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GLOBAL ATLAS OF ASTHMA

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THE ADAPTIVE IMMUNE RESPONSE IN ASTHMA - T CELLS

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- **Asthma** is a syndrome encompassing **different phenotypes/ endotypes** that is characterized by reversible airflow obstruction, bronchial airway hyperresponsiveness (BHR) and chronic airway inflammation.
- Patients can be broadly classified as **type 2 (T2) and non-T2 asthma** according to T2 biomarkers and clinical features.
- **Severe uncontrolled asthma** patients present frequent exacerbations and airway remodeling, contributing to disease chronicity.
- **A key feature of allergic asthma** is the recurrence of symptoms upon allergen exposure, highlighting the role of allergen-specific adaptive immune responses.
- Many studies convincingly demonstrated that **different T cell subsets** play *key roles in the pathophysiology of asthma* (Table 1).

TABLE 1

CD4⁺ T cell subpopulations and their role in asthma

CD4⁺ T cell	Polarising cytokines	Effector cytokines	Function	Role in asthma
T_H1	IL-12	IFN-γ	Protection against intracellular pathogens Activation of tissue cells Apoptosis of tissue cells	Bronchial epithelial cell apoptosis Epithelial shedding
T_H2	IL-4	IL-4, IL-13, IL-5, IL-9, IL-31	Effector T cell activation, IgE class switch in B cells and IgE local and systemic production, Mast cells activation, Eosinophil and inflammatory cells recruitment to the airways, Goblet cell hyperplasia, Smooth muscle cell contraction	Airway Inflammation, Mucus production, BHR, Airway remodelling
T_H9	TGF-β , IL-4	IL-9	Mast cell recruitment, survival, differentiation and activation	Mucus production, Airway inflammation
T_H17	IL-1β, IL-6, IL-23, TGF-β	IL-17A, IL-17E, IL-6, IL-8, IL-22, IL-26	Defence against extracellular pathogens Neutrophilic chemotaxis and activation	Neutrophilic inflammation
T_H22	TNF-α, IL-6	IL-22	Wound healing Epithelial hyperplasia Tissue reorganization	Epithelial cell barrier homeostasis Airway inflammation
T_{FH}	IL-21	IL-4, IL-21	Germinal centre formation Class-switching and affinity maturation B cell differentiation IgE class-switching	Airway inflammation
T_{REG}	IL-2, TGF-β	IL-10, IL-35, TGF-β	Suppress innate & adaptive responses Inhibit IgE production Promote IgG4 production Prevention of airway remodelling Prevention of smooth muscle contraction	Inhibits pathophysiology of asthma and promotes tissue homeostasis

THE ROLE OF TH2 CELLS IN ASTHMA

- **In T2 asthma**, **TH2** cells represent the key T cell subset in the orchestration of adaptive immune responses leading to chronic inflammation.
- **In allergic asthma**, **during sensitization**, airway DCs uptake allergens and migrate to the draining lymph nodes where processed allergen peptides are presented to naïve CD4+ T cells in the context of major histocompatibility complex II (MHC-II) molecules, thus inducing their activation, *proliferation and TH2 polarization* (Figure 1).
- **TH2 polarization is conditioned by epithelial derived cytokines** (IL-25, IL-33 or TSLP) produced by bronchial epithelial cells activated by environmental exposure.
- **Epithelial-derived cytokines activated DCs increase the expression of Notch-receptor ligand and OX40-L**, which together with IL-4 promote the differentiation of allergen-specific TH2 cells (Figure 1).

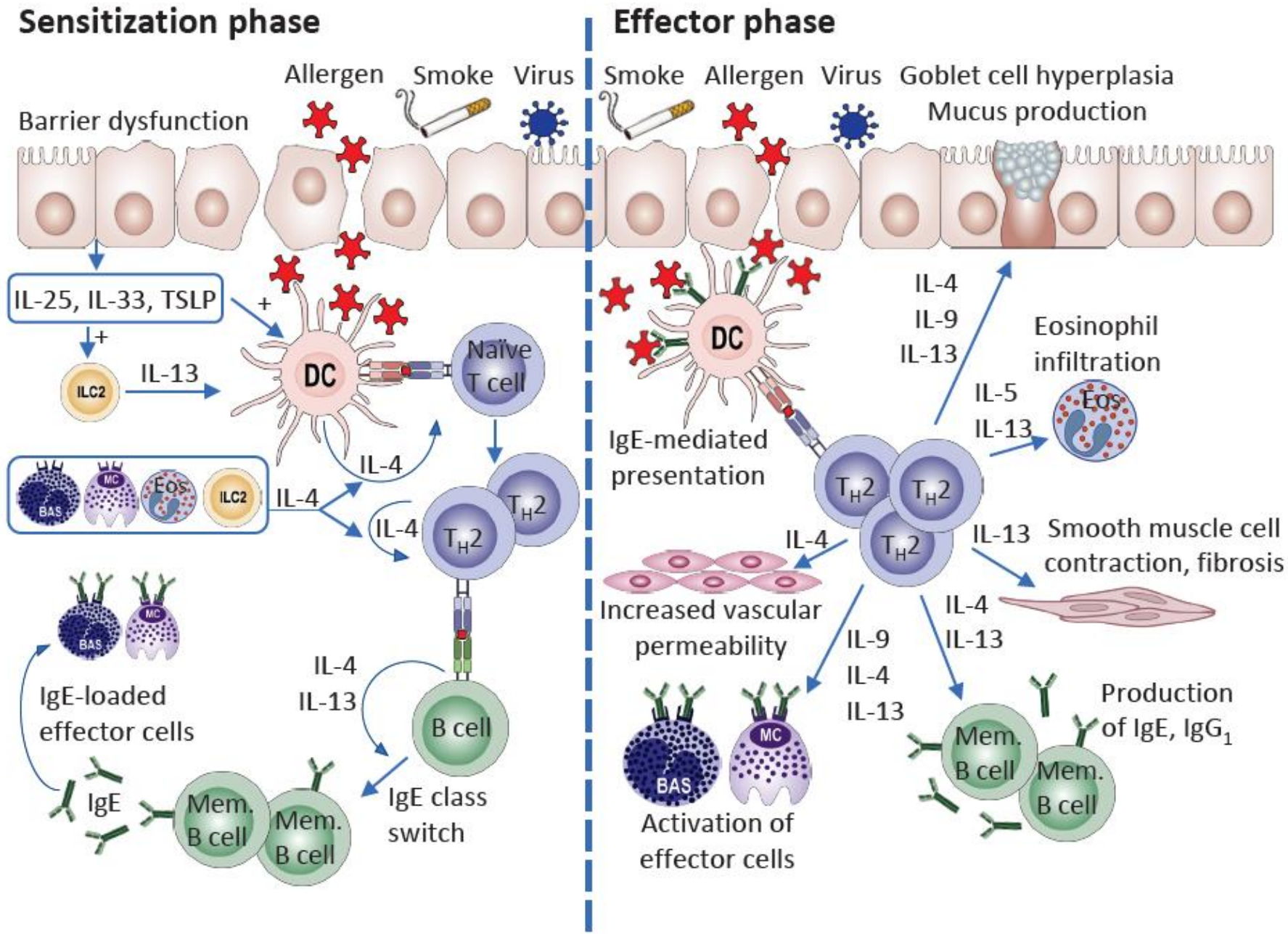

Figure 1 **The role of T_H2 cells in sensitization and effector phases of allergic asthma.** Upon environmental factors

- **In cooperation with B cells**, **DCs also generate T2 follicular T helper cells** (TFH) that support IgE class-switching in B cells (Figure 1).
- **Different TH2 subsets** are generated, including **effector** (TEFF), **central memory** (TCM) and **tissue-resident memory** (TRM) T cells, which contribute to the perpetuation of T2 inflammation.
- **During the effector phase**, **allergen-specific memory TH2 cells** are activated by airway DCs via IgE-facilitated presentation.
- **Activated memory TH2 cells** **produce large amounts of T2 cytokines** (IL-4, IL-13, IL-5, IL-9), amplifying the inflammation and contributing to the chronicity of asthma (Figure 1).

OTHER T CELL SUBSETS INVOLVED IN ASTHMA

- **In the airways of non-T2 asthma patients** and in ***some severe allergic asthma*** patients, **other CD4+ T cells** such as TH1, TH17, TH9, TH22 and TREG also play crucial roles in aggravating or suppressing excessive immune responses (Table 1).
- **Different subsets of NKT cells, γδ or CD8 T cells may also contribute** to the inflammation in different asthma endotypes.
- **TREG** are a **heterogeneous population** including natural (nTREG), inducible (iTREG), Type 1 (Tr1) and helper type 3 (TH3) regulatory T cells characterized by distinct phenotypes and functional immunosuppressive properties (Table 2).

TABLE 2

Treg phenotypes and function

Treg subset	Tissue generation	Phenotype	Main function
nTreg	Thymus	$CD4^+CD25^+FOXP3^+$	Prevention of autoimmunity Induction of transplant tolerance
iTreg	Induced in the periphery	$CD4^+CD25^+FOXP3^+$	Peripheral tolerance to allergens Prevention of autoimmunity Tumor immunity
Tr1		$CD4^+CD25^-Foxp3^-$	Peripheral tolerance to allergens Prevention of autoimmunity
T_H3		$CD4^+CD25^-Foxp3^+$	Oral tolerance Peripheral tolerance to allergens

- The **generation and maintenance of functional TREG** is a ***hallmark of allergen-specific immune tolerance.***
- **TREG keep immune homeostasis** by different mechanisms involving a wide range of surface-bound and soluble molecules (Figure 2).
- **TREG** are decreased in asthmatic patients and their numbers inversely correlated with the severity of T2 inflammation.
- **Treatment of severe asthma with Omalizumab**, a humanized monoclonal anti-IgE antibody, increases the frequency of TREG in asthmatic children, which correlates with better asthma control.

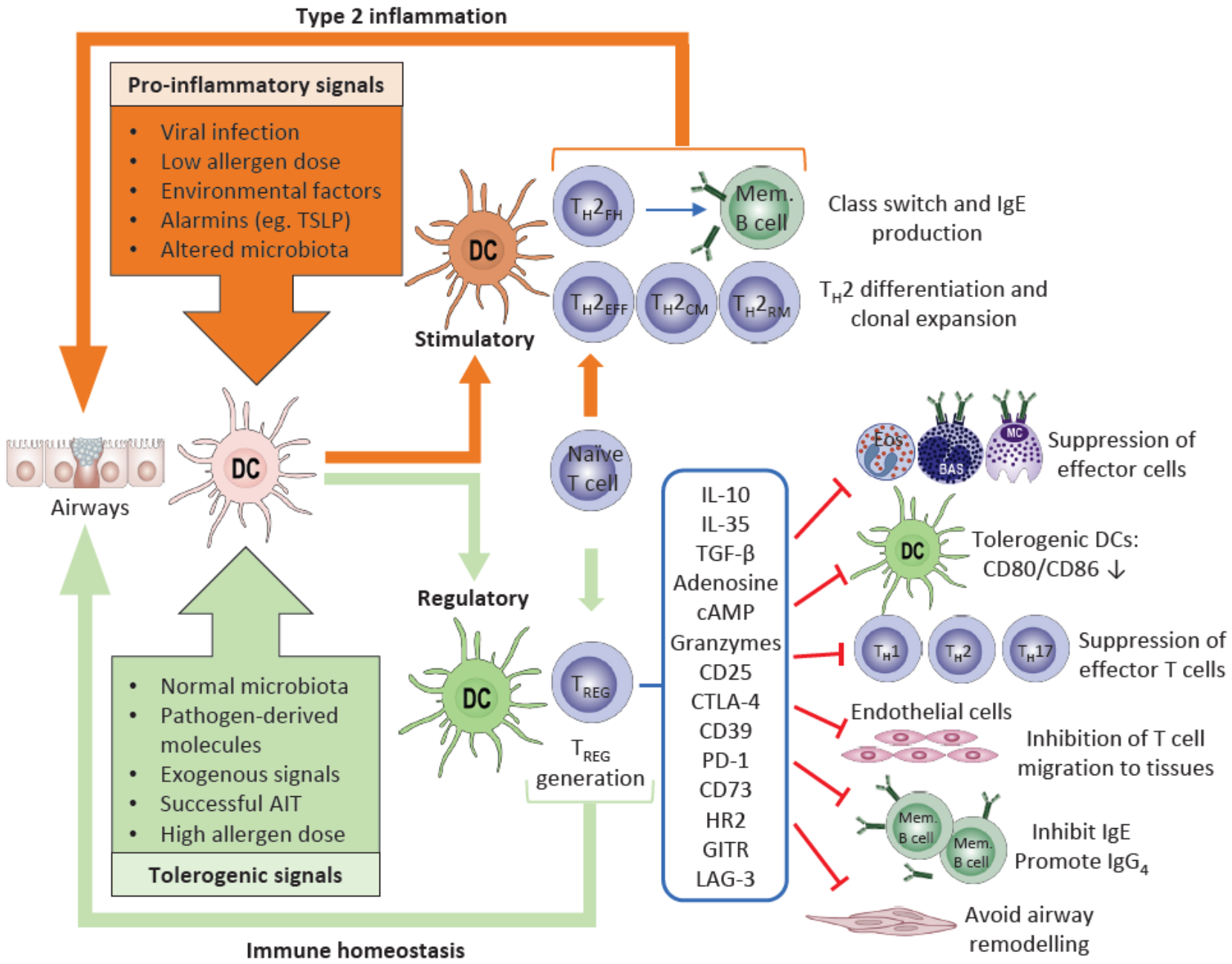

Figure 2 Balance between type 2 inflammation and immune tolerance in asthma. Under pro-inflammatory conditions,

KEY MESSAGES

- Bronchial epithelial barrier disruption and the production of epithelial derived cytokines in response to environmental insults contribute to the generation of allergen-specific T helper type 2 (T_H2) cells
- Allergen-specific T_H2 cells constitute key players in type 2 (T2) asthma. T_H2 cells contribute to the IgE class-switching in B cells, leading to the sensitization of mast cells and basophils, as well as to the chronic inflammation
- Different T cell subsets besides T_H2 such as T_H1, T_H17, T_H9, T_H22, natural killer T (NKT) cells, γδ and CD8 T cells, or regulatory T cells (T_{REG}) contribute to the perpetuation or suppression of immune responses in asthma
- Dendritic cells (DCs) may polarize T cells towards T2 inflammatory responses or T_{REG}-mediated immune homeostasis depending on the integration of pro-inflammatory and tolerogenic signals
- T_{REG} are the cornerstone of allergen-specific immune tolerance induction. These cells are decreased in asthmatic patients and their levels inversely correlate with asthma severity