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SPECIAL SUPPLEMENT

SIMILARITIES, EMERGING THERAPIES, AND THE BURDEN OF T HELPER TYPE 2 DISEASES

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SIMILARITIES, EMERGING THERAPIES, AND THE BURDEN OF T HELPER TYPE 2 DISEASES

Born in 470 BC, Socrates was a classical Greek philosopher regarded as the first moral philosopher and founder of Western ethical thought. According to Plato, Socrates' contemporaries called him atopos, typically translated as strange or absurd, but meaning out of place, without a place, or placeless for his nuanced thoughts and ideas.[1] 2300 years later, the term atopy describes the atopic family of diseases: atopic dermatitis (AD), allergic asthma (AA), hay fever, food allergy and allergic rhinitis (AR).[2]

By the end of the 19th century, scientists noticed that immune responses cause adverse reactions in specific instances. The concept that immune responses cause the disease seemed irreconcilable with the protective function of immunity; consequently, they were grouped as hypersensitivity reactions. Certain human illnesses belonging to the hypersensitivities group, now known as allergies, were ultimately classified in the early 20th century.

In 1986 Mosmann and Coffman observed that chronic antigenic stimuli led to the polarity of the immune response.[3] That polarity is defined by the pattern of cytokines produced by T lymphocytes. Lymphocyte clones can produce T helper type 1 profile cytokines (Interleukin (IL)-2, IFN-γ, TNF-β) or, in an exclusive way, the T helper type 2 (Th2) profile (IL-4, IL-10, IL-13). Of the pro-inflammatory Th cell subsets, Th2 cells are the main Th cell subset that drives allergic tissue inflammation.[4]

Coined in 1906 by Clemens von Pirquet, allergy combines the Greek word *allos*, implying other and ergon signifying action. An allergy means "other actions," different from the expected reactions of the immune system.[5] Allergies are typically triggered by otherwise harmless "environmental" antigens and represent the most frequent type of hypersensitivity. For example, we may encounter allergens derived from pollen, cat, and house dust mites. When a non-atopic person mounts an immune response, their T cells respond with a moderate degree of proliferation and production of IFN-γ. This cytokine leads to B lymphocyte-driven production of the allergen-specific antibodies of type IgG1 and IgG4. An atopic patient has a different profile of immune response.

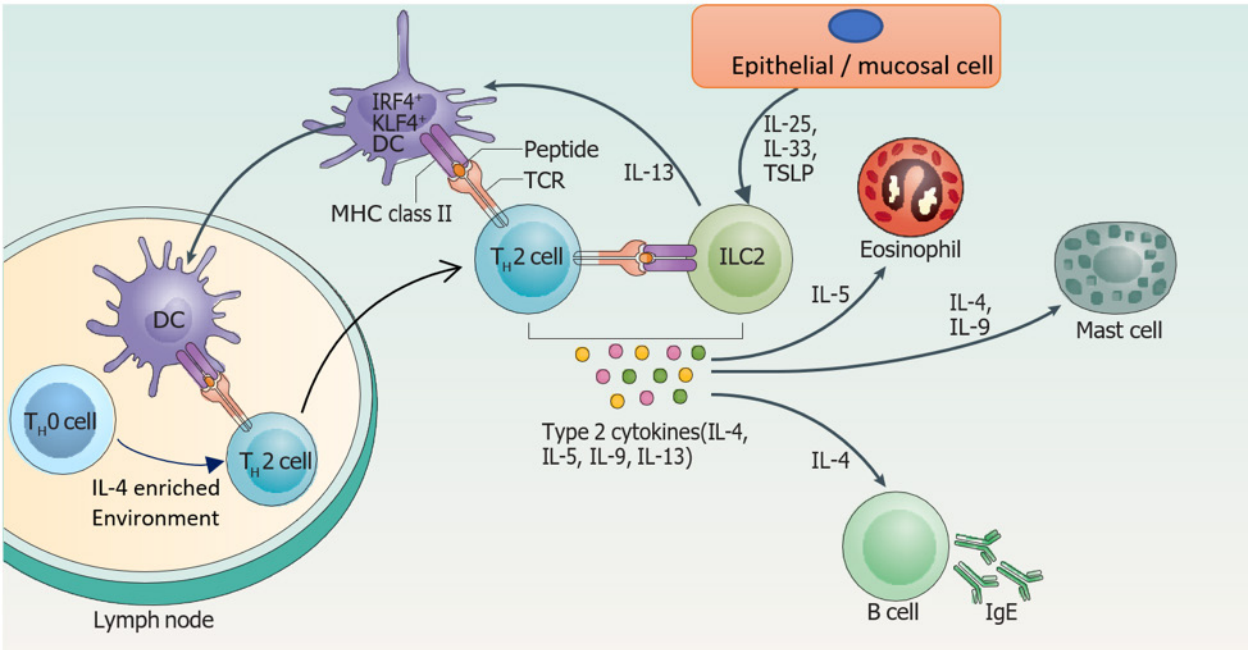

Figure 1. Overview of Type 2 immune responses; adapted from Walker and McKenzie, 2020

The atopic profile relies on T cell-secreted IL-4, -5, and -13 in response to an allergen. These cytokines stimulate the production of allergen-specific IgE antibodies (**Figure 1**). Elevated serum IgE levels and positive results on skin prick testing with allergen indicate Type 2 response. There are exceptions, but the pathognomonic marker of atopic disease is the infiltration of tissue affected by Th2 cells.

In this context, differentiation from naive CD4+ T cells toward the Th2 phenotype typically relies on the presence of IL-4 in the local cellular environment. The binding of IL4 to the IL4Ra triggers Janus Kinase (JAK) 1/3-mediated phosphorylation and dimerization of signal transducer and activator of transcription 6 (STAT6), which translocates into the nucleus inducing the expression of GATA3, the master transcription factor of the Th2 cell lineage. GATA3, together with the activated form of STAT5, promote type 2 cytokine expression, namely IL-4, IL-5, and IL-13. Stimulation of STAT6 by IL-4 and IL-13 induce the Th2, or more broadly described type 2 response.[6] Thus, STAT6, IL-4, and IL-13 are implicated in the pathophysiology of various type 2 inflammatory conditions, such as asthma, atopic dermatitis, eosinophilic esophagitis, chronic rhinosinusitis (with or without nasal polyps), and food allergies (**Figure 2**).

Emerging evidence suggests that human allergic disease results from a distinct subpopulation of pathogenic T helper type 2 cells in target organs.[12] Chronic rhinosinusitis is characterized by relentless inflammation of the nasal mucosa and nasal obstruction, with or without nasal polyposis; associated symptoms can be severe and difficult to treat. The disease is intimately associated with difficult-to-treat asthma, suggesting a pathogenic link.[13] Indeed, allergen-specific Th2 cells with pathogenic phenotypes have been identified in chronic rhinosinusitis and linked to eosinophilic tissue inflammation.[14] Recently, the targeting of the IL-4 receptor alpha has successfully demonstrated efficacy in clinical trials for chronic rhinosinusitis with nasal polyposis.[15]

Severe, difficult-to-treat asthma is a classic example of a chronic, type 2-driven disease illustrated by inflammation, obstruction, mucus secretion, and hyperresponsiveness of the lower airways. Pathogenic Th2 cells have long been implicated in allergic airway inflammation.[16] Omalizumab, a monoclonal antibody (mAb) directed against IgE, is a recognized adjunctive treatment for patients with uncontrolled allergic asthma. Monoclonal antibodies specific for IL-5 (mepolizumab, reslizumab) and IL-5R (benralizumab) are authorized as adjunctive treatments for uncontrolled eosinophilic asthma. Finally, a mAb specific for IL4R alpha, dupilumab, is approved for type 2 asthma that can include both allergic or eosinophilic asthma phenotypes. Moreover, other therapeutics targeting pathogenic Th2 cells, such as anti-thymic stromal lymphopoietin (TSLP) and anti-IL-33 treatments, are currently under investigation.[17]

Atopic Dermatitis (AD) is a widespread inflammatory skin disease with a genetic background characterized by skin barrier disruption and excessive type 2-mediated inflammation. Critically involved in AD is the subset CCR8+ memory Th2 cells, expressing high levels of IL-5, which drive chronic skin inflammation.[18] TARC (CCL17) is also overexpressed in AD lesional skin and is associated with disease severity.[19] Blocking the type 2 pathway with dupilumab shows high efficacy in moderate-to-severe AD.[20] Recently, new drugs interfering with JAK signalling, known as JAK inhibitors, have demonstrated promising results; these therapeutic agents are currently being evaluated for use in AD.[21] Several inhibitors targeting the IL-13 pathway are in development for the treatment of AD, such as lebrikizumab and tralokinumab. Tralokinumab, having completed Phase 3 studies,

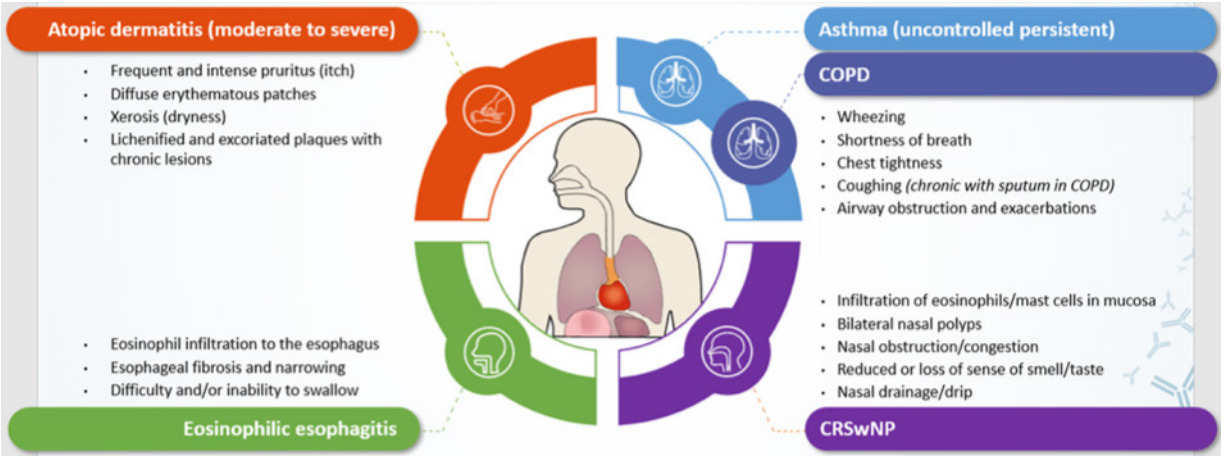

Figure 2. Type 2 inflammation in severe asthma, atopic dermatitis, eosinophilic esophagitis, and chronic sinusitis with nasal polyps.[7-11]

is currently under evaluation. Several other agents are in development targeting IL pathways in AD, including IL-12, IL-23, IL-17A, IL-31/31R, and anti-OX40.[22]

Food allergy, an immune-mediated undesirable reaction to food, has become an increasingly prevalent global health problem. Mechanistically, allergen-specific Th2 cells drive IgE class switching and the expansion of allergic effector cells. Proof is mounting to suggest that pathogenic Th2 cells are the key drivers of food allergy. For instance, IL-5, IL-9, and IL-33 are closely linked to intestinal pathology in food allergy.[23] In the context of established peanut allergy, the literature provides evidence that interruption of the Th2 pathway with a monoclonal antibody, dupilumab, inhibits IgE recall responses, skewing the type 2-dominant cytokine response and preventing the induction of anaphylaxis.[24]

Eosinophilic Esophagitis (EoE) is a recurring inflammatory disease of the esophagus, mediated by the T helper Type 2 cell, eosinophil-dominated inflammation, and consecutive esophageal dysfunction. EoE patients suffer from a range of symptoms such as dysphagia, chest pain, and reflux. Recent single-cell analysis of T cells isolated from EoE tissue identified a Th2 cell population that produces high IL-5 and IL-13 and correlates with disease severity.[25] Thus, these data add EoE to the growing list of diseases likely mediated by pathogenic T helper Type 2 cells. A phase II trial in 2020 demonstrated dupilumab's potential efficacy in treating EoE.[26]

A final similarity among these diseases is the substantial onus on morbidity, health service cost, and resource allocation. Allergic disorders are common throughout the world, affecting all genders, ages, social classes, and ethnic groups.[27] As highly ubiquitous conditions, they contribute to the prevalence of morbidity and mortality cases worldwide. Management and control of these conditions can be influenced, by among other things, the presence of comorbid conditions. Comorbidities among allergic patients include, but are not limited to depression, anxiety, other allergic disorders, and obesity leading to potential additional difficulties in managing these diseases.[28] It has been shown that in the presence of comorbid conditions, patients' and their families' health-related quality of life and activities of daily living diminish, and healthcare services and costs increase. Furthermore, since the inception of the Atopic March model, a substantial body of longitudinal epidemiological evidence has validated that the developmental profile of type 2 inflammatory diseases is heterogeneous.[29,30] In addition, other studies demonstrate that controlling these comorbid conditions at an early stage may improve outcomes for other coincidental allergic disorders.[31]

In examining the totality of the evidence, there is strong support that allergic inflammatory diseases are linked by specific T helper Type 2 cells with clinical manifestations depending on the target organ of the pathogenic Type 2 cells. Supporting the growing importance of these diseases is the increasing number of new drugs in trials targeting specific pathogenic Type 2 biology and showing greater efficacy in treating these diseases. Additional research will us help better understand this complex and fascinating immunologic relationship to reduce the burden of these diseases on patients, families, health systems, and society.

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