

Common Pathogeneses Underlying Asthma and Chronic Obstructive Pulmonary Disease -Insights from Genetic Studies

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Abstract: Neither asthma nor chronic obstructive pulmonary disease (COPD) is a single disease consisting of a uniform pathogenesis; rather, they are both syndromes that result from a variety of basic distinct pathogeneses. Many of the basic pathogeneses overlap between the two diseases, and multiple basic pathogeneses are simultaneously involved at varying proportions in individual patients. The specific combination of different basic pathogeneses in each patient determines the phenotype of the patient, and it varies widely from patient to patient. For example, type 2 airway inflammation and neutrophilic airway inflammation may coexist in the same patient, and quite a few patients have clinical characteristics of both asthma and COPD. Even in the same patient, the contribution of each pathogenesis is expected to differ at different life stages (eg, childhood, adolescence, middle age, and older), during different seasons (eg, high seasons for hay fever and rhinovirus infection), and depending on the nature of treatments. This review describes several basic pathogeneses commonly involved in both asthma and COPD, including chronic non-type 2 inflammation, type 2 inflammation, viral infections, and lung development. Understanding of the basic molecular pathogeneses in individual patients, rather than the use of clinical diagnosis, such as asthma, COPD, or even asthma COPD overlap, will enable us to better deal with the diversity seen in disease states, and lead to optimal treatment practices tailored for each patient with less disease burden, such as drug-induced side effects, and improved prognosis. Furthermore, we can expect to focus on these molecular pathways as new drug discovery targets.

Keywords: Asthma, chronic obstructive pulmonary disease (COPD), endotype, precision medicine, treatable traits approach

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both common diseases diagnosed by the presence of chronic symptoms such as cough, sputum, shortness of breath, and airflow obstruction. Several clinical/inflammatory factors are commonly associated with the risk of developing asthma or COPD or with important clinical outcomes such as reduced lung function, exacerbations, reduced quality of life and mortality.^{1,2} They are characterized by their complex and heterogeneous nature, both clinically and in their molecular pathogenesis. Endotype is a dynamic molecular network that arises when an individual's genetic factors interact with various environmental factors, such as infections, air pollution, tobacco smoke, antibiotics, and lung flora, driving the phenotype in a particular patient. Given the clinical and biological complexity and heterogeneity of the diseases, the development of therapeutic strategies targeting individual endotypes could help us enable early identification of disease risk with a high degree of accuracy and implementation of preventive strategies.³

Numerous genetic studies, including genome-wide association studies (GWAS), have found a number of loci that influence the development of asthma and COPD, and several genetic factors are common to both diseases. Genetic contribution of individual common variants to disease susceptibility is very small, especially in isolation, and the small proportion of heritability explained by these variants makes it difficult to predict disease onset in a practical clinical setting. At present, the more important significance of GWAS, however, is not to estimate individual risk, but rather to

discover the biological pathways underlying complex diseases.⁴ The pathophysiological pathways identified by GWAS for a disease have important implications not only for carriers of a particular genetic polymorphism, but also in the origins of the disease itself.

This review describes representative endotypes indicated by genetic and molecular data to be commonly involved in both asthma and COPD, including chronic non-type 2 inflammation, type 2 inflammation, increased susceptibility to viral infections, and impaired lung development and repair/remodeling. Advances in genomic medicine in asthma and COPD are critically important for achieving precision medicine, allowing a departure from the current one-size-fits-all medicine according to disease labels or clinical symptoms, and population approach to disease incidence prevention that does not consider individual disease susceptibility.⁵

Overlap Between Asthma and COPD

Dutch hypothesis was proposed more than 50 years ago.⁶ In this hypothesis, asthma and COPD are two phenotypes of a syndrome called chronic nonspecific lung disease (CNSLD), where CNSLD is defined as the result of an interaction between intrinsic genetic factors and extrinsic factors such as viral infection, air pollution, tobacco smoke exposure, and allergen exposure. The timing of this interaction during an individual patient's life stage determines which clinical syndrome develops (ie, asthma or COPD) or whether characteristics of both asthma and COPD appear. Thus, a particular genetic factor may combine with a particular environmental factor to cause asthma, or the same genetic factor may combine with another genetic or environmental factor to cause COPD.⁷ Several genes and loci have been reported as common factors in susceptibility to asthma and COPD.^{7,8} We performed a PubMed database search published through September 2012 for asthma, COPD, tuberculosis, and essential hypertension, respectively. For each disease, pathway-based analysis was performed to determine how the identified genes interacted with each other.⁸ In at least two independent reports, a total of 108 genes were found to be associated with asthma and 58 with COPD. These genes were grouped into multiple networks according to functional annotation. Twelve networks were found in asthma and 11 in COPD, and the overlapping network between the two diseases formed one complex network consisting of 229 common molecules (Figure 1). These overlapping molecules were significantly associated with aryl hydrocarbon receptor (AhR) signaling, the role of cytokines in mediating information transfer between immune cells, glucocorticoid receptor signaling, and pathways involved in IL-12 signaling and production in macrophages. At the network level, the Jaccard similarity index for asthma and COPD was 0.81, with an odds ratio of 3.62 for asthma/COPD pair in comparison to tuberculosis/essential hypertension pair. The overlap in the asthma and COPD gene networks indicated a high degree of pathobiological similarity between these two diseases.

Common Pathogenesis Characterized by Chronic Non-Type 2 Airway Inflammation

As discussed in the section above, AhR signaling is implicated in common pathologies of asthma and COPD; AhR acts as a regulator of mucosal barrier function and affects lung immunity by inducing changes in gene expression, intercellular adhesion, mucin production, and cytokine expression.⁹ Although the binding of this receptor to different ligands leads to what seems to be variable responses, AhR-regulated neutrophils and Th17 cells are involved in the responses to pro-inflammatory stimuli, including tobacco smoke and air pollutants.¹⁰ The AhR-ROS-NLRP3 inflammatory functional axis, which regulates Muc5ac expression and airway inflammation, may also be involved in airway inflammation in asthma and COPD.¹¹

We performed a GWAS of adult-onset asthma that developed over the age of 40 and identified the *HCG22* gene as a susceptibility gene.¹² This gene was also associated with diffuse panbronchiolitis (DPB) and COPD. DPB is a chronic neutrophilic bronchiolitis with chronic cough, sputum, and shortness of breath on exertion as the main symptoms, and its prevalence increases after the age of 40 years. *HCG22* is a novel mucin-like gene¹³ located at 6p21.3, the DPB susceptibility gene region. Furthermore, *HCG22* has been reported to be associated with tree-in-bud pattern identified on chest computed tomography in asthmatic patients and with steroid refractoriness requiring high doses of corticosteroids.¹⁴ Based on its amino acid sequence, *HCG22* has a chitin-binding protein-like structure.¹⁵ YKL-40, a chitinase-like protein similar to *HCG22*, has been reported to be associated with phenotypes characterized by

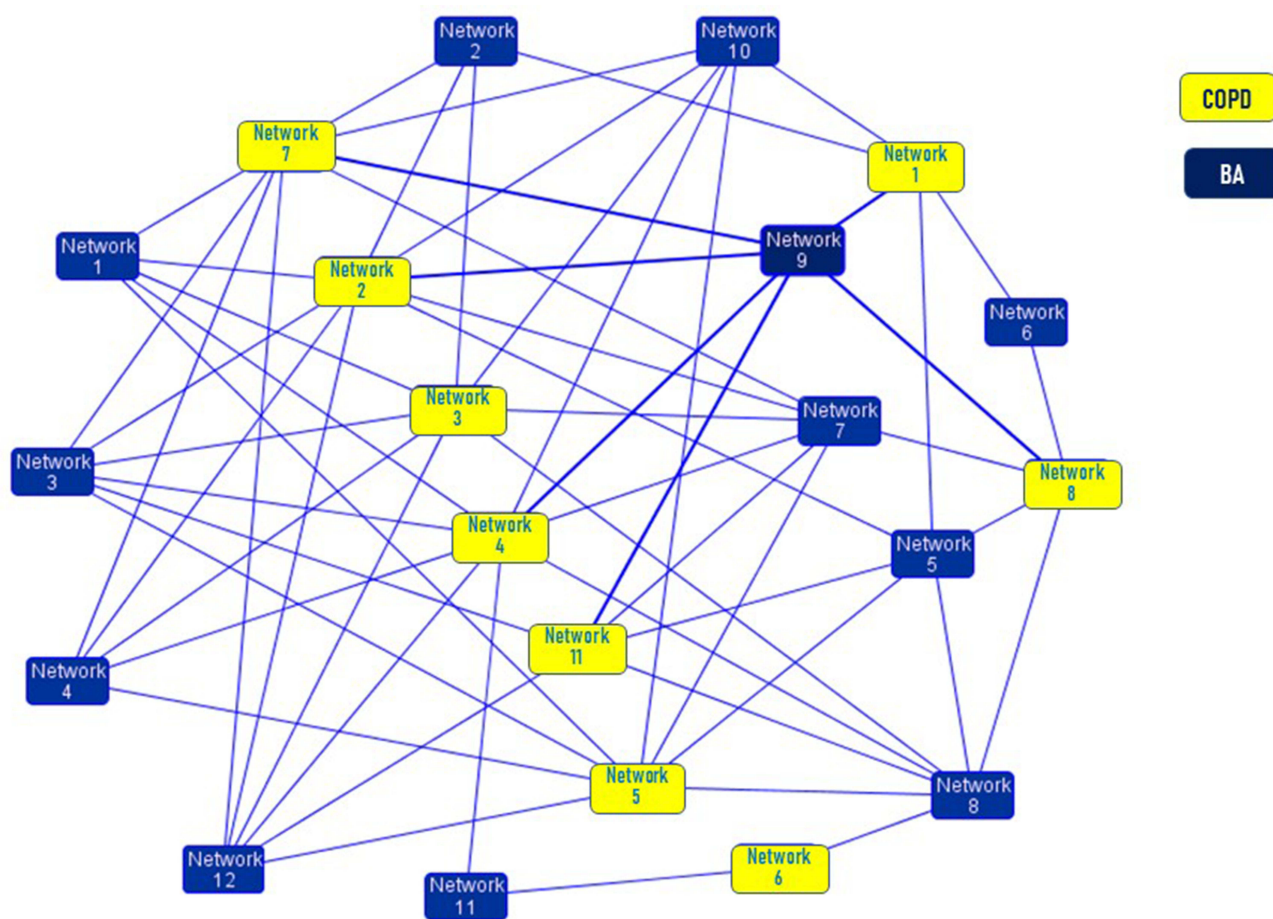


Figure 1 Overlapping networks between asthma and COPD. The Ingenuity Pathway Analysis software program identified 229 overlapping molecules between 12 asthma networks and 11 COPD networks, and merged them into a single larger network. In total, 229 genes were common to both diseases, and 190 and 91 genes were unique to asthma and COPD, respectively. Each network is represented by a colored rectangle, and is labeled with its corresponding network number. Adapted with permission from Dove Medical Press. Kaneko Y, Yatagai Y, Yamada H, et al. The search for common pathways underlying asthma and COPD. *Int J Chron Obstruct Pulmon Dis*. 2013;8:65–78.⁸

neutrophilic inflammation in asthma and COPD.^{16,17} Chitin is a pathogen-associated molecular pattern found in mites and fungi, and it is of interest due to its involvement in infection immunity in the airway mucosa, and its association with the pathogenesis of middle-age-onset asthma, COPD, and DPB. Recently, the new disease category of muco-obstructive lung disease has been proposed, and it includes COPD, primary ciliary dyskinesia, and bronchiectasis.¹⁸ Mucus-derived obstruction is characterized by altered airway microbiota, mucociliary dysfunction, neutrophilic inflammation, and airway destruction, which are also important features in DPB and a subgroup of patients with non-type 2 asthma.

We have found a gene encoding HA synthase 2 (*HAS2*) as associated with asthma.¹⁹ *HAS2* is a glycosaminoglycan found in the extracellular matrix and is highly expressed in the lung. Asthma-associated single nucleotide polymorphisms (SNPs) affected the expression levels of *HAS2* mRNA. Hyaluronic acid (HA) is involved in many physiological and pathological processes, including cell migration, morphogenesis, tissue regeneration, wound repair, and tumor cell proliferation and invasion, and increased levels of HA in sputum have been reported in COPD patients.²⁰ Patients with higher levels of hyaluronan had impaired lung function than patients with normal hyaluronan levels. In addition, influx of neutrophil and levels of interleukin-8 and soluble tumor necrosis factor (TNF) receptors were higher in COPD patients with elevated HA levels. Decreased *Has2* expression in mice enhanced ovalbumin (OVA)-induced airway inflammation, including increased neutrophils and eosinophils, airway hyperresponsiveness, and attenuated CD44 and transforming growth factor (TGF)- β signaling.²¹ CD44 is an HA binding protein and decreased CD44 downregulates TGF- β . In addition, lung mRNA sequencing and pathway analysis identified enriched terms “IL-17A signaling in

fibroblasts”, “NRF2-mediated oxidative stress response”, and “glucocorticoid receptor signaling”. These terms were thought to be associated with severe asthma and COPD. Furthermore, in a chronic OVA sensitization and challenge-induced asthma model,²² IL-17A levels in lung homogenates were higher in *Has2* heteroknockout OVA mice than in wild-type mice, and *Has2* heteroknockout OVA mice showed goblet cell hyperplasia and excessive mucus production. Thus, chronic OVA stimulation induced a characteristic phenotype of airway remodeling through *Has2*-mediated attenuation of IL-17 and TGF- β signaling.

Taken together, neutrophil inflammation is recognized as an important pathogenic factor in asthma as well as COPD.

Common Pathogenesis Characterized by Type 2 Inflammation

Eosinophilic airway inflammation is found in patients with COPD as well as asthma, and the presence of eosinophilic inflammation is associated with exacerbations and responsiveness to inhaled corticosteroids. Overall, 612 (56%) of 1094 Japanese COPD patients had an absolute eosinophil number of 150 cells/mm³ or greater, and 902 (69%) of 1304 Japanese patients had an eosinophil fraction of 2% or greater²³ (Figure 2). In a study comparing the comprehensive gene expression in the airway epithelial cells of asthma and COPD patients, the gene expression levels associated with type 2 inflammation were increased not only in asthma patients, but also in COPD patients.²⁴ In particular, the expression of type 2-related genes in COPD patients was associated with stronger airflow limitation, airway eosinophil infiltration, and even the responsiveness to inhaled corticosteroid (ICS).

In a large GWAS of 8068 patients with the overlapping asthma and COPD pathology in the UK Biobank and 4301 patients with the overlapping pathology from other cohorts, eight loci were identified,²⁵ including the thymic stromal lymphopoietin (*TSLP*) gene. These eight loci were not clearly associated with smoking habits, but they were strongly

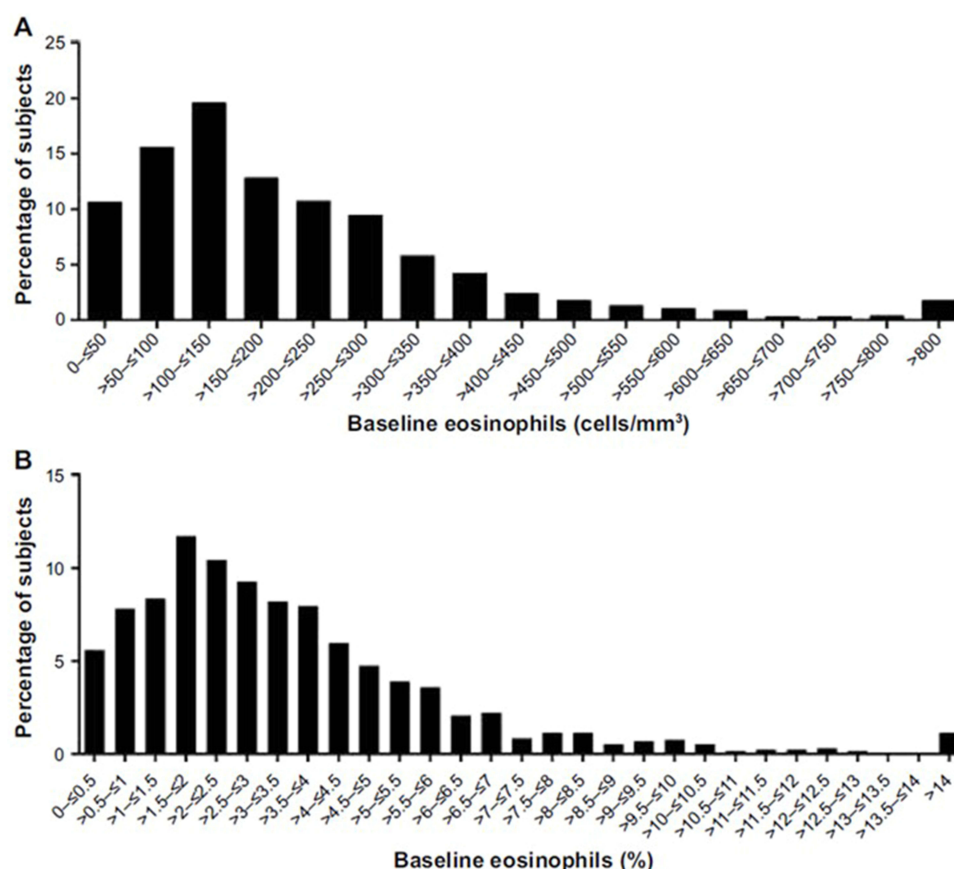


Figure 2 The distribution of blood eosinophil levels in a Japanese COPD clinical trial database. Distribution of (A) absolute blood eosinophil count and (B) percentage blood eosinophils among Japanese patients with COPD. Reprinted with permission from Dove Medical Press. Barnes N, Ishii T, Hizawa N, et al. The distribution of blood eosinophil levels in a Japanese COPD clinical trial database and in the rest of the world. *Int J Chron Obstruct Pulmon Dis*. 2018;13:433–440.²³

associated with the peripheral blood eosinophil counts, immunoglobulin (Ig) E sensitization and asthma, suggesting the importance of type 2 inflammation in the overlapping pathology. Elevated TSLP protein and *TSLP* mRNA levels have been reported in bronchial epithelium in COPD patients.²⁶ Multiple factors related to exacerbations of asthma and COPD, including respiratory viruses, cigarette smoke, and inflammatory cytokines, have been associated with increased TSLP production.^{27–30} *TSLP* gene was also identified as a potential susceptibility locus for impaired lung function in non-COPD, non-asthmatic healthy subjects, which supports the idea that *TSLP* is a genetic determinant of lung function that influences the risk of developing asthma and COPD.³¹

The *ORMDL3/GSDMB* gene located on chromosome 17q has been consistently associated with childhood-onset asthma, and most asthma patients associated with this gene are atopic. In addition, an association of the region with overlap between COPD and asthma without rhinitis has been reported.³² Susceptibility to rhinovirus (RV) infection is associated with this genetic region that affects transcription and protein expression of intercellular adhesion molecule 1 (ICAM1), a major receptor for human RV (HRV).³³ *ORMDL3/GSDMB* has also been implicated in the development of childhood asthma related to indirect exposure to smoking at home.³⁴ Furthermore, the importance of *ORMDL3/GSDMB* was indicated in susceptibility to early-onset adult asthma in Japanese. While the region was not associated with allergic sensitization, it was strongly associated with increased serum total IgE levels,³⁵ and therefore, the region appears to act as a stress sensor in the airways caused by viral infections and smoking, and promotes airway inflammation through an enhanced innate type 2 immune response.

Common Pathogenesis Characterized by Increased Susceptibility to Viral Infections

HRV is an important risk factor for exacerbations both in asthma and COPD. RV induces several cytokines including IFN α , IFN γ , TNF α , CXCL10/11, and CC chemokine ligand 5 (CCL5) in airway epithelial cells. The airway epithelial cell responses to RV was overlapped with gene expression signatures reported in patients with asthma or COPD.³⁶

We previously found that the gain-of-function –28G allele of a promoter SNP (rs2280788) in the *CCL5* gene was a risk factor for adult-onset asthma who developed the disease at age 40 years or older, and also for COPD who had less emphysema lesions.^{37,38} Given that the *CCL5* gene is a pathway involved in both the pathogenesis of older-onset asthma and COPD with less emphysema, it is interesting that *CCL5* is shown to contribute to tissue-resident T cell-associated T1 neutrophilic inflammation in asthma and correlates with T2 inflammation and sputum eosinophilia as well.³⁹

The *CDHR3* gene, which was identified in GWAS of childhood asthma with frequent severe exacerbations, was found to encode a receptor for RV type C.⁴⁰ We confirmed that the functional variant at *CDHR3* has a significant genetic influence in Japanese adult asthma patients with onset by age 10 years, and that the association is stronger when restricted to allergen sensitization-positive individuals.⁴¹ In addition, a 10-year observational study was conducted to examine the genetic impact of the *CDHR3* gene on the newly development of asthma or COPD in 1523 healthy adults with no pulmonary disease who had health checkups in 2008. During the 10-year period, a total of 79 cases and 25 cases newly developed asthma and COPD, respectively. The *CDHR3* gene had a genetic influence on the development of asthma or COPD, especially in adults with allergen sensitization in 2008.⁴² A molecular network (endotypes) derived from the susceptibility to RV infection and allergen sensitization was found to be responsible not only for childhood-onset allergic asthma, but also for adult-onset asthma or COPD.

Common Pathogenesis Characterized by Impaired Lung Development and Repair/Remodeling in Asthma and COPD

The primary risk factor for COPD is smoking. However, there is growing evidence to suggest that lung disease in adults may originate from prenatal or early-life exposures to harmful stimuli.⁴³ A whole genome sequencing study⁴⁴ that compared 3181 moderate/severe asthmatics with 3590 non-asthmatic controls showed that asthma risk is genetically correlated with lung dysfunction. This genetic factor associated with asthma development was shown to be independent of genetic factors associated with eosinophilic inflammation that also contribute to asthma. The polygenic score for impaired lung function was also associated with early-onset of asthma. Thus, genes that influence lung development in

utero and in early childhood, in combination with environmental exposure such as cigarette smoke and viral infections, all contribute to both childhood asthma and future COPD development.

Asthma and COPD are heterogeneous and complex diseases, because they are caused by multiple factors, and the impact of individual risk factors is small. A genetic risk score (GRS) has been applied to address the heterogeneity and complexity of these diseases.⁴⁵ We developed a quantitative GRS according to genotypes at 16 SNPs implicated in impaired lung function in both Japanese and non-Japanese individuals.⁴⁶ The modest effects of 16 SNPs were combined into a single variable, which was calculated as the weighted sum of the number of high-risk alleles at each SNP. The GRS with a reduced forced expiratory volume/forced lung capacity ratio was consistently associated with asthma or COPD in two independent Japanese populations. Clustering of patients with asthma according to their lung function GRS indicated that elevated GRS may be associated with the development of distinctive phenotype of asthma (early onset, atopy, and severe airflow obstruction). Analysis of the functional relevance of these 16 genes showed that lung function GRS is associated with molecular pathways involved in tissue repair and remodeling induced by lung injury. In addition, a study using UK Biobank data to examine the association of 391 genes known to regulate lung development and lung function in adults⁴⁷ found that 55 genes were significantly associated with four biological categories including growth factors, transcriptional regulators, intercellular adhesion, and extracellular matrix. These results together showed the importance of lung growth-related genes in regulating lung function and influencing airflow obstruction in adults. Thus, respiratory function measurements from infancy through adolescence may facilitate early identification of individuals prone to lung growth failure, leading to early intervention and prevention of asthma and COPD development.

Several GWAS have indicated the hedgehog signaling pathway as an important pathway underlying lung function and COPD; hedgehog-interacting protein (HHIP) is a negative regulator of the hedgehog pathway and patched 1 (PCTH1) is a receptor that activates the pathway.⁴⁸ In older adults with asthma, the *PTCHD4* gene has recently been associated with the responsiveness to ICS, as indicated by the presence of oral corticosteroid bursts.⁴⁹ *PTCHD4* encodes patched domain-containing protein 4, which represses hedgehog signaling.⁵⁰ Increased *PTCHD4* mRNA expression was associated with aging, and enrichment of methylated CpG sites in the *PTCHD4* gene was associated with COPD.^{51,52} Furthermore, COPD patients with larger lesion with airway smooth muscle cell of bronchial tissue responded better to ICS than those with smaller lesion with airway smooth muscle cell, suggesting that a detailed histological classification of COPD patients may reflect differences in endotypes and help determine treatment strategy.⁵³ These results suggest that responsiveness to ICS in asthma and COPD patients may be strongly influenced by specific patient endotypes, and that patients with specific endotypes related to lung growth abnormalities or impaired injury repair may be less responsive to ICS.

Treatable Traits Approach in Patients with Asthma and COPD

Given the complexity and heterogeneity of chronic inflammatory pulmonary diseases, including asthma and COPD, their appropriate management requires a new approach that includes multidimensional assessment. Patients with chronic inflammatory pulmonary diseases should not be treated according to disease labels such as asthma, COPD, or asthma COPD overlap, but rather on what endotypes play a critical role in individual patients.⁵⁴ In 2015, I had proposed a plausible approach for positioning ICSs and long-acting β 2-agonists (LABAs)/long-acting muscarinic antagonists (LAMAs) in the treatment of COPD based on both the extent of airflow obstruction and the presence of type 2 airway inflammation⁵⁵ (Figure 3). Thereafter, a management strategy based on the so-called treatable traits was proposed.^{56,57}

We attempted to identify a group of patients who were more prone to exacerbations beyond the name of the diseases using multiple risk factors common to asthma and COPD exacerbations.⁵⁸ As a result, we identified five distinct clusters, each characterized by high eosinophil counts, smokers with reduced lung function, gastroesophageal reflux, non-allergic women, or allergic rhinitis with high total IgE levels. Clinical heterogeneity of disease exacerbations was shown to possibly indicate the presence of exacerbation-prone endotypes common to asthma and COPD, supporting the benefit of a trait-based approach for exacerbation prevention in patients with chronic inflammatory pulmonary disease.

Recently, it was reported that in COPD patients with type 2 inflammation, in whom both blood eosinophil counts and FeNO are elevated, dupilumab, an antibody against the IL4 receptor alpha chain, leads to a reduction in exacerbation frequency, improvement in lung function and quality of life, and even improvement in respiratory symptoms compared to

Approach to COPD based on disease phenotypes

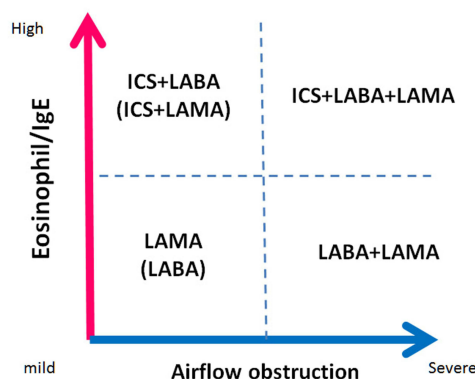


Figure 3 Approach to COPD treatment based on the degree of airflow obstruction and peripheral blood eosinophil counts. This proposal for positioning ICSs and bronchodilators for the treatment of COPD in clinical practice follows a personalized medicine approach that is not based on the stratification of patients into subgroups, but rather is based on individual characteristics that consider the heterogeneity and complexity of the disease in patients. Reprinted with permission from Dove Medical Press. Hizawa N. LAMA/LABA vs ICS/LABA in the treatment of COPD in Japan based on the disease phenotypes. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1093–1102.⁵⁵

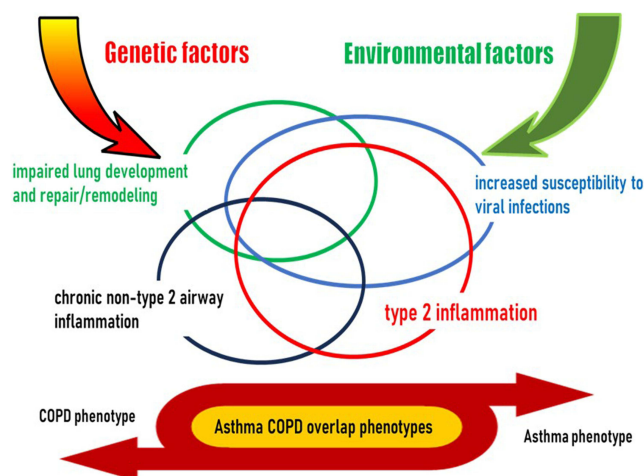


Figure 4 Common endotypes underlying asthma and COPD. Asthma and COPD are syndromes caused by complex interactions between individual genetic factors and various environmental factors. At any given time, the interaction of multiple endotypes drives individual patient pathologies and phenotypes.

placebo.⁵⁹ Considering that patients with currently diagnosed asthma or a history of asthma were excluded from the study, these results appear to support the usefulness of a treatable trait approach.

Conclusion

Both asthma and COPD are syndromes with highly variable clinical manifestations (phenotypes), including severity and course over time, and are caused by complex interactions between individual genetic factors and various environmental factors such as viral infection, allergen exposure, and tobacco smoke exposure (endotype). In this review, I have described four representative endotypes common to asthma and COPD (Figure 4). These endotypes are involved in patient pathogenesis in varying proportions. Furthermore, while the interactions of individual endotypes shape each patient's pathology, the relative contribution of each endotype in an individual patient may change over time. Clinical traits or biomarkers could be used to identify the presence of each endotype. We must consider that it is not one endotype per patient, but rather the interaction of multiple endotypes that drives individual patient pathologies. With the advancement of genomic medicine, our understanding of endotypes will advance, new therapeutic agents will be developed, and the diseases will be reclassified

according to specific phenotypes and biomarkers that reflect differences in molecular pathobiology, ushering in an era of precision medicine that targets the molecular mechanisms underlying the diseases in individual patients.

Disclosure

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