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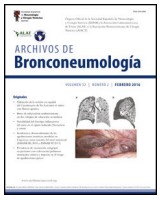

Editorial

Alpha-1 Antitrypsin Deficiency and *SERPINA1* Variants Could Play a Role in Asthma Exacerbations

Alpha-1 antitrypsin (AAT) is a monomeric glycoprotein that belong to the serum protease inhibitor (serpin) family, and is encoded by the *SERPINA1* gene. It is mainly synthesized and secreted by liver cells, but to a lesser extent by some immune cells and specific tissues. Its main function is to act as the major protease inhibitor of neutrophilic elastase, but its protease targets also include plasmin, thrombin, trypsin, chymotrypsin, and plasminogen activator.[1] AAT behaves like an acute phase reactant, increasing its levels to deal with inflammatory or infectious processes, and controlling the activity of human neutrophil peptides, which are involved in several inflammatory-related lung diseases.[2] In fact, the immunomodulatory role of AAT has been widely demonstrated in recent studies, as it is involved in the reduction of B4 leukotrienes expression in respiratory tissues, modulation of cytokine expression in the blood, and inhibition of pro-inflammatory interleukins (IL) synthesis, such as IL-1, IL-6, IL-8, IL-32, monocyte chemotactic protein type 1, or TNFα.[3] Interestingly, the immunomodulatory role of AAT seems to be independent of its anti-elastase activity,[4] suggesting that not only the blood AAT levels but also its correct recognition by immunomodulatory factors are important for the control of inflammatory processes.

Several genetic variants of *SERPINA1* gene lead to Alpha-1 antitrypsin deficiency (AATD), which is considered an underdiagnosed genetic condition, where patients show lower AAT levels than expected. This condition predisposes carriers to certain diseases, including lung disease (in the form of emphysema), liver disease (hepatic fibrosis or cirrhosis), panniculitis, and vasculitis.[5] Recent works strongly support the presence of more than 500 variants in the *SERPINA1* gene.[6] Although the vast majority of these variants do not decrease blood AAT levels, they could affect the AAT antielastase and/or immunomodulatory activities, thus highlighting the need to increase sequencing efforts of *SERPINA1* gene, not only in AATD patients, but also in individuals with inflammatory diseases, especially those that affect the respiratory system.

In this context, bronchial asthma is defined as a chronic inflammatory disease of the respiratory tract that involves different cells and inflammatory mediators. It is considered a multifactorial disease, conditioned by a combination of genetic and environmental factors, which causes bronchial hyperreactivity and variable airflow obstruction, totally or partially reversible, either by drug action or spontaneously.[7] Different immune cells are known to participate in asthma pathophysiology. Airways inflammation is mainly caused by eosinophils, while mastocytes are involved in bronchoconstriction, due to the release of histamine, tryptase, cysteinyl leukotrienes and prostaglandins, in addition to producing pro-inflammatory cytokines. Moreover, T cells play a fundamental role in the initiation and regulation of the inflammatory response by releasing cytokines, such as IL-4, IL-5, IL-9, and IL-13.[8] Other cells that participate in the asthma inflammation mechanisms are neutrophils (inflammation effector cells), macrophages (release of inflammatory mediators), or dendritic cells (presenting antigens from the surfaces of the airways to regional lymph nodes). Interestingly, a recent study also supports a direct role of AAT in the inflammatory process, as $CD4^+$ T cells are able to secrete AAT when exposed to active vitamin D. This induction of *SERPINA1* expression in CD4+ T cells requires a direct interaction between AAT and complement C3a, and produce an autocrine release of IL-10.[9] Other molecules that play an important role are IL-1 beta and TNFα, since they amplify the inflammatory response.[10]

Therefore, the correct balance between pro-inflammatory and anti-inflammatory factors, in which AAT seems to be somehow involved, is crucial to develop a controlled inflammatory response. However, the unbalance between these immune modulators could lead to develop an uncontrolled response, which results in an acute episode of asthma severity, usually known as asthma exacerbation. Indeed, prevention of asthma exacerbations is the main objective for controlling this chronic disease, decreasing the associated morbidity and mortality.[11] Given that AAT is an essential glycoprotein, associated with several inflammatory mechanisms, and that asthma exacerbations are mainly caused by an uncontrolled inflammatory process, we propose that AATD (whether deficient or qualitative) could cause an imbalance between pro-inflammatory and anti-inflammatory factors that would lead to subjects with bronchial asthma and AATD to develop a poor symptom control, and higher exacerbations rates. According to this hypothesis, Nishioka and coworkers demonstrated that AAT blood levels are altered during exacerbations in patients diagnosed with bronchial asthma, proposing AAT as a predictive biomarker of asthma exacerbations.[12] Accordingly, Dowson et al. have also shown that patients with AATD and asthma have decreased lung function, a worse prognosis and evolution than those without alterations in the *SERPINA1* gene.[13] More recently, in a study about AATD prevalence in a clinical population, a high frequency of *SERPINA1* gene S and Z alleles in patients with bronchial asthma has been also confirmed.[14] Regarding the immunomodulatory role of AAT in the development of allergic phenotypes in asthmatic patients, recent findings suggest that *SERPINA1* gene variants linked to AATD are significantly associated with atopy in asthma patients. Aiello et al.

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studied a cohort of 58 ambulatory patients with asthma (22 and 36 patients with and without AATD, respectively, according to their *SERPINA1* genotype). They hypothesized that asthma patients with pathogenic genetic variants in the *SERPINA1* gene exhibit distinctive clinical features. The presence of atopy was significantly higher in patients with AATD (91% vs. 64%; $p = 0.031$), and patients with AATD reported more allergic manifestations than controls (77% vs. 47%; $p = 0.030$), demonstrating that atopy in asthma patients with AATD is considerably higher than in asthma patients without *SERPINA1* pathogenic variants.[15] These results highlight the importance of the immunomodulatory role of AAT, as its blood levels may unbalance inflammatory cellular processes, leading to a different phenotype inside the asthma population, where AATD is related to a higher prevalence of allergic manifestations and atopy.

Overall, these findings lead us to consider that AATD, as well as *SERPINA1* variants that affect AAT immunomodulatory activity, could play a significant role in the development of asthma exacerbations. However, we have been unable to find studies in the reviewed literature that specifically explore this issue.

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Conflict of interests

The author declares have no conflicts of interest related directly or indirectly to the contents of the manuscript.

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José M. Hernández-Pérez [a,*], Elena Martín-González [b], Mario A. González-Carracedo [b,c]

[a] *Department of Respiratory Medicine, Hospital Universitario de N.S de Candelaria (HUNSC), Santa Cruz de Tenerife, Spain*
[b] *Genomics and Health Group, Department of Biochemistry, Microbiology, Cell Biology and Genetics, Universidad de La Laguna (ULL), La Laguna, Tenerife, Spain*
[c] *Instituto Universitario de Enfermedades Tropicales y Salud Pública de Canarias (IUETSPC), Universidad de La Laguna (ULL), La Laguna, Tenerife, Spain*

Corresponding author.
E-mail address: jmherper@hotmail.com (J.M. Hernández-Pérez).