a propensity to polymerize more readily compared with both the wild-type AAT and Z-AAT as it forms the polymerization intermediate more efficiently. Furthermore, the folding barrier for Ala336Pro AAT is notably lower compared with that of Z-AAT (83). Another novel mutant, Trento, has been shown to be secreted from cellular models; however, its conformational stability is compromised (82). By contrast, the Gly349Arg variant, which is part of the AAT response center loop, is classified as

Table III. Summary of AAT gene mutations and diseases.

Typical AAT genotype	Mutant amino acids	Cellular defects	Plasma AAT levels	Mutation loci
PiM	Ala213/Val213	None	Normal	II, III and V
PiS	Glu264Val	AAT variant degradation	Decreased	III
PiZ	Glu342Lys	AAT variant accumulation	Decreased	V
Null	Diverse mutant amino acids	AAT variant accumulation/degradation; AAT forms a functionally inactive polymer; AATmRNA not detected	Decreased	II, III, IV and V

AAT, α-1 antitrypsin; PiM, protease inhibitor M allele; PiS, protease inhibitor S allele; PiZ, protease inhibitor Z allele.

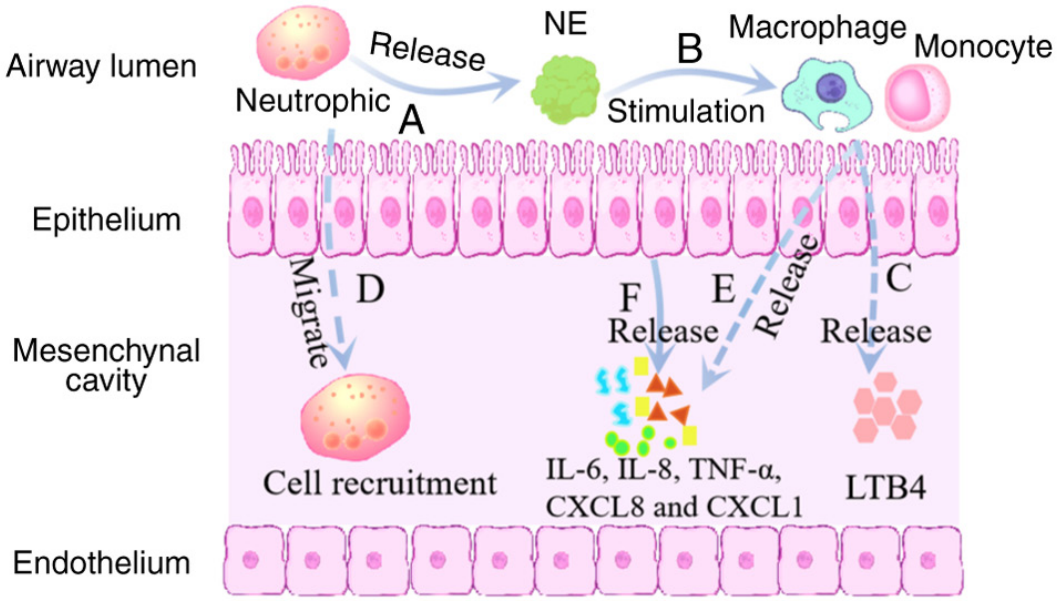

Figure 1. Z-AAT or AAT deficiency causes cells to release inflammatory factors. (A) In the presence of Z-AAT or in the absence of AAT, neutrophils are not inhibited and remain active, and thus release NE. (B) NE further stimulates macrophages. (C) Macrophages are stimulated to produce LTB4. (D) LTB4 recruits neutrophils, which remain in the interstitial cavity and can exacerbate the destruction of connective tissue. (E and F) Macrophages, monocytes, alveolar epithelial cells and endothelial cells release inflammatory cytokines IL-6, IL-8, TNF-α, CXCL8 and CXCL1. The figure was drawn using Adobe Illustrator 2024 (Adobe Systems, Inc.) and WPS Office Presentation (Beijing Kingsoft Office Software Co.; https://www.wps.com) software. AAT, α-1 antitrypsin; Z-AAT, Z variant of AAT; NE, neutrophil elastase; LTB4, leukotriene B4; CXCL, C-X-C motif chemokine ligand; TNF-α, tumor necrosis factor-α.

a functionally defective (type II) AATD mutant. Although it is secreted normally in cellular models of AATD, it exhibits reduced anti-neutrophil elastase activity. This variant also demonstrates an unfavorable presentation of the RCL to homologous proteases, and the insertion of the RCL into β-sheet A is impaired (84). The diversity of the AAT gene mutants results in various phenotypic characteristics, which are associated with diseases such as AATD (Table III).

AAT interacts with neutrophil elastase and cytokines. Serum AAT regulates ligand-receptor interactions, which in turn modulate cytokine and neutrophil intracellular signaling (85). *In vitro,* demonstrate that AAT reduces the expression of Superoxide anion (O_2^-) in neutrophils and inhibits the stimulation of cyclic adenosine monophosphate receptors as well as the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 (86). Neutrophil elastase, a serine protease, is a key enzyme produced by neutrophils (87). In patients with AATD, AAT levels are decreased, inactive polymers of AAT are present in the plasma and neutrophil elastase levels are increased, resulting in an imbalance in the pulmonary protease-antitrypsin system (88-91), as shown in Fig. 1. AAT acts as a serine protease inhibitor through RCL. At normal levels, AAT binds to the serine protease and causes aberration and inactivation of the serine protease. If the level of AAT is reduced or the level of serine protease is increased, the inhibitory effect cannot be played, resulting in the occurrence of disease (28,91). In addition, another serine protease, protease 3, is also thought to have the same or even greater impact on the disease process (92).

In addition to directly interacting with proteases, AAT also interacts indirectly with a variety of cytokines. The mechanisms of the innate immunity can be modulated by the anti-inflammatory activity of AAT, which is mediated through interactions at the cell surface (93). AAT inhibits the secretion of proinflammatory cytokines (94). Both native

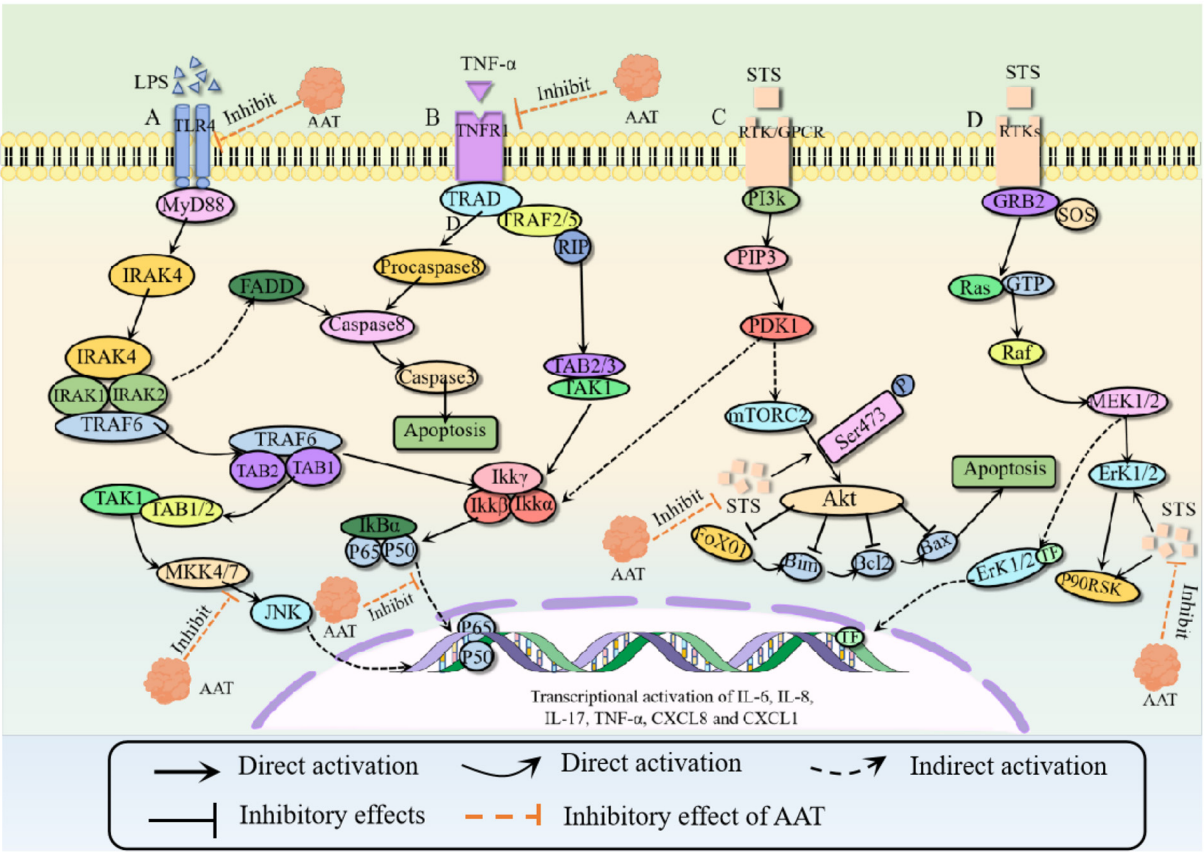

Figure 2. AAT is involved in the regulation of the cell signaling pathways and the pathogenesis of disease. AAT is involved in four main signaling pathways. (A) LPS binds to the ligand TLR4 and induces the release of cellular inflammatory factors due to the TLR signaling pathway. By contrast, AAT inhibits membrane TLR4 levels and IκBα phosphorylation, thereby reducing the release of cellular inflammatory factors. Tak1-tab1/2 is a protein kinase complex. TARF6 activates TAK1 kinase, TAK1 protein phosphorylates Mkk4/7, and MKK4/7 activates the JNK pathway by double-phosphorylating the JNK TPY domain. Eventually, inflammatory factors are produced. AAT inhibits the phosphorylation of MKK4/7, thereby inhibiting the production of inflammatory factors. (B) TNF-α binds to the receptor TNFR1 and induces the release of cellular inflammatory factors due to the NF-κB signaling pathway. AAT reduces TNFR1 levels and inhibits IκBα phosphorylation, thereby inhibiting the production of inflammatory factors. (C) STS binds to the receptor RTK/GPCR and induces the Akt signaling pathway. AAT blocks apoptosis induced by STS. (D) STS binds to receptor RTKs and induces the MAPK signaling pathway. AAT blocks the phosphorylation of ERK1/2 and P90RSK by STS, thereby inhibiting apoptosis. The figure was drawn using Adobe Illustrator 2024 (Adobe Systems, Inc.) and WPS Office Presentation (Beijing Kingsoft Office Software Co.; https://www.wps.com) software. AAT, α-1 antitrypsin; LPS, lipopolysaccharide; TLR, toll-like receptor; TAK1-TAB1/2, transforming growth factor-β activated kinase 1-TAK binding proteins 1/2; TNF-α, tumor necrosis factor-α; STS, staurosporine; RTK, receptor tyrosine kinase; GPCR, G protein-coupled receptor; P90RSK, 90 kDa ribosomal s6 kinases; MKK4/7, mitogen kinase kinase 4/7; MyD88, myeloid differentiation primary response 88; IRAK, IL-1 receptor associated kinase; TRAF, tumor necrosis factor receptor-associated factor; FADD, fas-associating protein with a novel death domain; TRAD, tumor necrosis factor receptor-associated death domain protein; RIP, receptor-interacting protein; P50, NF-κB1; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PDK1, pyruvate dehydrogenase kinase 1; Bim, bcl-2 interacting mediator of cell death; GRB, growth factor receptor-bound protein; SOS, son of sevenless protein; GTP, GTP binding protein; CXCL, C-X-C motif chemokine ligan.

and oxidized forms of AAT inhibit the ATP-induced release of IL-1β from human monocytes (95,96), independent of the antielastase activity of AAT. In addition, AAT regulates ATP-induced IL-1β release through a novel triple transmembrane signaling pathway. This triple transmembrane signaling pathway includes lipid scavenger receptor CD36, calcium-independent phospholipase A2β and the release of a small soluble mediator (96). This mediator activates nicotinic acetylcholine receptors, thereby inhibiting the ATP-induced release of IL-1β from human monocytes (96). In addition, glycosylated AAT binds to IL-8, the ligand for C-X-C motif chemokine receptor 1 (Cxcr1), and obstructs the interaction of IL-8 with Cxcr1, thereby inhibiting the release of pro-inflammatory cytokines (97). In the presence of Z-AAT and AATD, neutrophils remain active and accumulate in the interstitial space, exacerbating connective tissue destruction. It causes macrophages, monocytes, alveolar epithelial cells and endothelial cells to release inflammatory cytokines such as IL-6, IL-8, tumor necrosis factor-α (TNF-α) and C-X-C motif chemokine ligands 8 and 1 (8,95,96,98,99), as shown in Fig. 1. Circulating serine protease inhibitors, including human AAT (hAAT), inhibit the secretion of proinflammatory cytokines IL-17 and IL-6 (100). hAAT has a notable role in inducing the production of anti-inflammatory cytokines. It enhances the expression of IL-1 receptor (IL-1R) in macrophages and human monocytes and promotes distinct phosphorylation and nuclear translocation patterns of p65, a key transcription factor necessary for the expression of IL-1R (101) as shown in Fig. 2. Additionally, hAAT increases the number of T-regulatory cells as well as the expression of C-C chemokine receptor type 6 in animal models (100,102).

AAT is a key element involved in multiple signaling pathways. AAT is involved in a variety of complex signaling pathways.

Table IV. Mechanism of action of AAT in different exposure sources.

Exposure sources	Models	Mechanism of action	(Refs.)
Toxic agents			
Tramadol	Mouse	Dysregulation of the expression of AAT	(11)
SM	SM-exposed subjects	Upregulation of AAT expression levels	(12)
Heavy metals			
Arsenic	Arsenic-exposed subjects	Decreased AAT in sputum	(13)
Ionizing radiation			
11 Gy	Mouse	Upregulation of AAT expression levels	(127,128)
137 Cs	Mouse	Upregulation of AAT expression levels	(129)
Uranium tailings	Mouse	Upregulation of AAT expression levels	(14)
Others			
Organic dust	Organic dust-exposed subjects	AAT inhibits the production of proinflammatory cytokines	(130,131)
Vapor	Vapor-exposed subjects	AAT levels fail to inhibit serine proteases	(116)

AAT, α-1 antitrypsin; SM, sulfur mustard.

It attenuates coagulation and inhibits the cytokine-induced activation of JNK and NF-κB in the instant blood-mediated inflammatory response (103). Its anti-inflammatory activity also involves NF-κB-dependent mechanisms (24). The accumulation of the Z-AAT variant activates the NF-κB signaling pathway, leading to the hypothesis that the downstream targets of NF-κB are components of the proteostasis response network in this specific type of proteinopathy (104). Furthermore, the reduction of Z-AAT monomers may stimulate the expression of the PiZ by decreasing the activation of hepatic NF-κB and IL-6 levels (105). Additionally, respiratory epithelial cells induce oxidative stress and activate the NF-κB signaling pathway under senescent conditions (106).

Oxidative stress is implicated in both the physiological and pathological processes of AATD, suggesting that AAT may have a role in cellular senescence (107,108). Additionally, TNF-α is key to the pathogenesis of both hereditary AATD and non-hereditary COPD. TNF-α can induce signal transduction in immune cells and lung endothelial cells, and AAT is a key regulator of the TNF-α signaling pathway (109). AAT inhibits the activity of TNF-α-converting enzyme, suppresses the upregulation of TNF-α receptor 1 and reduces the expression of TNF-α (Fig. 2). Calpain is activated by TNF-α and AAT inhibits calpain activity, leading to a decrease in the level of AAT itself (99). In addition, AAT can inhibit the phosphorylation of IκBα, thereby reducing the activation of NF-κB and inducing target gene transcription (110). In alveolar epithelial cells, lipopolysaccharide (LPS) induces toll-like receptor (TLR) signaling pathways (54,96,111). AAT exerts anti-inflammatory effects by inhibiting the expression of TLR4 and the phosphorylation of IκBα (Fig. 2). This signaling pathway also activates the JNK signaling pathway to produce proinflammatory cytokines (103). However, AAT can inhibit the phosphorylation of JNK and thus inhibits the proinflammatory pathways (103,111). AAT also inhibits the TNF-α induced activation of the WNT/β-catenin signaling pathway in human bone marrow cells (61).

AAT inhibits the apoptosis of non-small lung cancer cells induced by STS (112). STS can induce apoptosis by downregulating the Akt/MAPK pathway. AAT can eliminate this downregulatory effect of STS and thus inhibit STS-induced apoptosis (38). AAT blocks the inhibition of Ser473 phosphorylation by STS, thereby inhibiting apoptosis. STS inhibits the MAPK signaling pathway by inhibiting the phosphorylation of ERK 1/2 and p90RSK (38). AAT is involved in blocking STS action as well as regulating cell proliferation and the transcription of cell survival genes (Fig. 2). AAT may also have a role in the Janus kinase-STAT and T-cell receptor signaling pathways (113), but the specific mechanism of action of AAT requires further investigation.

5. AAT is a potential target of environmental factor-induced senescence

Lifestyle factors such as smoking can cause lung disease. AAT protects the lung by blocking the constant influence of damage associated molecular patterns and/or pathogen associated molecular patterns caused by cigarette smoke, pollutants or infections (114). In patients with AATD, smoking exacerbates lung disease (10,115,116).

AAT is associated with damage caused by smoke exposure. Numerous studies suggest that chronic non-communicable diseases such as COPD develop as a result of a combination of exposure to various environmental factors (such as smoke, organic dusts, irradiation, toxic agents and metal substances) and genetic predispositions (11,13,115,117-119). Levels of AAT vary under different exposure conditions, and continued exposure of patients with AATD to certain environmental factors accelerates disease progression. There is a complex interrelationship between smoke exposure, circulating AAT levels, systemic inflammation and lung function (120). Furthermore, AAT levels differ between smokers and non-smokers (117). Cigarette smoke has been shown to inhibit AAT uptake in dermal cells and the lungs of mice (10); this inhibition is mediated by neutrophil-derived serine proteases, primarily neutrophil elastase, which can induce connective tissue

rupture, leading to alveolar space enlargement and emphysema in animal models (118). Exogenous AAT is protective and can inhibit thrombin and plasma proteins that leak into the lungs following cigarette smoke exposure, thereby preventing protease-activated receptor type 1 activation and the release of MMP-12 and TNF-α, which inhibits matrix degradation (121,122). Furthermore, cigarette smoke acts as a proinflammatory agent (123). In individuals with genetic defects in AAT, exposure to cigarette smoke accelerates the development of COPD, eliciting an inflammatory response from AATD macrophages to cigarette smoke-induced extracellular vesicles (124). This is evidenced by the additive role of smoking and intermediate AAT levels in PiMZ heterozygotes in the development of emphysema (125), suggesting that gene-environment interactions are key in the pathogenesis of COPD (119). AAT may mitigate smoking-induced inflammation and stromal breakdown through an anti-inflammatory mechanism that is associated with the inhibition of TNF-α, providing partial protection against emphysema (126).

AAT is involved in damage from other environmental factors. Various sources of exposure, including toxic agents, metals and irradiation, notably impact the expression of AAT. Chronic tramadol exposure leads to the dysregulation of α-1-antitrypsin (encoded by *SERPINA1b*) (11), while exposure to sulfur mustard notably increases AAT levels in saliva (12). In addition, arsenic metalloid exposure in tap water reduces AAT in sputum (13). Irradiation also alters AAT levels; in a mouse model subjected to total body irradiation with 11 Gy of cobalt-60 γ radiation, AAT expression levels were increased compared with that of non-irradiated controls (127,128). Furthermore, upregulation of the AAT precursor expression level was noted in the plasma of CBA/CaJ mice exposed to either 0 or 3 Gy of 137Cs gamma radiation (129). In a low-dose irradiated rat model, established using intratracheal drip injection of uranium tailings suspension, AAT expression levels were similarly upregulated (14). The protective mechanisms of AAT in environmental exposure injuries remain unclear and warrant further investigation.

Occupational dust exposure in patients with AATD also affects lung function (130). Organic dust can induce the production of proinflammatory cytokines *in vivo* (131). The *SERPINA1* PiMZ genotype interacts with outdoor particulate matter and occupational exposure to vapors, dust, gas and fumes, potentially diminishing lung function (116). Furthermore, occupational inhalation exposure has been independently associated with respiratory symptoms and airflow limitation in individuals with severe AATD (132) (Table IV).

6. Prospects

AAT has several key physiological and pathological functions, and alterations in its activity can result in disease. A deficiency or the abnormal expression levels of AAT can contribute to lung and liver-related disorders. AAT may have the potential to treat or prevent a range of diseases. In the context of autoimmune and immune-mediated inflammatory diseases, AAT may serve as a novel immunomodulator. Furthermore, AAT may influence cellular aging and has been demonstrated to enhance antioxidant activity and mitigate oxidative stress; however, the underlying mechanisms remain unclear and warrant further investigation. Environmental factors such as exposure to cigarette smoke, toxic substances and radiation can impair lung function and alter AAT expression levels, particularly in individuals with AATD. AAT is garnering increasing attention as a key regulator of inflammatory and immune-mediated diseases, and it may be a potential therapeutic target for these diseases. Continued research may yield new therapeutic strategies for specific diseases, offering more precise and effective treatment options for patients. The application of AAT as a small molecule immunomodulator also presents potential.

Acknowledgements

Not applicable.

Funding

This work was supported by Hunan Natural Science Foundation (grant no. 2022JJ30478), Scientific Research Innovation Project for Graduate Students in Hunan Province (grant no. CX20230991) and Innovative Entrepreneurship Training Program for college students in Hunan Province (grant nos. 2023-2600, 2023-2609 and 2023-4827).

Availability of data and materials

Not applicable.

Authors' contributions

LY and TW contributed to the conceptualization of the present study. TW, PS, SH and YL carried out the literature search and were involved in the study design and conceptualization. QW, CG and WW conducted the data/information search and critically revised article content. PS, SH and YL performed the analysis. The original draft was written by TW. The manuscript was subsequently reviewed and edited by TW and LY. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sabina J and Tobias W: Augmentation therapy with alpha1-antitrypsin: Novel perspectives. Cardiovasc Hematol Disord Drug Targets 13: 90-98, 2013.
2. Lechowicz U, Rudzinski S, Jezela-Stanek A, Janciauskiene S and Chorostowska-Wynimko J: Post-translational modifications of circulating alpha-1-antitrypsin protein. Int J Mol Sci 21: 9187, 2020.

3. Santangelo S, Scarlata S, Poeta ML, Bialas AJ, Paone G and Incalzi RA: Alpha-1 antitrypsin deficiency: Current perspective from genetics to diagnosis and therapeutic approaches. Curr Med Chem 24: 65-90, 2017.
4. Haq I, Irving JA, Saleh AD, Dron L, Regan-Mochrie GL, Motamedi-Shad N, Hurst JR, Gooptu B and Lomas DA: Deficiency mutations of alpha-1 antitrypsin. Effects on folding, function, and polymerization. Am J Respir Cell Mol Biol 54: 71-80, 2016.
5. van't Wout EF, van Schadewijk A, Savage ND, Stolk J and Hiemstra PS: α1-Antitrypsin production by proinflammatory and antiinflammatory macrophages and dendritic cells. Am J Respir Cell Mol Biol 46: 607-613, 2012.
6. de Serres F and Blanco I: Role of alpha-1 antitrypsin in human health and disease. J Intern Med 276: 311-335, 2014.
7. Rahaghi FF and Miravitlles M: Long-term clinical outcomes following treatment with alpha 1-proteinase inhibitor for COPD associated with alpha-1 antitrypsin deficiency: A look at the evidence. Respir Res 18: 105, 2017.
8. Stockley RA: Alpha1-antitrypsin review. Clin Chest Med 35: 39-50, 2014.
9. Song S: Alpha-1 antitrypsin therapy for autoimmune disorders. Chronic Obstr Pulm Dis 5: 289-301, 2018.
10. Serban KA, Petrusca DN, Mikosz A, Poirier C, Lockett AD, Saint L, Justice MJ, Twigg HL III, Campos MA and Petrache I: Alpha-1 antitrypsin supplementation improves alveolar macrophages efferocytosis and phagocytosis following cigarette smoke exposure. PLoS One 12: e0176073, 2017.
11. Jiang S, Liu G, Yuan H, Xu E, Xia W, Zhang X, Liu J and Gao L: Changes on proteomic and metabolomic profile in serum of mice induced by chronic exposure to tramadol. Sci Rep 11: 1454, 2021.
12. Yarmohammadi ME, Hassan ZM, Mostafaie A, Ebtekar M, Yaraee R, Pourfarzam S, Jalali-Nadoushan M, Faghihzadeh S, Vaez-Mahdavi MR, Soroush MR, *et al*: Salivary levels of secretary IgA, C5a and alpha 1-antitrypsin in sulfur mustard exposed patients 20 years after the exposure, sardasht-Iran cohort study (SICS). Int Immunopharmacol 17: 952-957, 2013.
13. Burgess JL, Kurzius-Spencer M, Poplin GS, Littau SR, Kopplin MJ, Stürup S, Boitano S and Clark Lantz R: Environmental arsenic exposure, selenium and sputum alpha-1 antitrypsin. J Expo Sci Environ Epidemiol 24: 150-155, 2014.
14. Yi L, Cui J, Hu N, Li L, Chen Y, Mu H, Yin J, Wei S, Gong Y, Wei Y, *et al*: iTRAQ-based proteomic profiling of potential biomarkers in rat serum for uranium tailing suspension intratracheal instillation. J Proteome Res 20: 995-1004, 2021.
15. Veith M, Tüffers J, Peychev E, Klemmer A, Kotke V, Janciauskiene S, Wilhelm S, Bals R, Koczulla AR, Vogelmeier CF and Greulich T: The distribution of alpha-1 antitrypsin genotypes between patients with COPD/emphysema, asthma and bronchiectasis. Int J Chron Obstruct Pulmon Dis 15: 2827-2836, 2020.
16. Alam S, Li Z, Atkinson C, Jonigk D, Janciauskiene S and Mahadeva R: Z α1-antitrypsin confers a proinflammatory phenotype that contributes to chronic obstructive pulmonary disease. Am J Respir Crit Care Med 189: 909-931, 2014.
17. Ordóñez A, Snapp EL, Tan L, Miranda E, Marciniak SJ and Lomas DA: Endoplasmic reticulum polymers impair luminal protein mobility and sensitize to cellular stress in alpha1-antitrypsin deficiency. Hepatology 57: 2049-2060, 2013.
18. Giri Rao VVH and Gosavi S: On the folding of a structurally complex protein to its metastable active state. Proc Natl Acad Sci USA 115: 1998-2003, 2018.
19. Ordóñez A, Harding HP, Marciniak SJ and Ron D: Cargo receptor-assisted endoplasmic reticulum export of pathogenic α1-antitrypsin polymers. Cell Rep 35: 109144, 2021.
20. Ronzoni R, Berardelli R, Medicina D, Sitia R, Gooptu B and Fra AM: Aberrant disulphide bonding contributes to the ER retention of alpha1-antitrypsin deficiency variants. Hum Mol Genet 25: 642-650, 2016.
21. Lockett AD: Alpha-1 antitrypsin transcytosis and secretion. Methods Mol Biol 1639: 173-184, 2017.
22. Lockett AD, Brown MB, Santos-Falcon N, Rush NI, Oueini H, Oberle AJ, Bolanis E, Fragoso MA, Petrusca DN, Serban KA, *et al*: Active trafficking of alpha 1 antitrypsin across the lung endothelium. PLoS One 9: e93979, 2014.
23. Kim M, Cai Q and Oh Y: Therapeutic potential of alpha-1 antitrypsin in human disease. Ann Pediatr Endocrinol Metab 23: 131-135, 2018.
24. Schuster R, Motola-Kalay N, Baranovski BM, Bar L, Tov N, Stein M, Lewis EC, Ayalon M and Sagiv Y: Distinct anti-inflammatory properties of alpha1-antitrypsin and corticosteroids reveal unique underlying mechanisms of action. Cell Immunol 356: 104177, 2020.
25. Ostermann L, Maus R, Stolper J, Schütte L, Katsarou K, Tumpara S, Pich A, Mueller C, Janciauskiene S, Welte T and Maus UA: Alpha-1 antitrypsin deficiency impairs lung antibacterial immunity in mice. JCI Insight 6: e140816, 2021.
26. Serban KA and Petrache I: alpha-1 antitrypsin and lung cell apoptosis. Ann Am Thorac Soc 13 (Suppl 2): S146-S149, 2016.
27. Han L, Wu X, Wang O, Luan X, Velander WH, Aynardi M, Halstead ES, Bonavia AS, Jin R, Li G, *et al*: Mesenchymal stromal cells and alpha-1 antitrypsin have a strong synergy in modulating inflammation and its resolution. Theranostics 13: 2843-2862, 2023.
28. Baraldo S, Turato G, Lunardi F, Bazzan E, Schiavon M, Ferrarotti I, Molena B, Cazzuffi R, Damin M, Balestro E, *et al*: Immune activation in α1-antitrypsin-deficiency emphysema. Beyond the protease-antiprotease paradigm. Am J Respir Crit Care Med 191: 402-409, 2015.
29. Jonigk D, Al-Omari M, Maegel L, Müller M, Izykowski N, Hong J, Hong K, Kim SH, Dorsch M, Mahadeva R, *et al*: Anti-inflammatory and immunomodulatory properties of α1-antitrypsin without inhibition of elastase. Proc Natl Acad Sci USA 110: 15007-15012, 2013.
30. Ehlers MR: Immune-modulating effects of alpha-1 antitrypsin. Biol Chem 395: 1187-1193, 2014.
31. Tawara I, Sun Y, Lewis EC, Toubai T, Evers R, Nieves E, Azam T, Dinarello CA and Reddy P: Alpha-1-antitrypsin monotherapy reduces graft-versus-host disease after experimental allogeneic bone marrow transplantation. Proc Natl Acad Sci USA 109: 564-569, 2012.
32. Blas-García A and Apostolova N: Novel therapeutic approaches to liver fibrosis based on targeting oxidative stress. Antioxidants (Basel) 12: 1567, 2023.
33. Feng Y, Xu J, Zhou Q, Wang R, Liu N, Wu Y, Yuan H and Che H: Alpha-1 antitrypsin prevents the development of preeclampsia through suppression of oxidative stress. Front Physiol 7: 176, 2016.
34. Chapman KR, Chorostowska-Wynimko J, Koczulla AR, Ferrarotti I and McElvaney NG: Alpha 1 antitrypsin to treat lung disease in alpha 1 antitrypsin deficiency: Recent developments and clinical implications. Int J Chron Obstruct Pulmon Dis 13: 419-432, 2018.
35. Janciauskiene S and Welte T: Well-known and less well-known functions of alpha-1 antitrypsin. its role in chronic obstructive pulmonary disease and other disease developments. Ann Am Thorac Soc 13 (Suppl 4): S280-S288, 2016.
36. Cosio MG, Bazzan E, Rigobello C, Tinè M, Turato G, Baraldo S and Saetta M: Alpha-1 antitrypsin deficiency: beyond the protease/antiprotease paradigm. Ann Am Thorac Soc 13 (Suppl 4): S305-S310, 2016.
37. Stockley RA: The multiple facets of alpha-1-antitrypsin. Ann Transl Med 3: 130, 2015.
38. Schwarz N, Tumpara S, Wrenger S, Ercetin E, Hamacher J, Welte T and Janciauskiene S: Alpha1-antitrypsin protects lung cancer cells from staurosporine-induced apoptosis: The role of bacterial lipopolysaccharide. Sci Rep 10: 9563, 2020.
39. Meghadri SH, Martinez-Delgado B, Ostermann L, Gomez-Mariano G, Perez-Luz S, Tumpara S, Wrenger S, DeLuca DS, Maus UA, Welte T and Janciauskiene S: Loss of Serpina1 in mice leads to altered gene expression in inflammatory and metabolic pathways. Int J Mol Sci 23: 10425, 2022.
40. Stolk J, Tov N, Chapman KR, Fernandez P, MacNee W, Hopkinson NS, Piitulainen E, Seersholm N, Vogelmeier CF, Bals R, *et al*: Efficacy and safety of inhaled α1-antitrypsin in patients with severe α1-antitrypsin deficiency and frequent exacerbations of COPD. Eur Respir J 54: 1900673, 2019.
41. McElvaney NG: Alpha-1 antitrypsin therapy in cystic fibrosis and the lung disease associated with alpha-1 antitrypsin deficiency. Ann Am Thorac Soc 13 (Suppl 2): S191-S196, 2016.
42. Demir N, Erçen Diken O, Karabulut HG, Karnak D and Kayacan O: Alpha-1 antitrypsin levels and polymorphisms in interstitial lung diseases. Turk J Med Sci 47: 476-482, 2017.
43. Oriano M, Amati F, Gramegna A, De Soyza A, Mantero M, Sibila O, Chotirmall SH, Voza A, Marchisio P, Blasi F and Aliberti S: Protease-antiprotease imbalance in bronchiectasis. Int J Mol Sci 22: 5996, 2021.

44. Murphy MP, McEnery T, McQuillan K, McElvaney OF, McElvaney OJ, Landers S, Coleman O, Bussayajirapong A, Hawkins P, Henry M, *et al*: α_1 Antitrypsin therapy modulates the neutrophil membrane proteome and secretome. Eur Respir J 55: 1901678, 2020.
45. Ritzmann F, Chitirala P, Krüger N, Hoffmann M, Zuo W, Lammert F, Smola S, Tov N, Alagem N, Lepper PM, *et al*: Therapeutic application of alpha-1 antitrypsin in COVID-19. Am J Respir Crit Care Med 204: 224-227, 2021.
46. Yang C, Keshavjee S and Liu M: Alpha-1 antitrypsin for COVID-19 treatment: Dual role in antiviral infection and anti-inflammation. Front Pharmacol 11: 615398, 2020.
47. Li Y, Miao L, Yu M, Shi M, Wang Y, Yang J, Xiao Y and Cai H: α1-Antitrypsin promotes lung adenocarcinoma metastasis through upregulating fibronectin expression. Int J Oncol 50: 1955-1964, 2017.
48. Khodayari N, Wang RL, Oshins R, Lu Y, Millett M, Aranyos AM, Mostofizadeh S, Scindia Y, Flagg TO and Brantly M: The mechanism of mitochondrial injury in alpha-1 antitrypsin deficiency mediated liver disease. Int J Mol Sci 22: 13255, 2021.
49. Tanash HA and Piitulainen E: Liver disease in adults with severe alpha-1-antitrypsin deficiency. J Gastroenterol 54: 541-548, 2019.
50. Franciosi AN, Ralph J, O'Farrell NJ, Buckley C, Gulmann C, O'Kane M, Carroll TP and McElvaney NG: Alpha-1 antitrypsin deficiency-associated panniculitis. J Am Acad Dermatol 87: 825-832, 2022.
51. Wang Q, Du J, Yu P, Bai B, Zhao Z, Wang S, Zhu J, Feng Q, Gao Y, Zhao Q and Liu C: Hepatic steatosis depresses alpha-1-antitrypsin levels in human and rat acute pancreatitis. Sci Rep 5: 17833, 2015.
52. Yu Y, Rubin AG, Gee S, Banker S and Kim CN: Ulcerative panniculitis with fevers and pleural effusions: A unique case of α1-antitrypsin deficiency. JAAD Case Rep 1: 1-2, 2014.
53. Jedicke N, Struever N, Aggrawal N, Welte T, Manns MP, Malek NP, Zender L, Janciauskiene S and Wuestefeld T: α-1-antitrypsin inhibits acute liver failure in mice. Hepatology 59: 2299-2308, 2014.
54. Elshikha AS, Lu Y, Chen MJ, Akbar M, Zeumer L, Ritter A, Elghamry H, Mahdi MA, Morel L and Song S: Alpha 1 antitrypsin inhibits dendritic cell activation and attenuates nephritis in a mouse model of lupus. PLoS One 11: e0156583, 2016.
55. Pervakova MY, Emanuel VL, Titova ON, Lapin SV, Mazurov VI, Belyaeva IB, Chudinov AL, Blinova TV and Surkova EA: The diagnostic value of alpha-1-antitrypsin phenotype in patients with granulomatosis with polyangiitis. Int J Rheumatol 2016: 7831410, 2016.
56. Mota A, Sahebghadam Lotfi A, Jamshidi AR and Najavand S: Alpha 1-antitrypsin activity is markedly decreased in Wegener's granulomatosis. Rheumatol Int 34: 553-558, 2014.
57. Mauro AG, Mezzaroma E, Marchetti C, Narayan P, Del Buono MG, Capuano M, Prestamburgo A, Catapano S, Salloum FN, Abbate A and Toldo S: A preclinical translational study of the cardioprotective effects of plasma-derived alpha-1 anti-trypsin in acute myocardial infarction. J Cardiovasc Pharmacol 69: 273-278, 2017.
58. Toldo S, Mauro AG, Marchetti C, Rose SW, Mezzaroma E, Van Tassell BW, Kim S, Dinarello CA and Abbate A: Recombinant human alpha-1 antitrypsin-Fc fusion protein reduces mouse myocardial inflammatory injury after ischemia-reperfusion independent of elastase inhibition. J Cardiovasc Pharmacol 68: 27-32, 2016.
59. Lockett AD, Petrusca DN, Justice MJ, Poirier C, Serban KA, Rush NI, Kamocka M, Predescu D, Predescu S and Petrache I: Scavenger receptor class B, type I-mediated uptake of A1AT by pulmonary endothelial cells. Am J Physiol Lung Cell Mol Physiol 309: L425-L434, 2015.
60. Zhou T, Huang Z, Zhu X, Sun X, Liu Y, Cheng B, Li M, Liu Y, He C and Liu X: Alpha-1 antitrypsin attenuates M1 microglia-mediated neuroinflammation in retinal degeneration. Front Immunol 9: 1202, 2018.
61. Ebrahimi T, Rust M, Kaiser SN, Slowik A, Beyer C, Koczulla AR, Schulz JB, Habib P and Bach JP: α1-Antitrypsin mitigates NLRP3-inflammasome activation in amyloid β_{1-42}-stimulated murine astrocytes. J Neuroinflammation 15: 282, 2018.
62. Park SS, Rodriguez Ortega R, Agudelo CW, Perez Perez J, Perez Gandara B, Garcia-Arcos I, McCarthy C and Geraghty P: Therapeutic potential of alpha-1 antitrypsin in type 1 and type 2 diabetes mellitus. Medicina (Kaunas) 57: 397, 2021.
63. Fleixo-Lima G, Ventura H, Medini M, Bar L, Strauss P and Lewis EC: Mechanistic evidence in support of alpha1-antitrypsin as a therapeutic approach for type 1 diabetes. J Diabetes Sci Technol 8: 1193-1203, 2014.
64. Kalis M, Kumar R, Janciauskiene S, Salehi A and Cilio CM: α 1-antitrypsin enhances insulin secretion and prevents cytokine-mediated apoptosis in pancreatic β-cells. Islets 2: 185-189, 2010.
65. Liu W and Wang Y: Protective role of the alpha-1-antitrypsin in intervertebral disc degeneration. J Orthop Surg Res 16: 516, 2021.
66. Pérez-Holanda S, Blanco I, Menéndez M and Rodrigo L: Serum concentration of alpha-1 antitrypsin is significantly higher in colorectal cancer patients than in healthy controls. BMC Cancer 14: 355, 2014.
67. Tountas Y, Sparos L, Theodoropoulos C and Trichopoulos D: Alpha 1-antitrypsin and cancer of the pancreas. Digestion 31: 37-40, 1985.
68. Vasishta A, Baker PR, Preece PE, Wood RA and Cuschieri A: Serum proteinase-like peptidase activities and proteinase inhibitors in women with breast disease. Eur J Cancer Clin Oncol 20:197-202, 1984.
69. Warwas M, Gerber J and Pietkiewicz A: Haptoglobin and proteinase inhibitors in the blood serum of women with inflammatory, benign and neoplastic lesions of the ovary. Neoplasma 33: 79-84, 1986.
70. Janciauskiene S, Wrenger S, Günzel S, Gründing AR, Golpon H and Welte T: Potential roles of acute phase proteins in cancer: Why do cancer cells produce or take up exogenous acute phase protein alpha1-antitrypsin? Front Oncol 11: 622076, 2021.
71. Hsu PI, Chen CH, Hsiao M, Wu DC, Lin CY, Lai KH and Lu PJ: Diagnosis of gastric malignancy using gastric juice alpha1-antitrypsin. Cancer Epidemiol Biomarkers Prev 19: 405-411, 2010.
72. Wu W, Juan WC, Liang CR, Yeoh KG, So J and Chung MC: S100A9, GIF and AAT as potential combinatorial biomarkers in gastric cancer diagnosis and prognosis. Proteomics Clin Appl 6: 152-162, 2012.
73. Geramizadeh B, Jowkar Z, Karami L, Masoumpour M, Mehrabi S and Ghayoumi MA: Alpha-1 antitrypsin deficiency in Iranian patients with chronic obstructive pulmonary disease. Iran Red Crescent Med J 15: e7508, 2013.
74. Matamala N, Lara B, Gomez-Mariano G, Martínez S, Retana D, Fernandez T, Silvestre RA, Belmonte I, Rodriguez-Frias F, Vilar M, *et al*: Characterization of novel missense variants of SERPINA1 gene causing alpha-1 antitrypsin deficiency. Am J Respir Cell Mol Biol 58: 706-716, 2018.
75. Foil KE: Variants of SERPINA1 and the increasing complexity of testing for alpha-1 antitrypsin deficiency. Ther Adv Chronic Dis (12 Suppl): 20406223211015954, 2021.
76. Tsutsui Y, Dela Cruz R and Wintrode PL: Folding mechanism of the metastable serpin α1-antitrypsin. Proc Natl Acad Sci USA 109: 4467-4472, 2012.
77. Marciniak SJ, Ordóñez A, Dickens JA, Chambers JE, Patel V, Dominicus CS and Malzer E: New concepts in alpha-1 antitrypsin deficiency disease mechanisms. Ann Am Thorac Soc 13 (Suppl 4): S289-S296, 2016.
78. Börner FR, Lechowicz U, Wrenger S, Martinez-Delgado B, Olejnicka B, Welte T, Chorostowska-Wynimko J, Kiehntopf M and Janciauskiene S: Plasma levels of α_1-antitrypsin-derived C-terminal peptides in PiMM and PiZZ COPD patients. ERJ Open Res 9: 00329-2023, 2023.
79. Fra AM, Gooptu B, Ferrarotti I, Miranda E, Scabini R, Ronzoni R, Benini F, Corda L, Medicina D, Luisetti M and Schiaffonati L: Three new alpha1-antitrypsin deficiency variants help to define a C-terminal region regulating conformational change and polymerization. PLoS One 7: e38405, 2012.
80. Salahuddin P: Genetic variants of alpha1-antitrypsin. Curr Protein Pept Sci 11: 101-117, 2010.
81. Karatas E and Bouchecareilh M: Alpha 1-antitrypsin deficiency: A disorder of proteostasis-mediated protein folding and trafficking pathways. Int J Mol Sci 21: 1493, 2020.
82. Miranda E, Ferrarotti I, Berardelli R, Laffranchi M, Cerea M, Gangemi F, Haq I, Ottaviani S, Lomas DA, Irving JA and Fra A: The pathological Trento variant of alpha-1-antitrypsin (E75V) shows nonclassical behaviour during polymerization. FEBS J 284: 2110-2126, 2017.
83. Laffranchi M, Berardelli R, Ronzoni R, Lomas DA and Fra A: Heteropolymerization of α-1-antitrypsin mutants in cell models mimicking heterozygosity. Hum Mol Genet 27: 1785-1793, 2018.

84. Laffranchi M, Elliston ELK, Gangemi F, Berardelli R, Lomas DA, Irving JA and Fra A: Characterisation of a type II functionally-deficient variant of alpha-1-antitrypsin discovered in the general population. PLoS One 14: e0206955, 2019.
85. Bergin DA, Reeves EP, Hurley K, Wolfe R, Jameel R, Fitzgerald S and McElvaney NG: The circulating proteinase inhibitor α-1 antitrypsin regulates neutrophil degranulation and autoimmunity. Sci Transl Med 6: 217ra1, 2014.
86. Hawkins P, McEnery T, Gabillard-Lefort C, Bergin DA, Alfawaz B, Shutchaidat V, Meleady P, Henry M, Coleman O, Murphy M, *et al*: In vitro and in vivo modulation of NADPH oxidase activity and reactive oxygen species production in human neutrophils by α_1-antitrypsin. ERJ Open Res 7: 00234-2021, 2021.
87. Voynow JA and Shinbashi M: Neutrophil elastase and chronic lung disease. Biomolecules 11: 1065, 2021.
88. Miravitlles M: Alpha-1-antitrypsin and other proteinase inhibitors. Curr Opin Pharmacol 12: 309-314, 2012.
89. Hurley K, Lacey N, O'Dwyer CA, Bergin DA, McElvaney OJ, O'Brien ME, McElvaney OF, Reeves EP and McElvaney NG: Alpha-1 antitrypsin augmentation therapy corrects accelerated neutrophil apoptosis in deficient individuals. J Immunol 193: 3978-3991, 2014.
90. O'Dwyer CA, O'Brien ME, Wormald MR, White MM, Banville N, Hurley K, McCarthy C, McElvaney NG and Reeves EP: The BLT1 inhibitory function of α-1 antitrypsin augmentation therapy disrupts leukotriene B4 neutrophil signaling. J Immunol 195: 3628-3641, 2015.
91. McCarthy C, Reeves EP and McElvaney NG: The role of neutrophils in alpha-1 antitrypsin deficiency. Ann Am Thorac Soc 13 (Suppl 4): S297-S304, 2016.
92. Fazleen A and Wilkinson T: The emerging role of proteases in α_1-antitrypsin deficiency and beyond. ERJ Open Res 7: 00494-2021, 2021.
93. O'Brien ME, Murray G, Gogoi D, Yusuf A, McCarthy C, Wormald MR, Casey M, Gabillard-Lefort C, McElvaney NG and Reeves EP: A review of alpha-1 antitrypsin binding partners for immune regulation and potential therapeutic application. Int J Mol Sci 23: 2441, 2022.
94. Joosten LA, Crişan TO, Azam T, Cleophas MC, Koenders MI, van de Veerdonk FL, Netea MG, Kim S and Dinarello CA: Alpha-1-anti-trypsin-Fc fusion protein ameliorates gouty arthritis by reducing release and extracellular processing of IL-1β and by the induction of endogenous IL-1Ra. Ann Rheum Dis 75: 1219-1227, 2016.
95. Agné A, Richter K, Padberg W, Janciauskiene S and Grau V: Commercial α1-antitrypsin preparations markedly differ in their potential to inhibit the ATP-induced release of monocytic interleukin-1β. Pulm Pharmacol Ther 68: 102020, 2021.
96. Siebers K, Fink B, Zakrzewicz A, Agné A, Richter K, Konzok S, Hecker A, Zukunft S, Küllmar M, Klein J, *et al*: Alpha-1 antitrypsin inhibits ATP-mediated release of interleukin-1β via CD36 and nicotinic acetylcholine receptors. Front Immunol 9: 877, 2018.
97. Bergin DA, Reeves EP, Meleady P, Henry M, McElvaney OJ, Carroll TP, Condron C, Chotirmall SH, Clynes M, O'Neill SJ and McElvaney NG: α-1 Antitrypsin regulates human neutrophil chemotaxis induced by soluble immune complexes and IL-8. J Clin Invest 120: 4236-4250, 2010.
98. Lee J, Lu Y, Oshins R, West J, Moneypenny CG, Han K and Brantly ML: Alpha 1 antitrypsin-deficient macrophages have impaired efferocytosis of apoptotic neutrophils. Front Immunol 11: 574410, 2020.
99. Lockett AD, Kimani S, Ddungu G, Wrenger S, Tuder RM, Janciauskiene SM and Petrache I: α_1-Antitrypsin modulates lung endothelial cell inflammatory responses to TNF-α. Am J Respir Cell Mol Biol 49: 143-150, 2013.
100. Zhukovsky N, Silvano M, Filloux T, Gonzalez S and Krause KH: Alpha-1 antitrypsin reduces disease progression in a mouse model of charcot-marie-tooth type 1A: A role for decreased inflammation and ADAM-17 inhibition. Int J Mol Sci 23: 7405, 2022.
101. Abecassis A, Schuster R, Shahaf G, Ozeri E, Green R, Ochayon DE, Rider P and Lewis EC: α1-Antitrypsin increases interleukin-1 receptor antagonist production during pancreatic islet graft transplantation. Cell Mol Immunol 11: 377-386, 2014.
102. Ozeri E, Mizrahi M, Shahaf G and Lewis EC: α-1 antitrypsin promotes semimature, IL-10-producing and readily migrating tolerogenic dendritic cells. J Immunol 189: 146-153, 2012.
103. Wang J, Sun Z, Gou W, Adams DB, Cui W, Morgan KA, Strange C and Wang H: α-1 antitrypsin enhances islet engraftment by suppression of instant blood-mediated inflammatory reaction. Diabetes 66: 970-980, 2017.
104. Mukherjee A, Hidvegi T, Araya P, Ewing M, Stolz DB and Perlmutter DH: NFκB mitigates the pathological effects of misfolded α1-antitrypsin by activating autophagy and an integrated program of proteostasis mechanisms. Cell Death Differ 26: 455-469, 2019.
105. Pastore N, Blomenkamp K, Annunziata F, Piccolo P, Mithbaokar P, Maria Sepe R, Vetrini F, Palmer D, Ng P, Polishchuk E, *et al*: Gene transfer of master autophagy regulator TFEB results in clearance of toxic protein and correction of hepatic disease in alpha-1-anti-trypsin deficiency. EMBO Mol Med 5: 397-412, 2013.
106. Rivas M, Gupta G, Costanzo L, Ahmed H, Wyman AE and Geraghty P: Senescence: Pathogenic driver in chronic obstructive pulmonary disease. Medicina (Kaunas) 58: 817, 2022.
107. Saferali A, Lee J, Sin DD, Rouhani FN, Brantly ML and Sandford AJ: Longer telomere length in COPD patients with α1-antitrypsin deficiency independent of lung function. PLoS One 9: e95600, 2014.
108. Escribano A, Pastor S, Reula A, Castillo S, Vicente S, Sanz F, Casas F, Torres M, Fernández-Fabrellas E, Codoñer-Franch P and Dasí F: Accelerated telomere attrition in children and teenagers with α1-antitrypsin deficiency. Eur Respir J 48: 350-358, 2016.
109. Hurley K, Reeves EP, Carroll TP and McElvaney NG: Tumor necrosis factor-α driven inflammation in alpha-1 antitrypsin deficiency: A new model of pathogenesis and treatment. Expert Rev Respir Med 10: 207-222, 2016.
110. Li Z, Alam S, Wang J, Sandstrom CS, Janciauskiene S and Mahadeva R: Oxidized {alpha}1-antitrypsin stimulates the release of monocyte chemotactic protein-1 from lung epithelial cells: Potential role in emphysema. Am J Physiol Lung Cell Mol Physiol 297: L388-L400, 2009.
111. Subramaniyam D, Glader P, von Wachenfeldt K, Burneckiene J, Stevens T and Janciauskiene S: C-36 peptide, a degradation product of alpha1-antitrypsin, modulates human monocyte activation through LPS signaling pathways. Int J Biochem Cell Biol 38: 563-575, 2006.
112. Antonsson A and Persson JL: Induction of apoptosis by staurosporine involves the inhibition of expression of the major cell cycle proteins at the G(2)/m checkpoint accompanied by alterations in Erk and Akt kinase activities. Anticancer Res 29: 2893-2898, 2009.
113. Campos MA, Geraghty P, Holt G, Mendes E, Newby PR, Ma S, Luna-Diaz LV, Turino GM and Stockley RA: The biological effects of double-dose alpha-1 antitrypsin augmentation therapy. A pilot clinical trial. Am J Respir Crit Care Med 200: 318-326, 2019.
114. Hunt JM and Tuder R: Alpha 1 anti-trypsin: One protein, many functions. Curr Mol Med 12: 827-835, 2012.
115. Berman R, Jiang D, Wu Q and Chu HW: α1-Antitrypsin reduces rhinovirus infection in primary human airway epithelial cells exposed to cigarette smoke. Int J Chron Obstruct Pulmon Dis 11: 1279-1286, 2016.
116. Mehta AJ, Thun GA, Imboden M, Ferrarotti I, Keidel D, Künzli N, Kromhout H, Miedinger D, Phuleria H, Rochat T, *et al*: Interactions between SERPINA1 PiMZ genotype, occupational exposure and lung function decline. Occup Environ Med 71: 234-240, 2014.
117. Wrześniak M, Kepinska M, Królik M and Milnerowicz H: The influence of tobacco smoke on protein and metal levels in the serum of women during pregnancy. PLoS One 11: e0161342, 2016.
118. Pemberton PA, Kobayashi D, Wilk BJ, Henstrand JM, Shapiro SD and Barr PJ: Inhaled recombinant alpha 1-antitrypsin ameliorates cigarette smoke-induced emphysema in the mouse. COPD 3: 101-108, 2006.
119. Molloy K, Hersh CP, Morris VB, Carroll TP, O'Connor CA, Lasky-Su JA, Greene CM, O'Neill SJ, Silverman EK and McElvaney NG: Clarification of the risk of chronic obstructive pulmonary disease in α1-antitrypsin deficiency PiMZ heterozygotes. Am J Respir Crit Care Med 189: 419-427, 2014.
120. Stearns K, Goldklang M, Xiao R, Zelonina T, Blomenkamp K, Teckman J and D'Armiento JM: Knockdown of alpha-1 antitrypsin with antisense oligonucleotide does not exacerbate smoke induced lung injury. PLoS One 16: e0246040, 2021.

121. Rangaraju M and Turner AM: Why is disease penetration so variable in alpha-1 antitrypsin deficiency? The contribution of environmental factors. Chronic Obstr Pulm Dis 7: 280-289, 2020.
122. Churg A, Wang X, Wang RD, Meixner SC, Pryzdial EL and Wright JL: Alpha1-antitrypsin suppresses TNF-alpha and MMP-12 production by cigarette smoke-stimulated macrophages. Am J Respir Cell Mol Biol 37: 144-151, 2007.
123. Thun GA, Ferrarotti I, Imboden M, Rochat T, Gerbase M, Kronenberg F, Bridevaux PO, Zemp E, Zorzetto M, Ottaviani S, *et al*: SERPINA1 PiZ and PiS heterozygotes and lung function decline in the SAPALDIA cohort. PLoS One 7: e42728, 2012.
124. Khodayari N, Oshins R, Mehrad B, Lascano JE, Qiang X, West JR, Holliday LS, Lee J, Wiesemann G, Eydgahi S and Brantly M: Cigarette smoke exposed airway epithelial cell-derived EVs promote pro-inflammatory macrophage activation in alpha-1 antitrypsin deficiency. Respir Res 23: 232, 2022.
125. Al Ashry HS and Strange C: COPD in individuals with the PiMZ alpha-1 antitrypsin genotype. Eur Respir Rev 26: 170068, 2017.
126. Geraghty P, Eden E, Pillai M, Campos M, McElvaney NG and Foronjy RF: α1-Antitrypsin activates protein phosphatase 2A to counter lung inflammatory responses. Am J Respir Crit Care Med 190: 1229-1242, 2014.
127. Rosen E, Fatanmi OO, Wise SY, Rao VA and Singh VK: Gamma-tocotrienol, a radiation countermeasure, reverses proteomic changes in serum following total-body gamma irradiation in mice. Sci Rep 12: 3387, 2022.
128. Rosen E, Fatanmi OO, Wise SY, Rao VA and Singh VK: Tocol prophylaxis for total-body irradiation: A proteomic analysis in murine model. Health Phys 119: 12-20, 2020.
129. Rithidech KN, Honikel L, Rieger R, Xie W, Fischer T and Simon SR: Protein-expression profiles in mouse blood-plasma following acute whole-body exposure to (137)Cs gamma rays. Int J Radiat Biol 85: 432-447, 2009.
130. Zutler M, Quinlan PJ and Blanc PD: Alpha-1-antitrypsin deficient man presenting with lung function decline associated with dust exposure: A case report. J Med Case Rep 5: 154, 2011.
131. Bolund AC, Miller MR, Sigsgaard T and Schlünssen V: The effect of organic dust exposure on long-term change in lung function: A systematic review and meta-analysis. Occup Environ Med 74: 531-542, 2017.
132. Liao SY, Lin X and Christiani DC: Occupational exposures and longitudinal lung function decline. Am J Ind Med 58: 14-20, 2015.