Re-defining Asthma – What's all the fuss about?

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Asthma is a descriptive term that has been used over the centuries to denote a condition that is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, without any assumption of pathophysiology. Under this definition many other conditions apart from asthma may be diagnosed but with the later ability to measure lung function, the addition of variable expiratory airflow obstruction brought more precision to its diagnosis. More recently, recognising the importance of airway inflammation as associated with causing the symptoms of asthma, its presence was another useful differentiating property. The recognition that eosinophilic inflammation was commonly associated with symptomatic asthma led to the use of inhaled steroids as being the most important anti-inflammatory management of asthma, and together with inhaled long-acting beta-agonist bronchodilators formed the basis of treatment for all asthmatic patients with the dose of these anti-asthma drugs dosed according to the degree of severity of the asthma (https://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/).

This led to the recognition that there was a group of asthma patients whose disease remained uncontrolled despite taking high doses of these inhaler therapies plus other asthma medications including oral corticosteroids who were therefore resistant to these existing therapies, the severe refractory asthma (1). In the search for new therapies, the development of antibody therapies targeted at specific components of the Type 2 inflammation led to the definition of specific groups of patients within this T2, such as anti-IgE antibody directed at severe allergic asthma and of anti-IL5 antibody directed at severe eosinophilic asthma associated with recurrent exacerbations (2). This has led to the recognition of these phenotypes that would respond specifically to these targets, bringing precision medicine to asthma (3).

The severe eosinophilic asthma phenotype is now well recognised phenotype of high T2 with IL-4, IL13 and IL5 being important drivers in this phenotype. Clinically it is recognised as being associated with severe asthma (ERS/ATS definition), an exacerbation frequency ≥ 2/year, a dependence on oral corticosteroids for asthma control and high circulating eosinophils. However, those phenotypes with a low T2 have remained poorly studied and these phenotypes do not have any specific targeted treatments. Omics data analysis has now allowed us to define T2 and non-T2 phenotypes. Using an analysis of sputum transcriptomics has allowed us to define a T2-high and 2 non-T2 high with airway neutrophilia with activated inflammasome and IL-1β signalling, and another with little inflammation but associated with elements of oxidative stress(4).

What does this mean regarding the taxonomy for asthma? The idea that the disease is heterogeneous has been recognised over the centuries and recently used in the GINA definition. While the definition from the clinician's point of view with a collection of symptoms will remain (physician-diagnosed asthma), it needs to be more granular with the definition of molecular phenotypes underlined by the driving mechanisms (leading to the endotype), since these will attach specific therapies to which these phenotyped patients will respond to. The definition of asthma according to treatable traits is not a useful concept as these classifications are not based on mechanisms and pathophysiology and therefore do not allow one to judge whether the trait is treatable or not . This new definition will not only apply to those with severe refractory asthma but to the whole spectrum of the disease from mild to severe disease. A re-definition of asthma is imperative: it needs to contain the concept of precision medicine, and this will represent the long journey from a cluster of symptoms to efficacious targeted therapies in specific well-defined endotypes.

References:

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