Asthma Endotypes and Phenotypes

Subjects: Pathology

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Asthma is considered an umbrella diagnosis comprising various distinct manifestations and mechanisms. The precise definition of these endotypes and subgroups is crucial for asthma management due to therapeutic and prognostic implications. A reductionist research approach to asthma complexity may explain the lack of translation of genomic findings into clinical practice to date, despite the abundance of low-to-modest effect genetic loci revealed by genomic studies of asthma. Shifting asthma diagnosis to specific endotypes and phenotypes may provide insights into features that can be prevented or alleviated by therapeutic intervention.

asthma GWAS genomics

1. Introduction

Asthma is a major noncommunicable, respiratory disease that affects an estimated 350 million people worldwide and is the most prevalent chronic disease in children globally [1]. It is a heterogeneous and complex disease, characterized by chronic airway inflammation and a history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation [2]. Different environmental, genetic, and behavioral factors interact to modify asthma's susceptibility and course, which contributes to the disease complexity [2]. Regrettably, despite asthma mortality having decreased in the last decades, still a substantial proportion of asthmatics remain difficult to treat, leading to significant economic consequences, including productivity losses and increased cost of public health expenditure [3][4][5].

Early genetic studies of asthma had limited success in associating genetic variation with asthma susceptibility using linkage analyses in large families with more than one person with asthma, as well as using candidate gene association analyses. Novel genetic signals arose with the advent of genome-wide association studies (GWAS), which are hypothesis-free scans that interrogate genetic variation across the genome for association with a phenotype of interest. Despite GWAS having revealed a large catalog of genetic loci for asthma, the genetic variation uncovered only accounts for a small fraction of asthma heritability [6]. Genomic research has investigated several asthma phenotypes or asthma-related traits in an attempt to unravel the complicated etiologic pathways of asthma and features that could be prevented or alleviated by therapeutic interventions such as pulmonary rehabilitation or pharmacological treatment.

2. Asthma Endotypes and Phenotypes

The asthma definition has largely evolved from the early clinical descriptions by Dr. Henry Hyde Salter in the 19th Century [7] to the current understanding of this heterogeneous disease as an umbrella term comprising numerous and different asthma subtypes [8]. A prevailing approach to categorize asthma has been to group patients on observable attributes arising from a complex interplay between hereditary, environmental, and behavioral influences. In fact, the first approach to asthma phenotyping was documented in the late 1940s when Rackemann distinguished between extrinsic—atopic—and intrinsic—unrelated to atopy—asthma [9], and skin tests were often helpful in confirming diagnosis and determining a specific treatment [10]. Since 1999, the clinical and physio-pathological characterization of severe asthmatics—according to the number of eosinophils in the airway—has subsequently inspired a myriad of studies aiming to discriminate between eosinophilic (EA) and non-eosinophilic asthma (NEA). In 2006, Hinks and colleagues assessed the proportion of eosinophils and neutrophils in induced sputum, depicting four asthma phenotypes—EA, NEA, paucigranulocytic asthma (PGA), and mixed-granulocytic asthma (MGA) [11]. Furthermore, gene expression analysis confirmed in 2009, two distinct asthma subgroups—Th2-high and Th2-low—defined by the degree of underlying Th2 inflammation and regardless of patients' demographic characteristics, lung function, or bronchodilator response [12]. Thus, the definition of the Th2-high asthma phenotype was initially based on atopic predisposition in combination with any of the following surrogate biomarkers for Th2 immune activation: serum immunoglobulin E (IgE) ≥ 100 IU/mL, blood eosinophil count ≥ 300/μL, and exhaled nitric oxide fraction (FENO) ≥ 30 ppb [13]. However, since the production of Th2-related cytokines such as interleukins 4, 5, and 13 (IL-4, IL-5, and IL-13) has been confirmed in further cell populations as type 2 innate lymphoid cells (ILC-2s), mast cells, basophils, and/or eosinophils, the term Th2 has been currently updated to the T2 immune phenotype in asthma [14]. Notably, some of these cytokines may also affect cell counts in asthmatics (i.e., IL5-promoted eosinophilia) [14]. Conventional asthma phenotyping classifies patients according to observable clinical features, including exacerbating factors, age of onset, concomitant comorbidities, and/or response to therapy [15]. As these clinical categories could not discriminate among groups or elucidate the underlying pathobiology, multivariate statistical cluster analysis performed on large asthma cohorts such as SARP [16], U-BIOPRED [17], or ADEPT [18] have greatly contributed to the unbiased description of specific asthma phenotypes [19]. Despite differences in clusters being found, two major groups, namely type 2 (T2)-high and non-T2-high, have been currently defined [20]. These evolving endotypes—associating plausible molecular and cellular mechanisms or therapeutic response to phenotypes—have, nowadays, pioneered asthma into the age of precision medicine [21][22].

2.1. T2-High Asthma

In T2-high asthma, the interaction of the airway epithelium with the external exposome activates the release of specific mediators—epithelial-derived alarmins—as thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, leading to the production of IL-4, IL-5, and IL-13 [23]. Subsequent tT2 immuno-responses include IgE-mediated hypersensitivity to aeroallergens, chemoattraction of mast cells, eosinophils, and basophils, and remodeling of the airway epithelium [14]. T2-high asthma has been clinically classified into three phenotypes, including early-onset allergic asthma, late-onset eosinophilic asthma, and nonsteroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (NERD) [20][24].

2.1.1. Early-Onset Atopic Asthma

The early-onset atopic asthma phenotype—most frequently identified in former hierarchical clustering analysis—is predominant in children, responsive to inhaled steroids, and commonly associated with increased T2 cytokines, serum-specific IgE to inhalants, and allergic comorbidities, i.e., allergic rhinitis, atopic dermatitis, and/or food allergy, with a relevant participation in the “atopic march” [8][25]. Multiple environmental factors, including allergens, viral infections, pollutants, and/or cigarette smoke, have been described as potential triggers to activate inflammatory responses, leading to clinical symptoms concerning this asthma phenotype [26][27][28]. Despite asthma symptoms—with variations in severity—that are elicited during childhood and may be resolved in adolescence, this phenotype can persist through life [19][29].

2.1.2. Late-Onset Eosinophilic Asthma

Late-onset eosinophilic asthma phenotype usually starts in adulthood, and its underlying pathobiology is also driven by a preponderant T2 inflammation response with apparently no evidence of atopy but the leading role of ILC-2 in the production of IL-5 and IL-13 [30]. Although this phenotype may show different clinical presentations, including comorbid chronic rhinosinusitis with and without nasal polyps, a significant proportion of patients are older and have a more severe disease, lower pulmonary function, increased blood and sputum eosinophils, and are partially responders to inhaled or systemic steroids [31][32].

2.1.3. Nonsteroidal Anti-Inflammatory Drugs-Exacerbated Respiratory Disease (NERD)

NERD is considered as a subset of the late-onset eosinophilic asthma phenotype—frequently associated with chronic rhinosinusitis with nasal polyps (CRSwNP)—presenting with rapid respiratory exacerbations immediately triggered after the intake of aspirin or other NSAID drugs that inhibit the cyclooxygenase-1 isoenzyme (COX-1). Despite the complete underlying pathogenic mechanism remaining unclear, NERD is characterized by a dysregulation in the arachidonic acid metabolism and a marked overproduction of cysteinyl leukotrienes (cysLTs), a potent lipid inflammatory mediator derived from arachidonic acid [33][34]. Mast cells, eosinophils and platelet-adherent leukocytes, which are present in the respiratory tissue of subjects with NERD have functional 5-lipoxygenase (5-LOX) and leukotriene (LT) C4 synthase enzymes [35]. Arachidonic acid is oxidized by 5-LOX to form short-lived LT mediators, such as LTC4, LTD4, and the stable metabolite LTE4 that has been formerly described as a biomarker in patients with NERD [36][37][38]. Interestingly, innate type 2 mediators from epithelial cells can be also activated after stimulation with cysLTs and further amplified by mast-cell-derived prostaglandin D2 gene (*PGD2*), leading to the persistent eosinophilic airway inflammation, bronchoconstriction, and mucus secretion related to refractory nasal polyposis and asthma [39][40].

2.2. T2-Low Asthma

Clinically, T2-low asthma—accounting for 33 to 50% of the asthmatics—has been grouped according to obesity, smoking exposure, and age. T2-low asthma is characterized by the activation of non-T2 inflammatory pathways, including helper T-lymphocytes type 1 (Th1) and/or Th17 cells, IL-6, IL-8, IL-17, and IL-22, and epithelial-derived

cytokines [41][42]. Despite no validated biomarkers having been confirmed yet, sputum cytology has defined different subsets for T2-low asthma: neutrophilic (sputum neutrophils > 40–60%) and paucigranulocytic (normal sputum levels of neutrophils and eosinophils) asthma [43]. Patients with T2-low asthma usually develop symptoms at adulthood, and they are frequently associated with obesity, cigarette smoke exposure, lower bronchodilator reversibility, chronic infection with atypical bacteria, and a limited response to inhaled and systemic steroids in combination with a metabolic dysfunction [44][45][46]. Comorbidities such as hypertension and diabetes are frequent in this subset of patients with lower lung function and increased blood IL-6 levels, which has been considered a putative biomarker for metabolic dysfunction [22][47].

PGA has been identified as a milder respiratory phenotype in terms of severity, number of clinically relevant exacerbations, and improved lung function compared to EA and neutrophilic asthma (NA) [48]. Patients with PGA show lower levels of biomarkers of both eosinophilic—blood and sputum eosinophils, serum periostin, eosinophilic cationic protein (ECP), and FENO—and neutrophilic inflammation—serum matrix metalloproteinase-9 (MM-9), and IL-8 [48][49]. Despite the immunopathological underlying mechanisms not having been elucidated yet, PGA is characterized by increased airway smooth muscle dysfunction—hyperplasia and hypertrophy—leading to chronic airflow obstruction and release of inflammatory mediators due to specific neurogenic pathways [50][51]. As no biological treatment is available for T2-low asthma, alternative therapy targeting airway smooth muscle dysfunction including mitogen-activated protein kinase inhibitors, tyrosine-kinase inhibitors, phosphatidylinositol 3 kinase inhibitors, or phosphodiesterase inhibitors is currently under investigation [52][53][54].

2.2.1. Obesity-Associated Asthma

Obesity-associated asthma is a complex asthma phenotype more frequently described in nonatopic middle-aged females, presenting with severe respiratory symptoms and a relatively preserved pulmonary function [55][56]. Interestingly, the inflammatory response in obesity is associated with a switch from Th2 cells to Th1, Th17, and cytotoxic T lymphocytes [57]. In addition, the levels of specific cytokines have been positively related to body-mass index (BMI) [58]. Further innate inflammatory pathways involving ILC-3s expressing IL-17 and IL-22 have been also described in obesity-associated asthma [59]. The proinflammatory cytokine IL-6, produced in adipocytes and adipose tissue macrophages, has been associated with obese T2-low asthma but not with obese atopic asthma [59][60]. Moreover, a reduction in arginine and nitric oxide (NO) bioavailability has been related to the increased oxidative stress occurring both in obesity and obese adults with the late-onset asthma phenotype [61].

2.2.2. Smoking-Associated Asthma Phenotype

The estimated prevalence of smokers within asthmatics—about 20%—is similar to that found in the general population [62][63]. Cigarette smoking in asthmatics has been previously related to poor control of symptoms, increased mortality, declined pulmonary function, lower response to steroids, and increased healthcare costs [64][65][66]. The recognition of a smoking-associated asthma phenotype has relevant implications to an improved management of patients afflicted with this specific asthma subtype. In this regard, smoking-associated asthma is considered a T2-low neutrophilic phenotype speculating that persistent exposure to cigarette smoke may induce a predominance of activated macrophages producing proinflammatory molecules, reactive oxygen species, matrix

metalloproteinases, and specific chemokines such as IL-8, contributing to the prolonged survival of neutrophils in the lung tissue [67]. In addition, cigarette smoke increases total IgE levels and the risk of sensitization to aeroallergens, thus enhancing a combined Th1/Th2 inflammatory response developing a more severe asthma phenotype and a putative link between asthma and chronic obstructive pulmonary disease (COPD) in subjects with a relevant smoking history, airflow obstruction, and overlapping features of asthma, termed asthma–COPD overlap syndrome (ACO) [53][68][69].

2.2.3. Elderly-Associated Asthma Phenotype

The age cutoff value in this underdiagnosed and sub-optimally treated very-late-onset asthma phenotype is >65 years [70]. Age-related changes in the lung structure such as airway narrowing, reduced elastic recoil, or alveolar dilation may lead to an overall decreased pulmonary function [71][72]. Although the pathobiology of this phenotype has not been totally elucidated the preponderant airway neutrophilic inflammation has been related to both Th1 and Th17 responses [73][74].

2.3. Overlapping in Asthma Phenotypes

An elevated rate of overlapping—above 70%—has been described in mild-to-severe asthmatics, including combinations among different inflammatory asthma phenotypes, such as T2-high, T2-low, and mixed T2/non-T2 [75] (**Table 1**). In this regard, occupational asthma (OA), a subtype of work-related asthma, currently shows as a challenging respiratory model to clinical phenotyping. As both high-molecular-weight (HMW) proteins and low-molecular-weight (LMW) chemicals can elicit OA, different clinical, physiological, and inflammatory profiles have been described, with HMW agents showing a higher baseline blood eosinophilia and a greater post-challenge elevation in associated FENO levels [76][77]. In fact, asthma has been proposed as a nonlinear complex dynamic system with both clinical and therapeutic implications, suggesting an evolution in the underlying inflammatory status from an initial T2-high profile moving towards an alternative T2-low or mixed T2/non-T2 asthma phenotype [78][79][80].

Table 1. Overview of asthma endotypes and phenotypes.

Endotype	Phenotype	Clinical Features	Molecular Mechanism	References
T2-high asthma	Early-onset atopic asthma	Trigger-induced phenotypes. Steroid-sensitive. Preserved lung function	Allergy to aeroallergens	[8][13][14][19][25][26][27][28][29]
	Late-onset eosinophilic asthma	CRSwNP frequently associated. Steroid-refractory	*Staphilococcus aureus* enterotoxin	[11][12][30][31][32]
	NERD	Samter´s Syndrome. Adult onset. Trigger-induced phenotypes	Arachidonic acid dysregulation	[33][34][35][36][37][38][39][40]

Endotype	Phenotype	Clinical Features	Molecular Mechanism	References
T2-low asthma	Non-atopic asthma	Neutrophilic or paucigranulocytic. Adult onset	Th1/Th17 inflammation	[22][41][42][43][44][45][46][47][48][49][50][51][52][53][54]
	Smoking-associated asthma	Adult onset. Lower lung function	Oxidative stress	[62][63][64][65][66][67]
	Obesity-associated asthma	Metabolic syndrome. Females. Preserved lung function	Th1/Th17 inflammation. Oxidative stress. IL-6	[55][56][57][58][59][60][61]
	Elderly-related asthma	Very late onset. Declined lung function	Th1/Th17 inflammation	[70][71][72][73][74]

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