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Unraveling the Pathogenesis of Chronic Obstructive Pulmonary Disease in Alpha-1 Antitrypsin Deficiency: Mechanisms, Biomarkers, and Therapeutic Implications

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Abstract

Chronic obstructive pulmonary disease (COPD) represents a significant global disease burden, with progressive and irreversible airflow limitation and respiratory symptoms. While cigarette smoking is the primary COPD risk factor, genetic predisposition like alpha-1 antitrypsin deficiency (AATD) also confers risk, often resulting in early-onset disease. Understanding COPD mechanisms in AATD can inform disease pathogenesis overall, biomarker development for detection/prognosis, and targeted therapies. This review explores the interplay between AATD and COPD, integrating genetic, environmental, and molecular contributors to pathogenesis and disease progression. Additionally, we discuss emerging treatment strategies that may mitigate COPD severity in AATD patients. Specifically, AATD arises from mutations in the SERPINA1 gene, resulting in reduced alpha-1 antitrypsin (AAT) levels. General COPD mechanisms (protease-antiprotease imbalance, oxidative stress, aberrant inflammation) are understood, but specifics in AATD remain unclear, hindering precision medicine approaches for this high-risk population. Elucidating exact disease pathways could enable treatments beyond standard augmentation therapy. Reasons to prioritize this include arresting disease progression and reducing the substantial AATD-COPD burden. Recent omics studies have uncovered promising biomarkers for molecular phenotyping of COPD subtypes. Further inquiry into novel pathways and integrating multi-omics data with clinical outcomes can provide frameworks for elucidating AATD-COPD mechanisms and validating predictors. However, gaps remain in connecting putative biomarkers and mechanisms with clinical endpoints. These must be addressed to develop targeted therapies and improve outcomes for this early-onset, rapid COPD progression population.

Keywords: COPD; Chronic Obstructive Pulmonary Disease; AATD; Alpha-1 Antitrypsin Deficiency; Biomarkers

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; AATD: Alpha-1 Antitrypsin Deficiency; AAT: Alpha-1 Antitrypsin; SERPINA1: Serpin Family A Member 1 (the gene that codes for AAT); FEV1 - Forced Expiratory Volume in one second; RCT - Randomized Controlled Trial; CT - Computed Tomography; FRC - Functional Residual Capacity; SGRQ - St George's Respiratory Questionnaire; hAAT - Human Alpha-1 Antitrypsin; NIH3T3 - Mouse Fibroblast Lineage; rAAV - Recombinant Adeno-Associated Virus; ROS - Reactive Oxygen Species; BAL - Bronchoalveolar Lavage; MRI - Magnetic Resonance Imaging; HRCT - High-Resolution Computed Tomography; iPSCs - Induced Pluripotent Stem Cells; RNA - Ribonucleic Acid; EU - European Union; PiMM, PiSZ, PiZZ - Phenotypes of Alpha-1 Antitrypsin; NK cell - Natural Killer cell; AECOPD - Acute Exacerbation of COPD

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a persistent and progressive lung condition characterized by airflow obstruction due to abnormalities in the alveoli and/or the airways. Often presenting as chronic respiratory symptoms, it encompasses emphysema and bronchitis [1]. With increased exposure to tobacco smoking, air pollution, and a plethora of other risk factors, COPD has become a significant burden to world health. It is projected to continue growing in the next decade [2]. Global Initiative for Obstructive Lung Disease (GOLD) suggests that the global prevalence rate of COPD is 10.7%, making it a leading cause of morbidity and mortality worldwide. Moreover, projections predict this number will continue to increase in the next decade due to the current smoking pandemic [3]. COPD-related mortality continues to rise, with an estimated death rate of 3 million people every year and another 300 million people affected, 4% of the world's population. It is additionally weighing down significantly on nations economically. In 2017, the EU spent 38 billion euros, 6% of total healthcare spending, on COPD alone [4]. Furthermore, considering the disparity between recorded diagnoses and the established prevalence rate, it suggests there is widespread underdiagnosis of COPD.

Consequently, this poses a great concern to the global health community and adds to the already heavy burden caused by COPD [5]. It is well documented that there is an increased familial risk to those who smoke and are also siblings of COPD patients. As a result, there may be a vital genetic component to the development of COPD, which needs to be considered when assessing the risk of the disease [6]. The most established genetic risk factor is Hereditary Alpha-1 Antitrypsin Deficiency (AATD), which results from mutations in the SERPINA1 gene [7]. Alpha-1 Antitrypsin, a protein produced in the liver, protects the lung tissue from damage caused by proteolytic enzymes, particularly neutrophil elastase, an inflammatory protease released by neutrophils. The mutation in SERPINA1 in AATD causes a decrease in the serum AAT by retaining polymerized molecules within the hepatocytes. This results in unchecked protease activity and subsequent destruction of lung tissue, a characteristic development of COPD [7]. This narrative review aims to understand the mechanism underlying COPD development in AATD, identify relevant biomarkers, and evaluate current and emerging therapeutic strategies for its management, synthesizing evidence from preclinical and clinical studies to give a comprehensive view of COPD in AATD.

Genetic Basis of AATD and its Relationship to COPD

Alpha 1 antitrypsin (AAT) is a protease inhibitor found in the serum and produced in the liver with the primary purpose of downregulating the protease activities in the lung, especially during periods of inflammation, infection, pregnancy, cancer, smoking, and other irritants [8,9]. The production of this protein can be altered when there is a genetic mutation in the SERPINA gene responsible for encoding the AAT-Z gene, leading to AAT deficiency (AATD). This mutation presents varying degrees of AAT concentration in the blood, which is inversely related to the disease severity [9]. AATD is an autosomal co-dominance genetic inheritance disorder that can lead to the early development of chronic obstructive pulmonary disease (COPD), particularly emphysema. People with severe Alpha-1 Antitrypsin Deficiency (AATD) who smoke are more likely to develop COPD at a younger age compared to smokers without AATD [10].

The pathogenesis of AATD involves the accumulation of the abnormal protein in the liver, causing liver disease, and low levels in the blood lead to upregulation of the protease activity in the lung, leading to lung diseases, including chronic obstructive pulmonary disease (COPD) (emphysema) and bronchiectasis in young adults [8,9]. More than 100 alleles and over 40 phenotypes have been discovered, with carriers of null alleles (null-null) and Z allele homozygotes (PiZZ) phenotypes exhibiting the lowest serum AAT levels [9,11]. The S allele (PiSZ) produces a less severe AAT deficit [11]. AATD is prevalent in individuals of Caucasian descent in Europe and North America, and an estimated 0.11% of Caucasian individuals in the United States have AATD [9]. More than 500,000 people in Europe have PiSZ phenotypic alleles with AAT levels less than half the AAT of a regular (PiMM) person [11].

Pathophysiological Mechanisms of COPD in AATD

The pathophysiological mechanism of COPD (Chronic Obstructive Pulmonary Disease) in AATD (A1 Antitrypsin deficiency) is classically explained by the protease/antiprotease imbalance and tissue damage. Stockley et al discuss how persistent or excessive protease/antiprotease imbalance, particularly the excess of neutrophil elastase, cathepsin G, cathepsin B, and proteinase 3 can contribute to destructive effects on the lungs in the context of AATD since a1-antitrypsin inhibits neutrophil elastase, cathepsin G, and proteinase 3, all of which are stored in the same granule in the neutrophil. Moreover, cathepsin B is released in the lung as a proenzyme and is activated by NE [12]. The literature discussed that besides the theory of protease/antiprotease imbalance, an adaptive immune response is identified in the pathophysiology of COPD in AATD. The response was similar to that in severe COPD with normal a1-antitrypsin levels. It may suggest immune involvement in lung destruction in AATD. This new approach to adaptive immune response highlights the need to move from classic protease/antiprotease imbalance to a more comprehensive pathophysiology model, which involves anti-inflammatory and immune functions of a1-antitrypsin [13]. There is evidence of immune tissue activation in AATD lungs, specifically lymphoid follicles, lymphocyte populations, B Cells, and T cells. These adaptive changes suggest the presence of antigens triggering an immune response. Overall, the pathophysiology of COPD in AATD seems to be beyond the simple protease/antiprotease imbalance and proposes the view of a1-antitrypsin in immune adaptive mechanisms [13].

Studies have shown that an excessive or persistent protease-antiprotease imbalance, even in the absence of antiprotease deficiency, is central to most pathogenic processes in COPD. This

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understanding is crucial for developing long-term therapeutic strategies to address the tissue damage and inflammation associated with COPD [12,13]. The other proposed mechanism of the pathophysiology of COPD in AATD is oxidative stress. Oxidative stress in COPD is described as a counterbalance between Reactive oxygen species (ROS) production and defense mechanisms, such as antioxidants. This disproportion can lead to airway destruction, which plays a crucial role in the pathogenesis of COPD. ROS like superoxide dismutase and hydrogen peroxidase are produced in excess, causing damage to lung cellular components and contributing to inflammation. Antioxidants that should usually amend ROS's effects may not be sufficient to handle the excessive oxidative burden in COPD. Inflammation, tissue damage, and remodeling are the results of this process [14]. The oxidants present in cigarette smoke may inactivate Alpha-1 Antitrypsin (AAT). This inactivation exacerbates the burden of antiprotease elastase, leading to emphysema development. Oxidative stress is associated with aging acceleration in patients with COPD.

Literature suggests that cigarette smoke exposure provokes inflammatory factors and changes the reactivity of smooth muscle of airways. Consequently, asthma and chronic obstructive pulmonary disease are characterized by hyperresponsive airways. This conclusion outlines the importance of therapeutic strategies in targeting inflammation and oxidative stress [15-17]. In discussion of the pathogenesis of COPD among patients with AATD, it is essential to consider lung microbiome dysbiosis and immune dysregulation. Boyton et al. [18] hypothesized that disruption of the lung microbial ecosystem by infection, inflammation, and/or antibiotic therapy creates a simplified microbial community with a downstream impact on immune function. These events lead to excessive NK cell activation and create a highly inflammatory lung environment. This activation creates and maintains chronic infection dominated by microbial pathogens [18].

Ananya et al. [19] discussed the relationship between gut-lung microbiota among patients with COPD exacerbation and suggested a potential link between gut health and respiratory conditions. Siva et al. outlined the independent relationship between peptic ulcer disease and worsening results of spirometry in COPD patients. As a result, gut health has been shown to have a significant influence on AECOPD (acute exacerbation of COPD). Sun et al. discovered an association between the microbiota of feces and sputum and exacerbation of COPD, suggesting that this microbiome can influence AECOPD. These studies collectively suggest that microbiome alteration, especially in the gut, has a significant role in lung health. This finding potentially influences the pathophysiology of COPD among patients with AATD [19-21]. The lung microbiome is a significant factor that helps to control the immune system, affecting airway inflammation. It focuses primarily on dysbiosis in the airways, causing inflammation, immunity, and tissue damage. In COPD, some bacterial species, such as H. influenzae, M. catarrhalis, and S. pneumoniae, may lead to inflammation and tissue destruction. Microbiome-derived signals activate alveolar macrophages and dendritic cells, stimulating different immune cellular players to maintain immune barrier function. The diseased airways become dysbiotic, leading to altered microbial diversity and composition, with the ultimate effect of persistent lung inflammation and tissue injury [22].

Biomarkers for COPD in AATD

Alpha-1 antitrypsin (AAT) deficiency is often underdiagnosed. Still, its early identification in asymptomatic or genetically predisposed individuals is crucial to apply preventive measures to reduce decrements in lung function. Diagnostic tests are performed in individuals diagnosed with COPD or who present cases in the family, patients diagnosed with asthma in adulthood whose airflow obstruction fails to revert despite adequate use of bronchodilators, and adults with bronchiectasis, among others [23,24]. As a result, preventive measures can be defined to prevent disease progression through habits such as quitting smoking and to ensure optimum treatment of the disease. Firstly, studies begin measuring serum AAT by nephelometry. However, AAT is an acute-phase protein; therefore, a false negative value in an infectious or inflammatory event is possible as it appears in normal ranges, and C-reactive protein levels are simultaneously quantified reactive to prevent misdiagnosis [24-26]. Afterward, protein phenotyping by electrofocusing is suggested to detect the most common AAT variants in the sample. Genotyping allows us to detect specific mutations instead, as long as it has specific primers for each allele [27]. The most common is M, also known as 'the normal variant'; the most common deficiency alleles are PiS and PiZ. As a result, genotypes can be cataloged, and treatment can be directed accordingly. PiZZ genotype is associated with emphysema and early onset COPD, and the ZZ and SZ genotypes are the most frequently associated with pathogenicity [24,27,28]. Gene sequencing should be conducted if a variant other than S or Z is suspected to be null or deficient [29].

The AAT's role as an inhibitor of proteolytic damage caused by neutrophil elastase in lung tissue by degrading elastin is known. Desmosine and isodesmosine, amino acids known as biomarkers of elastin degradation, are found in plasma, sputum, urine, and bronchoalveolar lavage (BAL) fluid in patients with COPD related or not to AAT deficiency [30]. In cases of COPD associated with AAT deficiency, a reduction in plasma levels of desmosine and isodesmosine is mentioned in patients on long-term intravenous augmentation therapy, compared to patients with the deficiency who did not receive it [31,32]. Regarding imaging markers, an initial CT scan is encouraged in patients with newly diagnosed COPD, emphasizing HRCT for accurate characterization of the presentation and extent of the disease, with pan lobular emphysema being the most predominant phenotype in individuals with AAT deficiency. The role of images as markers of progression and follow-up of the disease is a new line of development, mentioning within this the monitoring of the decrease in lung density using computed tomography, which has shown to be a promising possible long-term alternative to

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evaluate the progression of emphysema in patients with treatment [27,33]. However, its validation to evaluate disease progression is still under study. Lung MRI with hyperpolarized gas is a recent alternative to serial images for continuously monitoring the disease that does not use ionizing radiation such as CT. However, the literature on its use still needs to be improved [34].

Therapeutic Approaches for COPD in AATD

Augmentation therapy

Augmentation therapy stands as the primary specific treatment for AATD. The standard regimen is the weekly intravenous dosage of Alpha-1 Proteinase Inhibitor (ATT) at 60 mg/kg. Challenges include difficulty recruiting patients for clinical trials due to the rare nature of AATD. Studies suggest benefits in increasing AAT levels in blood and lungs. Clinical endpoints include improving CT lung density at total lung capacity (TLC) and functional parameters like forced expired volume in one second (FEV1). Observational studies show potential benefits in the FEV1 decline rate, but interpretation requires caution due to possible bias. The RAPID trial demonstrated a reduced rate of decline in lung density with augmentation therapy but showed no significant effect on lung function or quality of life. The impact on exacerbations remains uncertain [35-37].

Targeted anti-inflammatory therapies

Therapeutic aerosol delivery of AAT directly to the lungs is under investigation. A study by Brand et al. revealed older subjects with AAT compared to healthy groups. Ongoing studies are exploring the effects of direct AAT administration on the lungs [38].

Emerging therapies targeting disease-specific pathways

Gene therapy holds promise as a treatment for AATD, being a monogenic disorder. Early successes include in vitro human AAT (hAAT) gene transduction into cells using retrovirus vectors. Ex vivo gene therapy experiments demonstrated hAAT expression after transplantation into animal models. The current focus is on recombinant adeno-associated virus (AAV) as a vector for gene delivery. Challenges of gene therapy include the risk of immunogenicity, cytotoxicity, and mutagenesis, limiting human trials [39]. These approaches aim to address the underlying deficiency and associated complications of AATD, though each has its own challenges and ongoing research to optimize efficacy and safety.

Future Directions and Challenges

There are many challenges with studying AATD-related COPD. One of these challenges is underdiagnosis. Some patients can seek medical attention for 5.6 years before diagnosis, with fewer than 10% of affected individuals being clinically diagnosed [40]. The need for confirmed diagnosis decreases the pool for recruitment into clinical trials to develop new treatments [41]. Newborn screenings have been suggested for early detection of Alpha-1 antitrypsin deficiency; however, while this could offer early diagnosis, it has not been included in RUSP (recommended uniform screening panel) due to questions such as cost, privacy, and discrimination due to genetic sequencing. The National Detection Program for AATD is the most extensive targeted testing program in the United States. The program suggests targeted genotyping to determine allele status for patients diagnosed with COPD. Since 2017, the number of samples tested annually has increased to more than 100,000.

Other Strategies suggested are campaigns for early detection and diagnosis focusing on patients diagnosed with COPD to advocate for early testing [42]. The goal of early detection in many of these programs is to begin preventative treatment and provide information on environment and lifestyle habits, such as smoking, that could affect AATD-related COPD. The lack of consensus between studies also poses a challenge. For example, the EXACTLE trial evaluated the changes in CT lung density in patients receiving AAT augmentation therapy versus placebo. The trial demonstrated a significant improvement in lung density decline, and other meta-analyses and the RAPID clinical trial supported its results. However, a Cochrane review determined that new evidence was necessary to assess the potential therapeutic effectiveness of augmentative therapy. [40].

New methodologies such as helium, xenon, and carbon monoxide diffusing capacity have been proposed. Early studies have suggested a high correlation between time trends in the diffusing capacity of the lungs for carbon monoxide. Studies indicate that MRI is better at scanning lung structure than CT scans and could detect lung disease earlier [42]. Circulating polymers as diagnostic and possible biomarkers for AATD continue to be studied as they contribute to lung function deterioration. Other biomarkers studied as indicators of lung and liver function, disease progression, and response to augmentation therapy are fibrinogen levels and their degradation product (Aa-Val360) linked to lung elastin and degradation and the development of COPD as well as desmosine and isodesmosine [40]. Researchers are exploring varying therapeutic strategies such as gene therapy, induced pluripotent stem cells (iPSCs), gene-editing cell-based therapy, autophagy-enhancing drugs, and silencing RNA. While there is still a long way to go, this new approach has considered factors such as genetics, epigenetics, environment, and lifestyle for early detection and therapy [40-42].

Conclusion

Chronic Obstructive Pulmonary Disease (COPD), encompassing emphysema and bronchitis, poses a significant global health challenge fueled by factors like tobacco smoking and air pollution. The burden of COPD, projected to increase further, underscores the urgent need for effective management strategies. Among the genetic predispositions to COPD, Hereditary Alpha-1 Antitrypsin Deficiency (AATD) stands out, presenting a unique

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set of challenges and therapeutic opportunities. Understanding the genetic basis of AATD and its intricate relationship with COPD is crucial. AATD, resulting from mutations in the SERPINA1 gene, leads to decreased serum levels of Alpha-1 Antitrypsin, allowing unchecked protease activity and subsequent lung tissue destruction, characteristic of COPD. This intricate pathogenesis extends beyond classic protease/antiprotease imbalance, implicating immune dysregulation, oxidative stress, and lung microbiome dysbiosis. Identifying biomarkers for COPD in AATD is essential for early diagnosis and monitoring of disease progression.

Biomarkers like desmosine and isodesmosine offer insights into elastin degradation, while imaging modalities like HRCT and lung MRI provide valuable data for disease characterization and progression monitoring. Therapeutic approaches for COPD in AATD encompass augmentation therapy, targeted anti-inflammatory therapies, and emerging gene-based treatments. Augmentation therapy aims to restore AAT levels, while targeted anti-inflammatory therapies explore direct administration of AAT to the lungs. Emerging gene therapies hold promise for correcting the underlying genetic defect. Future directions include addressing underdiagnosis, lack of research consensus, and exploring novel diagnostic and therapeutic avenues. Strategies like newborn screenings, advancements in imaging techniques, and the exploration of new biomarkers and therapeutic modalities offer hope for improved management of COPD in AATD. A multifaceted approach integrating genetics, environment, and lifestyle factors will be pivotal in advancing early detection and personalized therapy, ultimately alleviating the burden of COPD worldwide.

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