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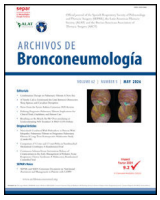

Review Article

Type 2 Endotypes in Airway Diseases

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ABSTRACT

Asthma and chronic obstructive pulmonary disease (COPD) are the most prevalent chronic inflammatory airway diseases worldwide, significantly affecting patients' quality of life and mortality and imposing a substantial socioeconomic burden. Increasing insights into their pathophysiology have led to the recognition of both conditions as complex syndromes encompassing distinct pheno-endotypes. Asthma patients can be broadly stratified into type 2 (T2)-high and T2-low phenotypes based on biomarker expression and clinical features. More than half of asthma patients exhibit a T2-high phenotype, which includes two principal endotypes: allergic eosinophilic and non-allergic eosinophilic asthma. In COPD, traditionally associated with type 1 and type 3 immune responses and neutrophilic inflammation, around 20–30% of patients display a marked T2 signature, defining a novel T2-COPD endotype. In both diseases, epithelial and innate immune cells cooperate to orchestrate adaptive and effector T2 responses characterized by blood and airway eosinophilia and elevated fractional exhaled nitric oxide (FeNO). In asthma, 6 biologics targeting key T2 inflammatory pathways are approved as add-on treatment (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab). In T2 COPD, 2 biologics have recently been approved (dupilumab and mepolizumab) and others are under clinical evaluation. Other emerging strategies, including next-generation allergen-specific immunotherapy and trained immunity-based vaccines, offer promising new therapeutic avenues. A better understanding of the molecular mechanisms driving T2-high asthma and T2 COPD endotypes is essential to identify reliable biomarkers and novel therapeutic targets. Such advances will improve patient stratification, optimize disease management, and foster the development of preventive and precision medicine approaches in chronic airway diseases.

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Introduction

The immune system orchestrates three major types of immune responses to protect the host against distinct classes of pathogens: type 1 (T1) immunity, which primarily targets intracellular pathogens; type 2 (T2) immunity, which is directed against helminths, venoms and toxins; and type 3 (T3) immunity, which defends against extracellular pathogens [1–3].

Under physiological conditions, T2 immunity is critical not only to protect the host against large parasites, venoms and toxins but also in promoting tissue repair and maintaining homeostasis. For long time, T2 immunity was thought to be exclusively mediated by adaptive immune responses involving IgE-switched B cells, T-helper 2 cells (Th2) and T-cytotoxic 2 cells (Tc2) generated by dendritic cells (DCs) through IL-4-dependent mechanisms (Fig. 1). More recent findings have demonstrated that innate immune cells, such as type 2 innate lymphoid cells (ILC2) activated by epithelial-derived alarmins (thymic stromal lymphopoietin (TSLP), IL-33 or IL-25) also play a central role in the initiation and amplification of T2 immune responses [1–3] (Fig. 1). Additionally, TL1A is a novel alarmin constitutively expressed in alveolar epithelial cells that cooperates with IL-33 to potentiate IL-9 expression on ILC2s thus modulating eosinophilic inflammation [4,5]. T2 immunity is typically initiated by following epithelial cells damage induced by exposure to allergens, bacteria, viruses, pollutants, or other noxious stimuli. Disruption of epithelial barrier facilitates the penetration

Abbreviations: AIT, allergen-specific immunotherapy; AHR, airway hyperresponsiveness; Breg cells, regulatory B cells; CGRP, calcitonin-gene regulated peptide; CCL26, eotaxin 3; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; DC, dendritic cell; ECP, eosinophilic cationic protein; EPX, eosinophilic peroxidase; FcεRI, high-affinity Fc receptor for IgE; FeNO, fraction of exhaled nitric oxide; GINA, Global Initiative for Asthma; ICAM-1, intercellular adhesion molecule-1; ILC2, type 2 innate lymphoid cells; KO, knock-out; MBP, major basic protein; MMP12, matrix metalloproteinase 12; PGD2, prostaglandin D2; RBM, reticular basement membrane; T1, type 1; T2, type 2; T3, type 3; TGF-β, transforming growth factor; Th2, T-helper 2; TIbV, trained immunity-based vaccines; Treg cells, regulatory T cells; TSLP, thymic stromal lymphopoietin; VCAM-1, vascular cell adhesion molecule-1.

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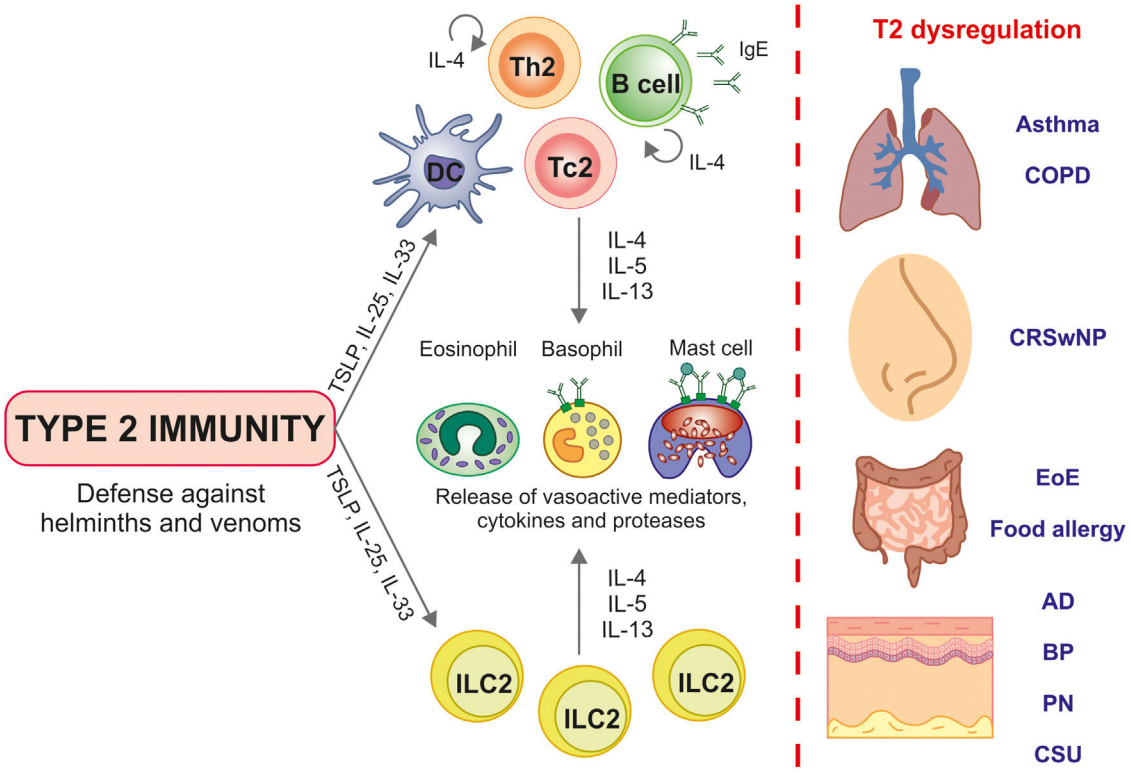

Fig. 1. Overview of type 2 immunity and type 2-mediated inflammatory diseases. Type 2 immunity protect the host from helminths and venoms by mechanisms depending on epithelial-derived alarmins (TSLP), innate, adaptive, effector cells and type 2 cytokines (IL-4, IL-5 or IL-13). Type 2 dysregulation leads to aberrant inflammatory responses underlying a plethora of diseases affecting different tissues. AD, atopic dermatitis; BP, bullous pemphigoid; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; CSU, chronic spontaneous urticaria; DC, dendritic cell; ILC2, group 2 innate lymphoid cell; IgE, immunoglobulin E; IL, interleukin; PN, prurigo nodularis; Tc2, cytotoxic T cells type 2; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

of allergens, microbiota and other potentially harmful substances into the submucosa, triggering the release of epithelial alarmins. Activated Th2 cells and ILC2s subsequently produce a plethora of mediators and effector T2 cytokines (IL-4, IL-5 or IL-13) that contribute to the tissue recruitment and activation of effectors cells such as eosinophils, basophils and mast cells (Fig. 1). These activated effector cells release vasoactive mediators, proteases and T2 cytokines that cooperatively induce smooth muscle cell contraction, mucus production, endothelial permeability, pruritus and other protective mechanisms aimed at expelling helminths, venoms and toxins while preventing their systemic dissemination. Dysregulation of T2 immunity, often without the causative factors being known, leads to persistent and uncontrolled T2 inflammatory responses underlying different T2-mediated inflammatory diseases. These include atopic dermatitis (AD), prurigo nodularis (PN), chronic spontaneous urticaria (CSU), and bullous pemphigoid (BP) affecting the skin; eosinophilic esophagitis (EoE) and food allergy affecting the gastrointestinal tract; chronic rhinosinusitis with nasal polyps (CRSwNP) in the upper airways; and asthma and chronic obstructive pulmonary disease (COPD) in the lower airways (Fig. 1) [1–3].

Asthma and COPD are the most prevalent chronic inflammatory airway diseases, significantly impacting patients' quality of life and mortality, and imposing a high socioeconomic burden [6–8]. A growing understanding of the pathophysiological mechanisms underlying asthma and COPD supports the concept that both conditions should be regarded as complex syndromes encompassing different phenotypes and endotypes (Table 1) [6,9–11]. The term *phenotype* refers to the set of observable clinical characteristics resulting from the interaction between an individual's genotype and environmental factors, thereby describing how the disease manifests within a group of patients. In contrast, an *endotype* is defined by distinct cellular and molecular pathophysiological mechanisms that categorize patients more precisely and ultimately determine the clinical phenotype [2].

Asthma patients can be broadly stratified into two main phenotypes based on the expression of T2 biomarkers and clinical features: T2-high and T2-low asthma (Table 1). More than 50% of asthma patients exhibit a T2-high phenotype, which encompasses two major endotypes: allergic eosinophilic asthma and non-allergic eosinophilic asthma [12,13]. COPD has traditionally been associated with altered T1 and T3 immune responses and predominantly neutrophilic inflammation, largely driven by tobacco smoke and other noxious exposures. However, a subset of patients displays T2-mediated eosinophilic airway inflammation, thus defining a distinct COPD endotype, hereafter referred to as T2 COPD (Table 1) [14,15].

Asthma and COPD should therefore be regarded as distinct chronic inflammatory airway diseases with different clinical manifestations that, in specific endotypes, share common underlying T2 inflammatory pathways. Over recent years, an improved understanding of the mechanisms underlying T2-mediated airway inflammation has revealed complex immune networks that extend beyond those solely involving eosinophilic pathways. Mast cells and airway smooth muscle cells engage in bidirectional interactions, exchanging a wide range of soluble mediators that promote mast cell recruitment and survival, while simultaneously inducing airway smooth muscle contraction, proliferation, and remodeling, thereby contributing to airway hyperresponsiveness in an eosinophil-independent manner. Similarly, under type 2 inflammatory conditions, inflammatory monocytes are recruited into the airways and differentiate into TGF-β-producing M2 macrophages, which in turn promote fibrosis and basement membrane thickening. In addition, airway epithelial cells function not only as

Table 1
Cellular and molecular mechanisms underlying asthma and COPD pheno-endotypes.

Disease entity	Pheno-endotype	Definitions	Altered cellular/molecular mechanism
Asthma	T2-high asthma	Asthma endotype characterized by dysregulated T2 immune response	Epithelial cells, Th2, ILC2s, elevated T2 cytokines
	T2-low asthma	Asthma endotype characterized by dysregulated T1/3 immune response	Epithelial cells, Th1/Th17, neutrophils, elevated T1/3 cytokines
COPD	T1/T3 COPD	COPD endotype characterized by dysregulated T1/3 immune response	Epithelial cells, Tc1/Th1/Th17, ILC3s, neutrophils, elevated T1/3 cytokines
	T2 COPD	COPD endotype characterized by dysregulated T2 immune response	Epithelial cells, Th2, ILC2s, elevated T2 cytokines

a physical barrier but also as an active immune organ, directly contributing to inflammation, cell death, oxidative stress, and metabolic reprogramming, processes that are associated with microbial dysbiosis and bacterial colonization. In this article, we will comprehensively review the molecular pathways and mechanisms underlying T2 endotypes in asthma and COPD. We will further discuss the similarities and differences between T2 asthma and T2 COPD endotypes at the molecular level, their clinical implications, and current as well as emerging therapeutic strategies targeting T2 inflammation in both diseases.

Methods for the literature search

We conducted a systematic literature search across PubMed and scientific web resources, complemented by data retrieval from ClinicalTrials.gov to identify ongoing clinical trials. The search included peer-reviewed full-text original articles, reviews, and book chapters published up to February 2026, focusing on the pathogenesis of T2-high asthma and T2 COPD, as well as current and emerging therapeutic approaches. Priority was given to studies employing human or mouse in vivo data, published between 2022 and 2026 in Q1-ranked journals. The search terms used included “asthma”, “asthma endotypes”, “asthma biomarkers”, “eosinophilic asthma”, “epithelial barrier theory”, “alarmins”, “biologics”, “COPD”, “type 2 COPD”, “allergen immunotherapy”, “trained immunity-based vaccines”, and “allergoids-mannan conjugates”. Studies focusing exclusively on non-eosinophilic asthma, T1/T3 COPD, or allergic diseases not involving the airways were generally excluded.

Type 2 endotypes in asthma

Around 400 million people suffer from asthma worldwide, thus representing a high healthcare and socioeconomic burden [16]. According to the Global Initiative for Asthma (GINA) 2025, asthma should be considered as a heterogeneous syndrome characterized by common intermittent and recurrent respiratory symptoms including cough, wheeze, shortness of breath, chest tightness and reversible airflow limitation [6,17,18]. Asthma has been historically regarded as an allergic disease associated with excessive Th2 cells, eosinophilia, allergen-specific IgE and atopy that leads to airway hyperresponsiveness (AHR) [19]. Although this is still correct for allergic asthma, compelling experimental and clinical evidence pinpoint novel molecular mechanisms and pathways underlying different asthma pheno-endotypes (Fig. 2).

More than 50% of asthma patients exhibit a T2-high phenotype characterized by aberrant T2 inflammatory responses and a generally earlier asthma onset than T2-low asthma phenotype. T2-high asthma patients are diagnosed by high levels of different biomarkers: blood eosinophilia (>150 cells/μL), elevated fraction of exhaled nitric oxide (FeNO) (>20 ppb), eosinophils in sputum (>2%), clinically relevant allergen-induced asthma and the need for oral corticosteroids [6,20–22]. Advances on the characterization of the molecular pathways involved in asthma pathophysiology showed that T2-high asthma encompasses two major endotypes: allergic eosinophilic asthma and non-allergic eosinophilic asthma (Fig. 2). T2-low asthma affects less than half of asthma patients and is currently defined by the absence of T2 inflammatory biomarkers rather than by the presence of measurable markers. Clinically, T2-low asthma is typically characterized by adult onset, a higher likelihood of poor disease control, and reduced responsiveness to corticosteroid therapy. T2-low asthma encompasses two major endotypes: neutrophilic (>60% of neutrophils and <2% of eosinophils in the sputum) and paucigranulocytic (without increased levels of neutrophils or eosinophils) asthma [23–26]. Of note, when pheno-endotyping patients with T2-low asthma, potential confounding factors must be carefully considered. In particular, the use of high-dose corticosteroids may transiently suppress or normalize T2 biomarkers, leading to the potential misclassification of truly T2-high patients as T2-low [27]. These drugs may also induce neutrophilia misleading the classification of some patients or suggesting that neutrophilic asthma could be a misnomer [28]. However, it is also noteworthy to mention that within the U-Biopred cohort different studies reported that neutrophilic asthma patients display a unique gene signature [29,30].

Allergic eosinophilic asthma is the most prevalent asthma endotype and it is characterized by an early onset after allergen sensitization in childhood [31]. The diagnostics relies on a compilation of T2 biomarkers with clinical history of allergen-triggered asthma symptoms, serum allergen-specific IgE, positive skin-prick test and enhanced FeNO [6]. Despite certain controversy, allergic or IgE-mediated asthma does not always present with eosinophilic airway inflammation. A subset of patients with clear allergic sensitization may display neutrophilic or paucigranulocytic inflammatory patterns, particularly in severe asthma, steroid-treated patients, or during certain disease phases.

Airway epithelial cells play a pivotal role in the pathogenesis and progression of all asthma endotypes (Fig. 2). Bronchial epithelial cells are the first line of defense against allergens and other environmental insults by forming a sealed barrier with selective permeability due to a tightly interconnected network of tight junctions (zonula occludens-1, occludin, claudin), adherens junctions (E-cadherin) and desmosomes [5,32]. The epithelial barrier of asthma patients shows a leaky structure with reduced expression of tight junctions and an influx of eosinophils in the epithelium [33–35]. These patients also display a microbial dysbiosis with increase in pathogenic Proteobacteria (*Haemophilus* spp.) and a reduction in tolerogenic Bacteroidetes (*Prevotella* spp.), underscoring the relevance of the epithelial barrier integrity for the development of non-communicable diseases [33,36]. In this regard, coexposure of allergens with already established barrier disruptors such as laundry detergents significantly disrupted the airway epithelial barriers and promoted T2 inflammatory responses, allergen sensitization and asthma development [37]. Similarly, the concomitant exposure to particulate matters of less than 2.5 μm (PM2.5) and allergens, critically impacts on the sensitization and severity of allergic asthma [38].

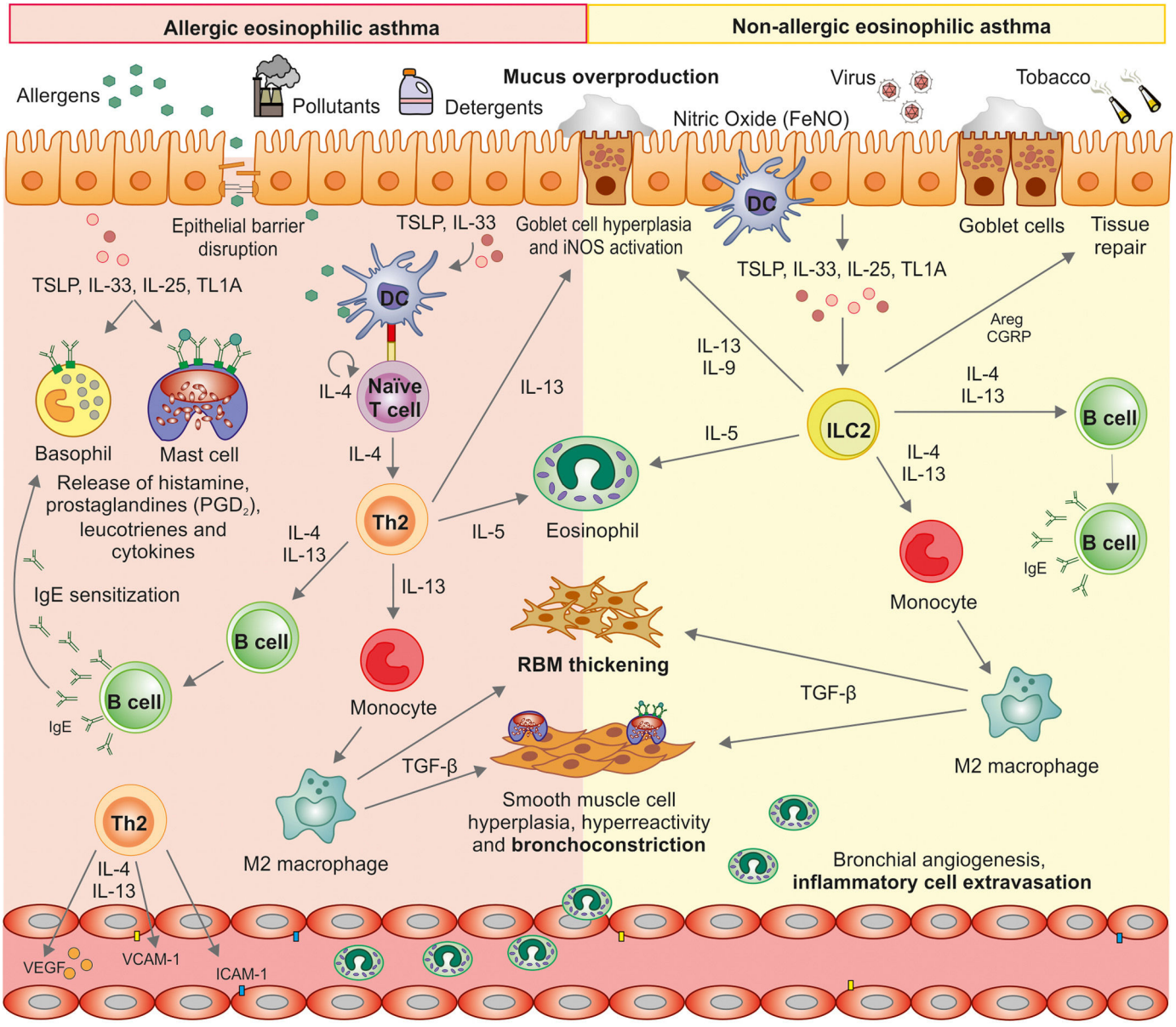

Fig. 2. Cellular and molecular mechanisms underlying allergic and non-allergic eosinophilic asthma. Type 2-high asthma includes two main endotypes: allergic and non-allergic eosinophilic asthma. Both are characterized by airway inflammation and eosinophilia, but differ in triggers and immune pathways. Areg, amphiregulin; CGRP, calcitonin gene related peptide; DC, dendritic cell; ICAM-1, intercellular adhesion molecule-1; IgE, immunoglobulin E; IL, interleukin; ILC2, group 2 innate lymphoid cell; TGF-β, transforming growth factor-beta; NO, nitric oxide; Th, T helper cell; TL1A, TNF-like ligand 1A; TSLP, thymic stromal lymphopoietin; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor.

In a sensitization phase, environmental substances and allergens directly (some allergens such as Der p 1 from house dust mite present proteolytic activity) or indirectly are able to disrupt the epithelial barrier's integrity, allowing the penetration of allergens, pathogens, microbiota, inflammatory and noxious substances into the submucosa, thus favoring allergen sensitization (Fig. 2) [39–41]. Activated bronchial epithelial cells produce and release alarmins such as TSLP, IL-33, IL-25 or TL1A able to activate and regulate the functional properties of DCs [4,42–44]. DCs represent a heterogeneous population composed of conventional DCs (cDCs), plasmacytoid DCs (pDCs) and monocyte-derived DCs. cDCs are classified in type 1 (cDC1s) and 2 (cDC2s), which are further divided into type 2a (cDC2a) and type 2b (cDC2b). cDC1s are mostly associated with asthma prevention and progression whereas cDC2s are the main subset involved in the initiation of Th2 polarization and asthma development [45]. Alarmin-activated airway DC2s capture the allergens and migrate to draining lymph nodes to polarize naïve T cells into allergen-specific Th2 cells, thus promoting and perpetuating T2 inflammation. In this process, TSLP in the absence of IL-12 induces the expression of OX40 ligand in DCs, which skews Th2 polarization by mechanisms mainly dependent on T cell-derived IL-4 [3,46]. Activated allergen-specific Th2 cells secrete a plethora of T2 cytokines including IL-4, IL-5 and IL-13, which contribute to the pathophysiological alterations connected to the main clinical features associated to the allergic asthma endotype (Fig. 2). IL-4 and IL-13 drive IgE class-switching in B cells that expand and differentiate into allergen-specific memory B and IgE-secreting plasma cells. Allergen-specific IgE binds to the IgE high-affinity receptor (FcεRI) on the surface of basophils and mast cells (effector cells), thus leading to allergic sensitization (Fig. 2) [39]. Upon re-exposure to the causative allergen, the effector phase is triggered through an immediate hypersensitivity

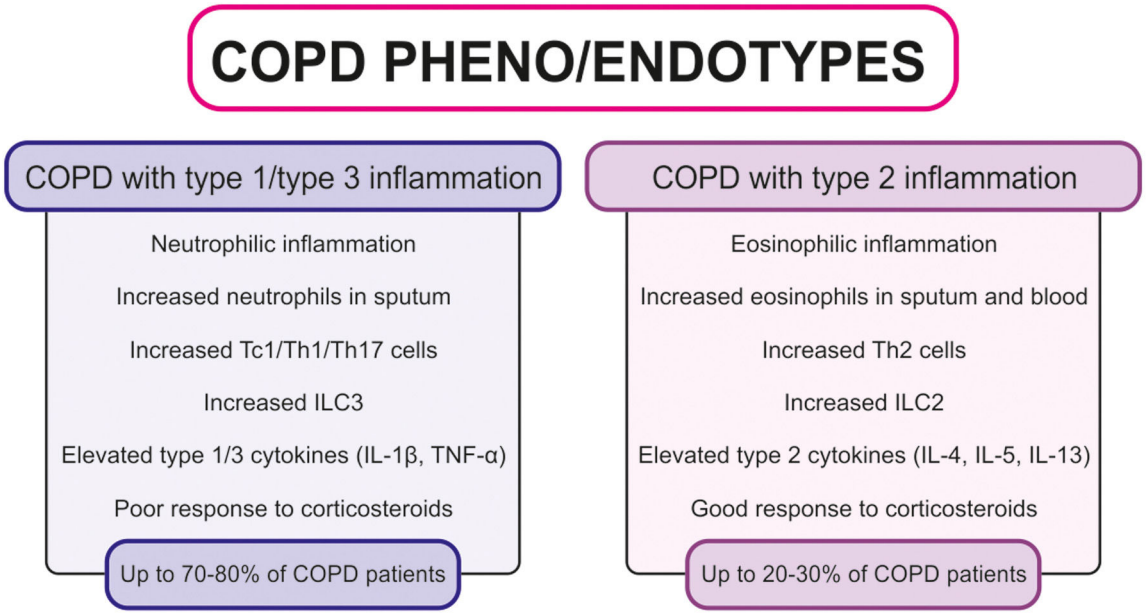

Fig. 3. COPD pheno/endotypes: type 1/type 3 (neutrophilic) vs. type 2 (eosinophilic) inflammation. COPD, chronic obstructive pulmonary disease; ILC2, group 2 innate lymphoid cell; ILC3, group 3 innate lymphoid cell; IL, interleukin; Tc1, type 1 cytotoxic T cell; Th, T helper cell; TNF-α, tumor necrosis factor-alpha.

reaction mediated by allergen-induced cross-linking of IgE bound to FcεRI receptors on sensitized effector cells. As a result, basophils and mast cells degranulate and release firstly pre-synthesized anaphylactic mediators, such as histamines, proteases and heparin, and later eicosanoids (prostaglandins and leukotrienes), cytokines and chemokines that amplify the inflammatory reaction through increasing vascular permeability, inducing vasodilation, inflammation, bronchial smooth muscle contraction and mucus secretion. DCs and B cells activate allergen-specific memory Th2 cells by mechanisms depending on IgE-facilitated presentation, leading to the secretion of T2 cytokines that contribute to the pathophysiological features of the disease (Fig. 2) [39,47]. IL-13 disrupts the epithelial barrier integrity by impairing the network of cell-to-cell connections, induces goblet cell hyperplasia and mucus production, promotes the differentiation of macrophages towards pro-fibrotic M2 macrophages, induces lung angiogenesis through increased vascular endothelial growth factor, promotes bronchial hyperreactivity and activates iNOS thus increasing the levels of NO that promotes oedema, eosinophil and T cell chemotaxis, oxidative stress, direct cell damage and AHR [48,49]. IL-13 and IL-4 activate vessel wall by inducing intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [50]. IL-5 is related to eosinophil differentiation, maturation, activation, proliferation and survival (Fig. 2) [46,51]. Additionally, eosinophil-extracellular traps contribute to allergic airway inflammation through a neuro-immune axis correlating with the severity of the disease [52]. The maintained inflammatory status is associated to the most severe symptoms of allergic eosinophilic asthma including airway remodeling, asthma exacerbations and lung function decline [21].

Non-allergic eosinophilic asthma is characterized by increased percentage of eosinophils in blood and sputum without concomitant allergen-triggered asthma symptoms. These patients generally display a later asthma onset and clinical symptoms are typically associated with viral and bacterial infections as well as with exposure to pollutants and other epithelial barrier disruptors such as fire smoke [21,39,53]. These patients usually display severe exacerbations, comorbidities such as CRSwNP, and the need for high doses of corticosteroids [21]. Mechanistically, airway epithelial cells also play a central role in the initiation and perpetuation of T2 inflammatory responses within this asthma endotype. Bronchial epithelial cells-derived alarmins prime and activate ILC2s to secrete large amounts of T2 cytokines (IL-4, IL-5, IL-9, IL-13), amphiregulin, and other mediators such as calcitonin-gene regulated peptide (CGRP), or eicosanoids. Effector T2 cytokines drive all the downstream cellular mechanisms as above described, leading to the pathophysiological features (eosinophilia, AHR and airway remodeling) linked to the clinical manifestations including recurrent symptoms, exacerbation and lung function decline (Fig. 2). In particular, IL-13 increases the susceptibility to bronchial hyperreactivity and, in cooperation with IL-4, drives M2 macrophage differentiation leading to eosinophilia and transforming growth factor (TGF)-β secretion with pro-fibrotic and airway remodeling effects, while also promoting polyclonal B-cell activation and IgE production in a non-antigen specific manner. IL-13 and IL-9, promote goblet cell hyperplasia and metaplasia leading to mucus overproduction. IL-5 plays a key role in eosinophil maturation, activation and recruitment. Among eicosanoids, ILC2s produce prostaglandin D2 (PGD2) with autocrine effects enhancing ILC2 activity. Amphiregulin and CGRP display pro-resolving effects leading to tissue repair and remodeling (Fig. 2) [3,39,46,54,55].

Type 2 endotype in COPD

COPD is a heterogeneous chronic inflammatory airway disease with persistent and progressive obstructive airflow limitation. The pathophysiology of COPD is characterized by chronic and persistent inflammation in the airways (bronchitis or bronchiolitis), airway remodeling, lung parenchyma destruction (emphysema) and mucus hypersecretion [7,8]. Chronic inflammation arises from epithelial cells- and macrophages-derived oxidative stress induced by environmental insults such as cigarette smoke or pollutants. Inflammation is associated to small airway remodeling and airway obstruction in COPD, thus playing a very important role in worsening COPD symptoms (dyspnea, cough and sputum production). Mucus hypersecretion is also linked to chronic inflammation and leads to mucus plugging, which is associated to airflow limitation and air trapping in COPD. Around 70–80% of COPD patients feature altered type 1 (Th1 and type 1 cytotoxic T cells (Tc1)) and type 3 (Th17 and ILC3) immune response with neutrophilic inflammation and are characterized by a low response to inhaled corticosteroids

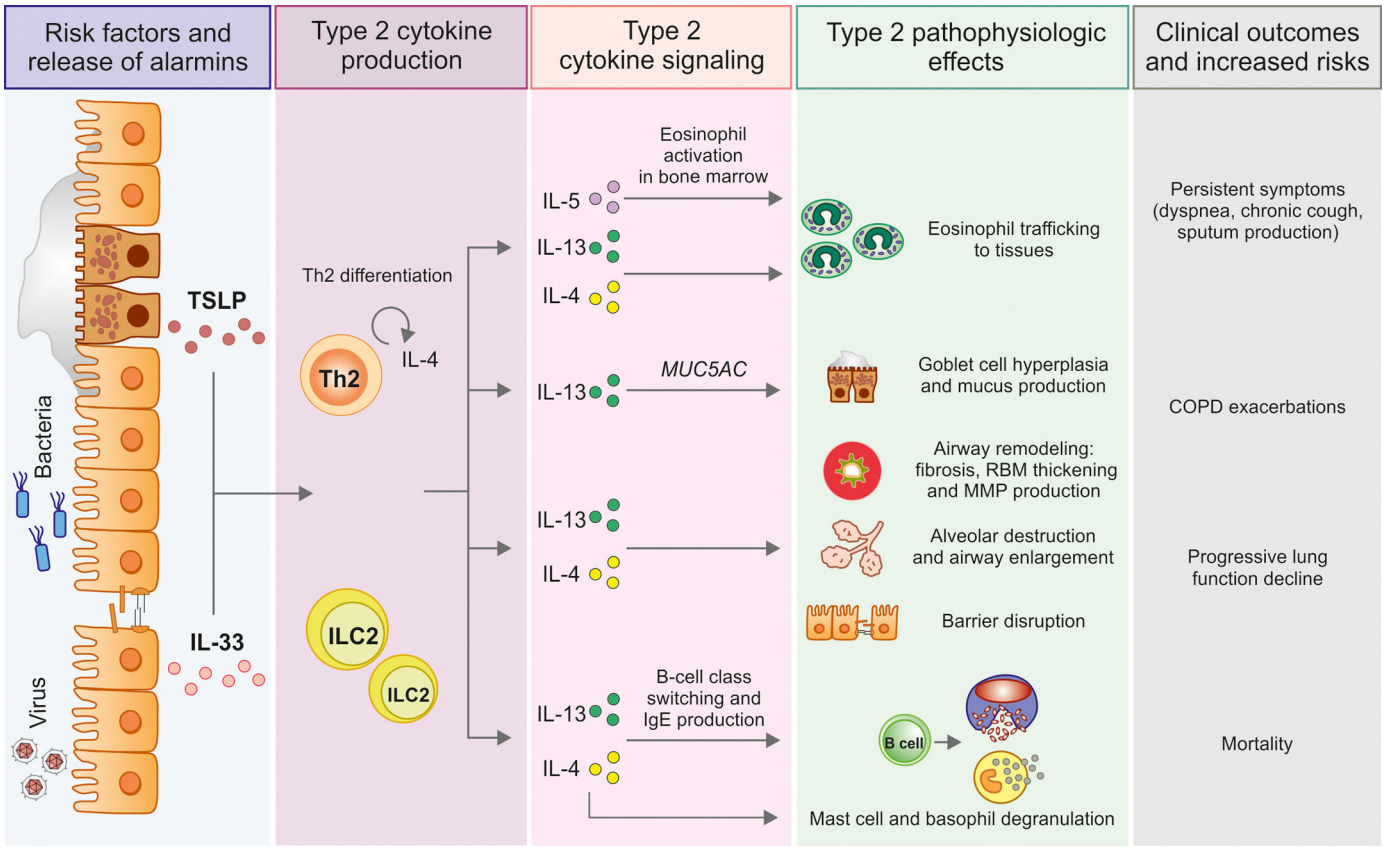

Fig. 4. Cellular and molecular mechanisms underlying T2 COPD endotype. Environmental exposures, epithelial-derived alarmins and type 2 cytokine signature leads to the pathophysiological features linked to the clinical outcomes and increased risk of T2 COPD patients. COPD, chronic obstructive pulmonary disease; ILC2, group 2 innate lymphoid cell; IgE, immunoglobulin E; IL, interleukin; MMP, matrix metalloproteinase; MUC5AC, mucin 5AC; RBM, reticular basement membrane; Th2, T helper 2 cell; TSLP, thymic stromal lymphopoietin.

(Fig. 3) [56–58]. Around 20–30% of the COPD patients present a T2-high inflammation mediated by Th2 cells, ILC2s, eosinophils (>3% in the sputum and >2% in the serum) and T2 cytokines (IL-4, IL-5 and IL-13), thus defining a new T2 COPD endotype. These patients usually present a higher risk of exacerbations and a better response to corticosteroids (Fig. 3) [59–63]. The identification and validation of reliable biomarkers are of utmost importance for the accurate stratification of these patients, potentially enabling optimal treatment selection. To date, blood eosinophil counts and FeNO levels are the most well-established biomarkers for identifying T2-high COPD patients. These two biomarkers have been shown to help predict the risk of exacerbations and to identify patients who are more likely to respond to corticosteroid therapy in COPD [64–66].

In T2 COPD, the T2 inflammatory cascade is initiated following bronchial epithelial injury induced by cigarette smoke, pathogens, or other noxious components of the exposome, leading to the release of alarmins such as IL-33 and TSLP. These epithelial-derived alarmins activate ILC2s and Th2 cells, which subsequently secrete IL-4, IL-5, and IL-13. Together, these T2 cytokines promote the recruitment and activation of effector cells – including eosinophils, basophils, and mast cells – and contribute to epithelial barrier dysfunction, mucus hypersecretion, airway remodeling, fibrosis, and alveolar destruction, all pathophysiological features associated to obstructive airflow limitation, persistent symptoms, COPD exacerbations, progressive lung function decline and mortality (Fig. 4) [56,65].

IL-5 is a key cytokine to initiate the mobilization and maturation of eosinophil precursors from the bone marrow to the bloodstream. Local T2 inflammation in the airways contributes to eosinophil chemotaxis from the bloodstream to the lung by mechanisms depending on IL-4 and IL-13. IL-4 induces endothelial VCAM-1 expression and IL-13 induces eotaxin 3 (CCL26) secretion from bronchial epithelial cells, promoting eosinophil chemotaxis to the airways and lung where they perpetuate the inflammatory process. Activated eosinophils in the lung release pro-inflammatory mediators such as eosinophilic cationic protein (ECP), major basic protein (MBP) or TGF-β, which, in conjunction with IL-4 and IL-13, contribute to epithelial damage, subepithelial fibrosis, increase mucus density and mucus plugging, all of them associated with COPD symptoms and exacerbations, airway remodeling and lung dysfunction (Fig. 4) [67–69]. Supporting these data, in a longitudinal follow up study of 10 years, Colak et al. showed a direct correlation between eosinophilia and FeNO levels with lung function decline in COPD patients [70]. Additionally, different studies discuss the role of IL-4 in increasing CCL26 and maintaining eosinophil viability. Recent data showed that dupilumab treatment significantly reduced CCL26 production in IL-4- and IL-13-activated bronchial epithelial cells from T2 COPD patients and similar findings were observed upon rhinovirus infection, in which antiviral responses were preserved [71]. IL-13 plays a pleiotropic role in T2 COPD. IL-13 not only induces goblet cell dysfunction, hyperplasia and mucus overproduction, but also reduces the number, activity and function of ciliated cells, which contribute to mucus plugging. In this context, activated eosinophils further enhance the process by secreting eosinophilic peroxidase (EPX) and galectin 10, thus increasing mucus viscosity and plugging. Of note, IL-13 also modulates MUC5, a family of proteins responsible of mucus formation and density, by increasing MUC5AC and reducing MUC5B, that

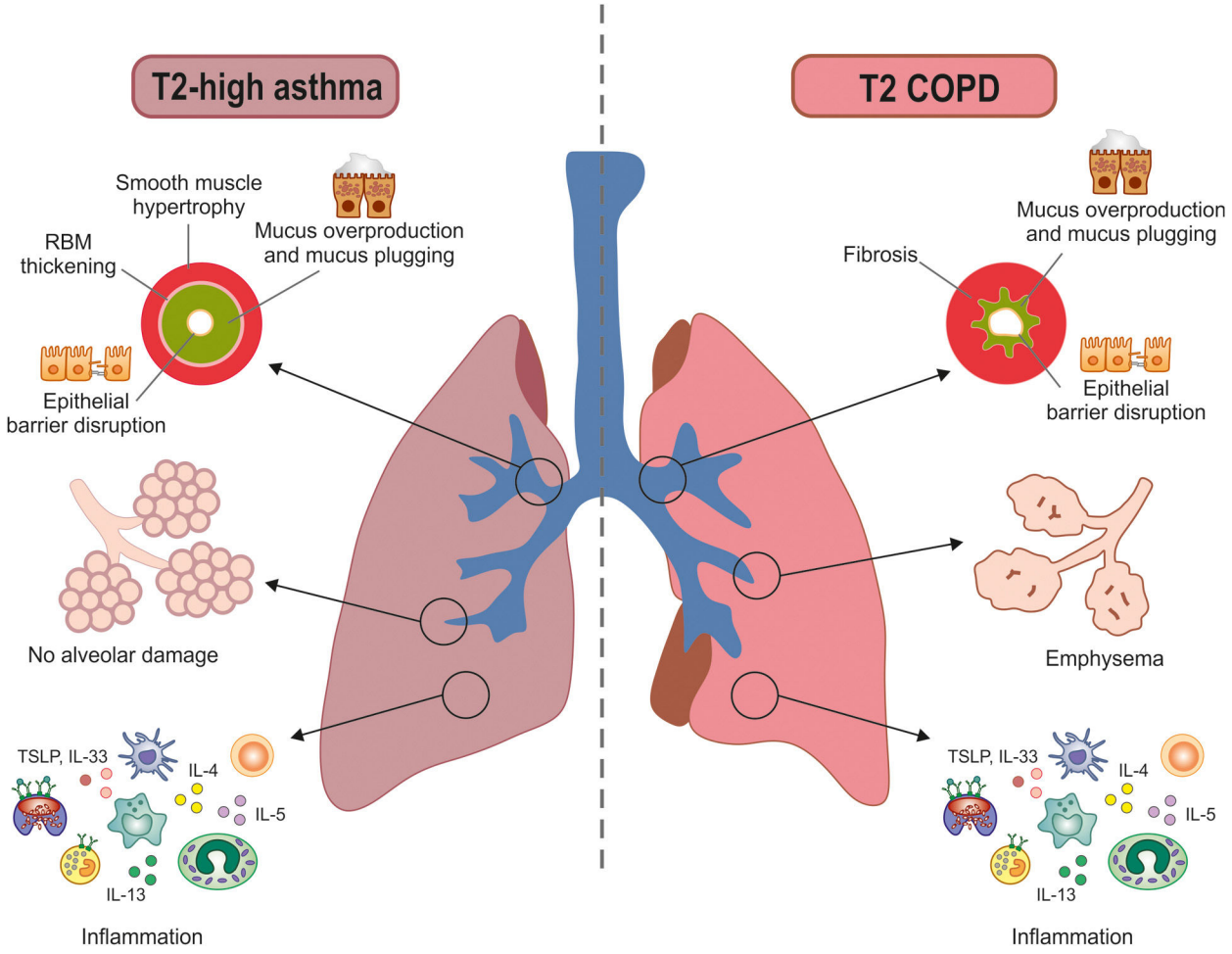

Fig. 5. Comparison of type 2 (T2)-high asthma and T2-COPD. Left panel, T2-high asthma is characterized by RBM thickening, airway smooth muscle hypertrophy, epithelial barrier disruption, mucus overproduction, inflammation, and preserved alveolar architecture. Right panel, T2-COPD patients display epithelial barrier disruption, mucus overproduction, fibrosis, alveolar destruction (emphysema), and inflammation. COPD, chronic obstructive pulmonary disease; RBM, reticular basement membrane; T2, type 2.

results in an increased viscosity of the mucus, promoting mucus plugging that obstruct the airways driving lung function decline [72–74]. A direct correlation between mucus plugging and the number of exacerbations, worse lung function and increased mortality has been reported in T2 COPD [74–76]. More recent findings indicate that IL-13 and IL-4 participate not only in airway remodeling, but they might also contribute to alveolar destruction, resulting in emphysema. Preclinical *in vivo* models of eosinophil-dependent lung parenchyma injury demonstrated the accumulation of alveolar macrophages-derived matrix metalloproteinase 12 (MMP12) associated with lung parenchyma enlargement and destruction. In this study, a selective knock-out (KO) of IL-4 and IL-13 in eosinophils totally impaired MMP12 secretion and avoided lung emphysema. Supporting this data, an accumulation of MMP12 and eosinophilia was also demonstrated in the sputum of T2 COPD patients with emphysema [77]. As described above, IL-4 plays a central role in promoting the differentiation of naïve T cells into Th2 cells [46] and, together with IL-13, induces IgE class switching in B cells. However, the potential contribution of IgE to the clinical manifestations of T2 COPD, if any, remains unclear and continues to be a matter of debate. Although the role of IL-9 has not been extensively studied in T2 COPD, blocking IL-9 in a cigarette smoke *in vivo* model, significantly impaired COPD features through an inhibition of IL-9^{+} cells, phospho-STAT3 signaling and oxidative stress, thus highlighting the potential relevance of this T2 cytokine as an upstream mediator of COPD [78].

Common features and differences of T2-high asthma and T2 COPD

Asthma and COPD are distinct chronic inflammatory airway diseases in which specific T2-high asthma and T2 COPD endotypes share common T2 inflammatory pathways, resulting in unique overlapping yet disease-specific pathophysiological and clinical features. Although some older patients may present overlapping clinical features of T2-high asthma and T2 COPD (historically referred to as asthma–COPD overlap syndrome) not all T2 COPD patients exhibit asthma-like clinical features or have a previous diagnosis of asthma [59,79]. As described above, both disorders are characterized by aberrant T2 inflammatory responses characterized by excessive production of T2 cytokines. This leads to the chemotaxis and activation of effector cells (mainly eosinophils, but also basophils and mast cells), which cooperatively contribute to AHR and airway remodeling. While these molecular pathways are shared, their relative contributions differ between asthma and COPD, ultimately shaping distinct clinical manifestations and, therefore, phenotypes in each disease (Fig. 5) [21,57,65,79].

Both diseases present airway remodeling, epithelial barrier disruption and goblet cell hyperplasia with mucus overproduction. In contrast, T2-high asthma endotypes present a significantly superior thickening of the airway smooth muscle and RBM compared with T2 COPD, while T2 COPD is defined by alveolar destruction (emphysema) and fibrosis. Thickening of the RBM in asthma patients is

mainly driven by increased deposition of collagen I and laminin [80], while in COPD the slight thickening is mainly associated with TGF-β-induced tenascin C production in epithelial cells (Fig. 5) [81,82].

T2-high asthma endotypes generally present an earlier onset than T2 COPD, with greater AHR and variability and reversibility of airflow obstruction than T2 COPD [6]. T2-high asthma endotypes are also characterized by a greater eosinophilia in the large airways than T2 COPD [83], which frequently correlates with blood eosinophil counts, the magnitude of T2 inflammation and clinical symptoms and signs, thus highlighting the key pathophysiological and clinical role played by eosinophils in T2-high asthma endotypes [81,84,85]. Transcriptomic analysis of bronchial brushes from COPD and asthma patients showed minimal overlap in the genes and molecular pathways associated with blood eosinophil counts in the two diseases. Of note, *CST1* was the only gene shared between the COPD and asthma cohorts, suggesting that despite similarly elevated blood eosinophil levels, the underlying molecular mechanisms driving these conditions are largely distinct. Recent findings, convincingly demonstrated that eosinophils represent a heterogeneous population with different phenotypic and functional properties: (i) tissue resident eosinophils (rEos) present in the lung parenchyma; (ii) inflammatory eosinophils (iEos) that are recruited to the bronchial mucosa upon inflammatory processes [47,86]. In eosinophilic asthma, different models have described an increased eosinophilia mediated by a recruitment of iEos to the lung [47,86]. Importantly, in COPD, despite increased blood eosinophil counts, the proportion of rEos and iEos remained comparable to smokers without COPD and non-smokers. Additionally, in total COPD patients, there was no relation between iEos number and the use of inhaled corticosteroids, disease severity or exacerbations rate [87,88]. These data further imply that the functional properties and clinical relevance of eosinophils may differ substantially between asthma and COPD. In T2-high asthma endotypes, eosinophils are closely linked to clinical symptoms and disease activity, whereas in COPD they may be functionally distinct and should perhaps be regarded primarily as an endotype biomarker rather than a direct effector of pathophysiology [89]. Additionally, mast cells also present a different functional role and transcriptome signature in asthma and T2 COPD. Mast cells from asthma patients are located in close proximity to smooth muscle bundles and are mainly activated by IgE-triggering in allergic eosinophilic asthma or non-IgE-mediated pathways in non-allergic eosinophilic asthma, while in T2 COPD patients, mast cells co-localize in the alveolar parenchyma and are mainly activated by IgE independent mechanisms [90–93]. Supporting these findings, in a bronchoscopy study of COPD patients some genes like *IL-13*, *CST1*, *CLCA1* and *CCL26* were enriched in T2 COPD patients, but not the classical asthma markers or IgE-dependent mast cell activation gene sets [69]. Additionally, asthma classical markers like *POSTN* or *SERPINB2* showed low accuracy in identifying T2 COPD patients [59].

Collectively, although T2 inflammatory pathways are commonly activated in both T2-high asthma and T2 COPD, the specific interplay among different cell types and their distinct contributions to structural changes underlie key pathophysiological differences between these diseases, which may in turn be linked to their respective clinical manifestations.

Current treatments and novel approaches in T2-high asthma and T2 COPD

Asthma and COPD management and treatment aim to alleviate symptoms and reduce exacerbation risk, lung function decline and mortality. The choice of therapeutic strategies depends on disease severity, clinical phenotype (the observable clinical features of the patients) and underlying inflammatory endotype (molecular mechanisms linked to the phenotypes) [6–8].

Asthma management follows a stepwise approach aimed at achieving and maintaining symptom control while minimizing the risk of exacerbations and long-term airway remodeling. Initial therapy is based on inhaled corticosteroids, either alone or in combination with bronchodilators, with treatment intensity adjusted to disease severity and level of control [6]. Around 10% of asthma patients develop a severe form of the disease, and a subset of these individuals remains uncontrolled despite optimized high-intensity standard therapy. For such patients, several biologics (monoclonal antibodies (mAb)) targeting specific inflammatory pathways have been developed and approved by FDA and EMA as add-on treatments, particularly for those with moderate-to-severe T2-high asthma [2]. Among these agents, omalizumab, a mAb that binds to the Cε3 domain of IgE, prevents the interaction of free IgE with its high- and low-affinity receptors (FcεRI and CD23), and was the first biologic approved for the treatment of allergic eosinophilic asthma. Mepolizumab and reslizumab target IL-5, thereby impairing eosinophil maturation, recruitment, and survival, whereas benralizumab binds to the α-chain of the IL-5 receptor (IL-5Rα) and induces near-complete eosinophil depletion through antibody-dependent cellular cytotoxicity. Dupilumab targets the α-chain of the IL-4 receptor (IL-4Rα), thereby inhibiting both IL-4- and IL-13-mediated signaling pathways and the downstream pathophysiological mechanisms driven by these key T2 cytokines. Tezepelumab blocks TSLP and represents the first monoclonal antibody directed against an epithelial-derived alarmin, acting at the upstream level of the T2 inflammatory cascade (Fig. 6). All these mAbs have been shown, to varying degrees, to reduce asthma exacerbations, improve disease control, decrease corticosteroids use, and enhance lung function and asthma-related quality of life [6,94–98].

COPD management primarily focuses on symptom relief, reduction of exacerbations, preservation of lung function, and improvement of quality of life. First-line pharmacologic therapy consists of long-acting bronchodilators (LABA and/or LAMA), with escalation to dual bronchodilation in patients with persistent symptoms [7,8]. In individuals with a history of exacerbations and evidence of T2 inflammation (e.g., elevated blood eosinophil counts), inhaled corticosteroids may be added to bronchodilator therapy [6,8]. Nevertheless, a substantial proportion of individuals with COPD continue to experience exacerbations. Consequently, in recent years, emerging biologic therapies targeting T2 pathways are currently being investigated or selectively used in T2 COPD, reflecting a growing recognition of inflammatory endotypes within COPD [99]. To date, dupilumab and mepolizumab are the only mAbs approved by FDA and EMA for the treatment of uncontrolled COPD in patients with high levels of eosinophils [7]. Dupilumab was the first mAb approved for COPD and it has consistently demonstrated a reduction in exacerbations, accompanied by improvements in lung function as well as symptoms and quality of life [100]. For mepolizumab, in the METREX and MATINEE studies but not in the METREO trial, it was demonstrated a reduction in exacerbation rates in patients with eosinophilic COPD, although no significant improvements were observed in lung function or quality of life [101,102]. Other studies targeting upstream alarmins, such as IL-33 (itepekimab, tozorakimab) or IL-33 receptor ST2 (astegolimab) and TSLP (tezepelumab) have not yet achieved the expected results, but phase 3 clinical trials are still ongoing [99,103–106].

Alternative therapeutic strategies might also have a relevant role in asthma and COPD T2 endotypes. Allergen-specific immunotherapy (AIT), which consists of the administration of high doses of the causative allergens to induce immune tolerance, remains the only treatment with demonstrated disease-modifying potential in allergic disorders. Although AIT is not recommended

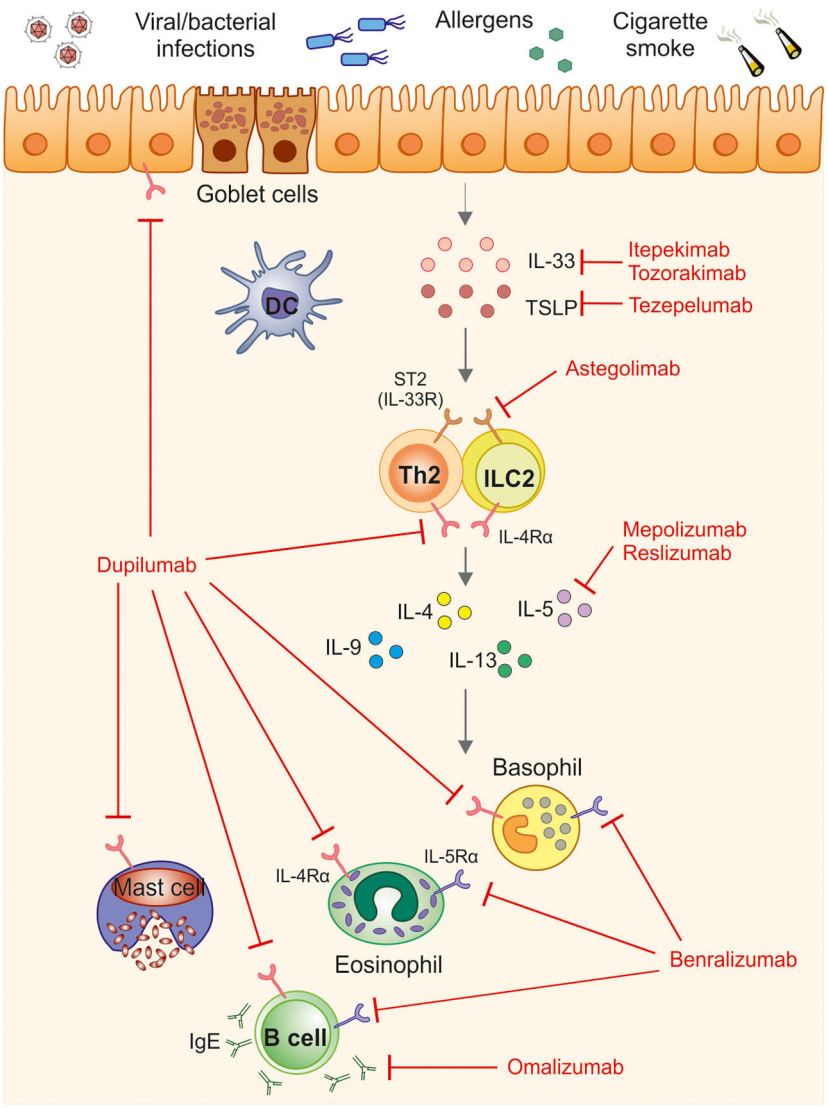

Fig. 6. Current and emerging biologic therapies targeting type 2 (T2)-driven inflammation in asthma and T2 COPD. Different biologics have been approved for asthma (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab) or T2 COPD (dupilumab and mepolizumab). Other biologics (itepekimab, tozorakimab or astegolimab) are under clinical investigation for COPD. Biologics are depicted at their sites of action in the inflammatory cascade: omalizumab (anti-IgE); mepolizumab and reslizumab (anti-IL-5); benralizumab (anti-IL-5Rα, blocking IL-5 signaling); dupilumab (anti-IL-4Rα, blocking IL-4 and IL-13 signaling); tezepelumab (anti-TSLP); itepekimab and tozorakimab (anti-IL-33); astegolimab (anti-ST2/IL-33R). COPD, chronic obstructive pulmonary disease; IL, interleukin; ILC2, group 2 innate lymphoid cell; Th2, T helper 2 cell; TNF-α, tumor necrosis factor-alpha; TSLP, thymic stromal lymphopoietin.

in patients with uncontrolled or severe asthma due to safety concerns, several studies suggest that AIT may prevent allergic asthma development and reduce disease progression in selected patients. In this regard, the combination of AIT with biologics targeting different T2 inflammatory pathways such as omalizumab, dupilumab or tezepelumab has been investigated in asthma, with variable clinical outcomes [107,108]. Moreover, allergoids-mannan conjugates are next-generation AIT vaccines targeting DCs with demonstrated capacity to generate tolerogenic DCs able to polarize functional Tregs and induce allergen-specific blocking Abs as well as to reprogram monocytes into tolerogenic DCs by mechanisms depending on metabolic and epigenetic rewiring [109,110]. Mechanistically, allergoids-mannan conjugates are engulfed by DCs in a much more efficient manner than conventional vaccines, simultaneously conferring a tolerance program characterized by increased expression levels of PD-L1, SOCS1/3, IDO or IL-10 production, which directly contribute to the generation of highly suppressive FOXP3^{+} Tregs. Phase II and III clinical trials have demonstrated the safety and efficacy of allergoids-mannan conjugates for the treatment allergic rhinitis/rhinoconjuntivitis [111–113]. Whether these vaccines may also represent a promising therapeutic strategy for allergic eosinophilic asthma remains to be determined, and further research is warranted.

Trained immunity-based vaccines (TIbV) are vaccines able to induce innate immune memory, generating broader responses against both related and unrelated antigens contained in the vaccine formulation [114–116]. In this regard, MV130, a whole heat-inactivated polybacterial mucosal vaccine, confers heterologous protection against viral respiratory infections in murine models through the induction of trained immunity [117]. In addition, MV130 prevents allergic eosinophilic asthma development, and all the associated asthma features in preclinical *in vivo* mouse models of airway inflammation, conferring protection up to 9 weeks upon treatment discontinuation [47]. Notably, in a placebo-controlled phase III clinical trial in preschool children with recurrent wheeze, sublingual MV130 administration significantly reduced wheezing attacks, symptoms, and medication score [118]. Future clinical research is needed to determine whether these

whole heat-inactivated polybacterial formulations may represent a promising alternative for T2-high asthma and T2 COPD endotypes.

Conclusions

The immune system orchestrates T2 immune responses to protect the host against large parasites, toxins and venoms. These responses require tight regulation and involved the coordinated interplay of epithelial derived-alarmins (TSLP, IL-33 or IL-25), adaptive immune cells (Th2, Tc2 and IgE-switched B cells), innate immune cells (epithelial cells, ILC2s and M2 macrophages), effector cells (eosinophils, mast cells and basophils) and key effector T2 cytokines (IL-4, IL-5, IL-9 or IL-13). Under certain circumstances, often with unknown etiology, T2 immunity becomes dysregulated, resulting in aberrant T2 inflammatory responses underlying a wide spectrum of diseases affecting different tissues, including asthma and COPD in the respiratory tract.

Advancing in the understanding of the molecular mechanisms underlying asthma demonstrated that, in patients with T2-high asthma, distinct molecular pathways (endotypes) converge into shared pathophysiological mechanisms that give rise to shared clinical manifestations (phenotypes). The allergic eosinophilic asthma endotype is primarily mediated by alarmin-activated DCs/Th2 cells/IgE-switched B cells axis whereas non-allergic eosinophilic asthma endotype is mainly driven by alarmin-activated ILC2s. Despite different upstream mechanisms, both pathways converge to promote eosinophilia, IL-13-mediated epithelial barrier dysfunction and smooth muscle cells and fibroblast alterations, which collectively determine the key clinical signs and symptoms of T2-high asthma. Several mAbs targeting specific molecules and pathways are approved as add-on treatments for moderate-to-severe T2 asthma, including omalizumab (anti-IgE), mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5Rα), dupilumab (anti-IL-4Rα) and tezepelumab (anti-TSLP). These biological agents have not only significantly improved the quality of life of many severe T2 asthma patients but have also contributed to a more precise delineation of the molecular pathways and mechanisms underlying different T2 asthma endotypes.

For long time, COPD was considered to be predominantly driven by altered type 1 and type 3 immune responses, leading mainly to neutrophilic inflammation. However, up to 30% of COPD patients display T2-high inflammation, a subgroup characterized by increased risk of exacerbations and more favorable response to corticosteroids, thus defining a distinct T2 COPD endotype. A substantial proportion of T2 COPD patients continue to experience exacerbations despite of maximal inhaled therapy (triple therapy with dual bronchodilators and corticosteroids). Therefore, biologics targeting T2 inflammatory pathways such as dupilumab and mepolizumab have recently been approved for T2 COPD, while others (including itepekimab, tozorakimab, astegolimab and tezepelumab) are currently under investigation. As previously observed in asthma, the advent of biologics for COPD marks a new era, not only by advancing disease management and treatment but also by shedding light into clinically relevant molecular mechanisms. These advances may ultimately facilitate the identification and characterization of novel COPD endotypes.

An important unmet need in the field is the identification and validation of novel suitable biomarkers. The advent of profound transcriptomic studies has paved the way to novel approaches analyzing transcriptomic signatures or epithelial-derived markers that might well contribute to better stratifying asthma and COPD patients leading to better personalized treatments.

Collectively, asthma and COPD are distinct chronic inflammatory airway diseases with different clinical manifestations that, in specific endotypes, share common underlying T2 inflammatory pathways. This convergence gives rise to disease-specific yet partially overlapping pathophysiological mechanisms. A deeper understanding of the molecular mechanisms underlying these endotypes, as well as their prevalence and longitudinal stability, will enable a more precise delineation of T2 asthma and T2 COPD subtypes. Ultimately, this will improve patient stratification, optimize disease management, and facilitate the implementation of patient-tailored therapies, thereby contributing to advance precision medicine in asthma and COPD.

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Conflict of interests

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