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REVIEW ARTICLE

A pathogenic integrated view explaining the different endotypes of asthma and allergic disorders

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Abstract

The inflammation of allergic diseases is characterized by a complex interaction between type 2 and type 3 immune responses, explaining clinical symptoms and histopathological patterns. Airborne stimuli activate the mucosal epithelium to release a number of molecules impacting the activity of resident immune and environmental cells. Signals from the mucosal barrier, regulatory cells, and the inflamed tissue are crucial conditions able to modify innate and adaptive effector cells providing the selective homing of eosinophils or neutrophils. The high plasticity of resident T- and innate lymphoid cells responding to external signals is the prerequisite to explain the multiplicity of endotypes of allergic diseases. This notion paved the way for the huge use of specific biologic drugs interfering with pathogenic mechanisms of inflammation. Based on the response of the epithelial barrier, the activity of resident regulatory cells, and functions of structural non-lymphoid environmental cells, this review proposes some immunopathogenic scenarios characterizing the principal endotypes which can be associated with a precise phenotype of asthma. Recent literature indicates that similar concepts can also be applied to the inflammation of other non-respiratory allergic disorders. The next challenges will consist in defining specific biomarker(s) of each endotype allowing for a quick diagnosis and the most effective personalized therapy.

KEYWORDS
allergic inflammation, cell plasticity, endotypes, environmental signals, immune response

Abbreviations: AD, atopic dermatitis; AHR, airway hyper-responsiveness; AIT, allergy immunotherapy; AR, allergic rhinitis; BA, bronchial asthma; BALF, bronchoalveolar alveolar lavage fluid; Chr, chromosome; CRS, chronic rhinosinusitis; CRSsNP, chronic rhinosinusitis without nasal polyps; CRSwNP, chronic rhinosinusitis with nasal polyps; DAMPs, damage-associated molecular patterns; DC, dendritic cells; EoE, eosinophilic esophagitis; FA, food allergy; FcεRI, high affinity Fcε receptor; FeNO, fractional exhaled nitric oxide; GWAS, genome-wide analyses; HDAC, histone deacetylase complex; IDO, indoleamine 2,3-dioxygenase; IFN-γ, interferon gamma; IL, interleukin; ILCs, innate lymphoid cells; iNKT, invariant natural killer T cells; HLA, human leucocyte antigens; LTi, lymphocytes tissue-inducer cells; MAIT, mucosal-associated invariant T cells; MC, mast cells; NETs, neutrophil extracellular traps; PAMPs, pathogens-associated molecular patterns; PG, prostaglandin; SNPs, single nucleotide polymorphism; STAT, signal transducer and activator of transcription; TAP, transporter associated with antigen processing; Tc, cytotoxic T cells; TGF-β, transforming growth factor beta; Tfh, T follicular helper cells; Th, T helper cells; Tr1, IL-10-producing T regulatory cells; Tr35, IL-35-producing T regulatory cells; TSLP, thymic stromal lymphopoietin; Trm, tissue-resident memory T cells.

1 | INTRODUCTION

Allergic disorders, including bronchial asthma (BA), allergic rhinoconjunctivitis (AR), chronic rhinosinusitis with/without nasal polyps (CRSw/sNP), some food allergies (FA) eosinophilic esophagitis (EoE), and atopic dermatitis (AD), display a chronic inflammation sharing several pathogenic mechanisms.[1,2] In the last five decades, the knowledge of such mechanisms extraordinarily improved with relevant clinical outputs and radical changes in the therapeutic approaches.[3-10]

These diseases, in particular BA, are multifactorial disorders, influenced by genetic and environmental factors.[11-14] Asthma displays a marked heterogeneity in etiology, symptom triggers, clinical characteristics, and response to therapy.[15-17] Research has been determinant to define various phenotypes combining clinical patterns, relevant outcomes, inflammatory features, and response to treatment.[18] By contrast, the term endotype has been introduced to describe "a subtype condition defined by an unique or distinctive functional or pathophysiologic mechanism".[19,20] Recent data provide evidence that BA and other allergic diseases share endotypes or sub-endotypes corresponding to defined clinical phenotypes[21] Both innate and acquired immune responses contribute to the different endotypes while non-allergic mechanisms such as environmental factors, activation of metabolic pathways, resident cells, or epithelial barrier dysfunction have been shown to modulate the profile of inflammation.[22] This review will focus on genetic/epigenetic and environmental factors conditioning innate and adaptive immunity, mucosal barrier, tissue environmental, and effector cells plasticity which, in different combinations, may explain the heterogeneity of endotypes/sub-endotypes and the related phenotypes in these patients (Figure 1).

2 | GENETIC AND EPIGENETIC FACTORS CONTRIBUTE TO THE DEVELOPMENT OF ALLERGIC INFLAMMATION

Genetic-epigenetic alterations influence the development of allergic diseases: the main well-documented genes involved in genetic/epigenetic alterations in these diseases are listed in Tables 1–4. Gene markers and loci associated with asthma susceptibility have been identified; alterations close to ORMDL3/GSDMB genes have been associated with childhood-onset asthma, IL-33 and IL1RL1, single-nucleotide polymorphisms (SNPs) associated with atopic asthma, and thymic stromal lymphopoietin (TSLP) gene with the protection from the T2-high asthma endotype.[23]

The human genes involved in IgE response include those controlling the IgE locus and those encoding the HLA class II complex favoring the expansion of allergen-specific Th2 cells and the IgE switch of B cells. These genes are located in the chromosome (chr) 5 (region 5q23-35) encoding type-2 cytokines, chr6 encoding HLA class II alleles and the peptide transport molecules TAP1 and TAP2, chr11 for the high-affinity Fcε receptor (FcεRI), chr12 for the signal transducer and activator of transcription 6 (STAT6), and chr16 for the IL-4R α-chain.[24-26] Several polymorphisms associated with candidate genes for respiratory allergy have been described, which may vary according to racial diversity.[27] The principal well-documented genes involved in the genetic alterations in these diseases are listed in Table 1.

Among epigenetic factors, DNA methylation is the most described mechanism, while others include histone modifications and changes in miRNAs expression. Since DNA methylation pattern is tissue- and cell-specific, several studies have focused on DNA methylation of different cell types and tissues of asthmatic patients

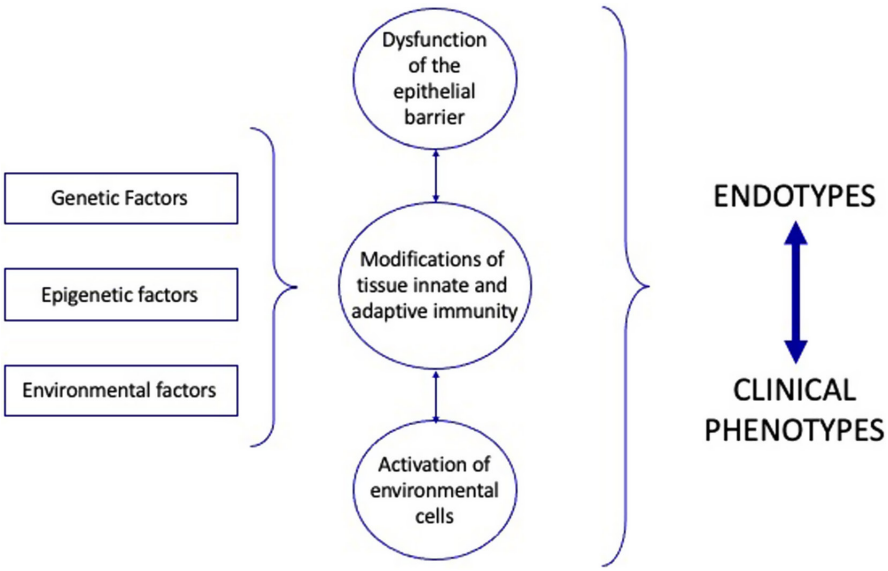

FIGURE 1 A comprehensive view of factors contributing to the different endotypes and related phenotypes in allergic diseases

TABLE 1 Reported genes associated with asthma, allergic rhinitis, and chronic rhinosinusitis (in bold loci involved in the pathogenesis of asthma)[a]

Chr-	Genes	Possible function in allergy	Refs
1	*SFPQ, ZMYM4, RUNX3, RERE, TNFRSF14, FAM213B, C1orf54, MRPS21, FLG,* ***IL6R****, RORC, RPTN, HRNR,* ***PYHIN1,*** *DARC, FCER1A, OR10J3, NDUFS2, FCER1G,* ***CD247****, FASLG,* ***TNFSF18, TNFSF4, CRB1****, DENND1B, CHI3L1, ITPKB*	IgE receptor in epithelial and immune cells, apoptosis-associated transcription factor, cytokine receptor	28-33
2	*ASB3, SOCS, JUND, CEBPB,* ***IL18R1****,* ***IL1RL1, IL1RL2****, BCL2L11, ANAPC1, IL1B, KYNU, ARHGAP15, PLCL1, IKZF2, CCL20, DAW1, INPP5D,* ***D2HGDH***	Cytokines and chemokines, cytokine receptors	29,31,34,35,42
3	*RYBP, GLB1, IL5RA, ABI3BP, FAM172B, TRMT10C, SLC15A2, GATA2, RASA2, BCL6,* ***LPP****, DLG1, FBXO45, CEP19*	Cytokine receptor, transcription factor	29,31
4	***TLR1,*** *TLR6, TLR10, STX18, MSX1, SRIP1, GC, MANBA, ADAD1, IL2, IL21, GAB1*	PRR of innate immunity, NFκB-dependent activation of inflammatory pathways, immune regulatory effects, cytokines	31,34,36
5	*DAB2, PTGER4, IL7R, FBXL7, FAM105A,* ***PDE4D****, TMEM232,* ***SLC25A46, TSLP****, WDR36, CAMK4, TNFAIP8, C5orf56, IL13,* ***RAD50,*** *IL5, DIAPH1,* ***NDFIP1****, LMAN2, RGS14*	Type 2 immune response, Immature IL-7R+T cells subset	29,31,34,37,42
6	***GRM4****,* ***HGMA1****, ITPR3,* ***BTNL2, C6orf10****,* ***HLA-DPB1****,* ***HLA-DOA****, HLA-DPA1,* ***HLA-DQA1, HLA-DQA2, HLA-DQB1****,* ***HLA-DRA****, BTNL2,* ***NOTCH4, PBX2,*** *HLA-B,* ***MICA, HLA-C****, NCR3, AIF1, PSORS1C1, TNXB, CREBL1, HLA-A, HLA-G, HLA-J,* ***BACH2,*** *ATG5, PTPRK, TNFAIP3, ARID1B, RNASET2*	Antigen presentation, self tolerance	29,31,34,35,36,37,38,39,40
7	*C7orf72, IKZF1, JAZF1, NPY, FERD3L, ITGB8, ABCB5, GSAP,* ***CDHR3***	Transcription repressor	29,31
8	*TUSC3,* ***ZBTB10****,* ***TPD52****,* ***SLC30A8****, MYC*	Unknown	31,39
9	***EQTN****,* ***TEK****,* ***MOB3BZBTB10,*** *JKAMPP1, TYRP1, JAK2,* ***RANBP6, IL33****, PHF19, TRAF1, C9orf114, LRRC8A,* ***PTGES***	Defensins	29,31,35,40
10	***GATA3****, SFTA1P, AKR1E2, IL2RA, ZNF365,* ***JMJD1C****, REEP3, PSAP, HPSE2, C10orf95, ACTR1A, TCF7L2*	Transcription factor of the type 2 response, NFκB complex subunit involved in TLR signaling regulation	28,29,31,36,40,42
11	*DBX1, NAV2, HTATIP2, PRMT3, AP5B1, OVOL1, WNT11,* ***LRRC32****, C11orf30, SESN3, FAM76B, LAYN, SIK2, DDX6, CXCR5, KIRREL3-AS3, ETS1*	T cells regulation, TGF-β signaling, epithelial barrier function, chemokine receptors expressed on Tfh or B cells	29,31,33,34
12	*HDAC7, AQP2,* ***CDK2****, SUOX,* ***IKZF4****,* ***STAT6****, NAB2, ATXN2, SLC22A5, C12orf65, CDK2AP1, SPPL3, HNF1A-AS1*	Transcription factor of Th2 cells, hematopoiesis, and downstream of TCR activation	29,31,36
13	*FOXO1, PIBF1, KLF5*	B cell re-editing	18,29
14	*PSMA6, FOXA1, TTC6,* ***RAD51B****, JDP2, BATF, RCOR1, TRAF3*	TLR signaling	4,18
15	*RTF1, ITPKA,* ***RORA****,* ***SMAD3****, IQGAP1*	Inhibition of immune signaling, tyrosine kinase activity downstream TCR activation, natural helper cells	2,4,8
16	***CLEC16A****, RMI2, LITAF*	Expression in the lung, in T and B cells with unknown function	4,44
17	*SMTNL2, ALOX15,* ***GRB7****,* ***GSDMA, GSDMB,*** *CRKRS,* ***ORMDL3****, PERLD1,* ***IKZF3,*** *PNMT, PSMD3,* ***ZPBP2****, CCR7, SMARCE1, STAT5B, MAP3K14, ARHGAP27,ZNF652*	Chemokine receptor, transcription factor of Tfh cells	31,35,41,42
18	*LPIN2, DYNAP, RAB27B, TNFRSF11A*	Unknown	23,44
19	*SLC7A10, CEBPA, ZNF614, ZNF841, ZNF432, ZNF776*	Lung development, inflammatory adhesion process	28
20	*NFATC2, ZNF217, RTEL1*	Unknown	23,44
21	*RUNX1, SIK1*	Unknown	23,44
22	***IL2RB****, TEF, TOB2*	Cytokine receptor	35,43

[a]GWAS/SNPs with p level $<10^{-8}$.

TABLE 2 miRNAs, target genes, epigenetic modifications, and clinical outcomes in bronchial asthma and allergic rhinitis

miRNAs	Target genes	Function	Clinical outcomes	Refs
miR-21	*IL-3, IL-5, IL-12*	Suppression of eosinophil response	BA	46
miR-21	*IL-12p35*	Induction of type 1 response	Severe BA	46,47
miR-146a	*IRAK1*	Neutrophil migration, IL-5/IL-13 expression	BA	48
miR-1248	*IL-5*	Eosinophil response	BA	50
miR-1	*VEGF/Mpl, SELP, CCL26, TSLP*	Th2 inflammation, eosinophil regulation	BA	53
miR23	*IL-4 regulator genes*	IL-4 expression	BA	54
miR27	*IL-4 regulator genes*	IL-4 expression	BA	54
circHIPK3	*miR326/STIM1 axis*	Airway remodeling	BA	56
miR-15a	*VEGF*		BA	58
miR-19b	*TSLP*	Airway remodeling	BA	59
miR-192-5p	*MMP-16, ATG7*	Airway remodeling	BA	60
miR-27-b-3p	*SYK, EGFR*		Pediatric BA	61
miR-323-3p	*IL-22*		BA	62
miR-20a-5p	*HADAC4*	Allergic inflammation	BA	63
Let-7	*JAK1/STAT3, IL-13, SOCS4*	Regulation of IL-13 secretion, modulation of type 2 inflammation	BA/AR	49,64,73
miR-16	*ADRB2, Ikb/NFkB*	Prevents IL-13-driven cytokine secretion	BA/AR	55,65,73
miR-155	*S1pr1, IL-13Ra1*	Th1/Th2 response, control of proliferation of Treg cells, regulates IL-13 pathway in macrophages	BA/AR	52,65,66,73
miR-126	*VEGF, IRS1, TOM1*	Regulation of IL-4 effects, eosinophil recruitment	BA/AR	51,67,73
miR-19a	*TGF-β1PTEN/A20*	Reduces allergen suppression by IL-10 in peripheral DC, airway remodeling	BA/AR	57,67,73
miR-206	*S100A7A, VEGF*	VEGF pathway	AR	68
miR-338-3p	*WNT/β-catenin*	E-M transition by inhibiting the WNT-β catenin pathway	AR	68
miR-498	*STAT3*	Inhibition of Th17 differentiation	AR	64,68
miR-187	*CD276*	T cell response regulation	AR	64,69
miR-143	*TGF-β1*	Inhibition of memory T cell differentiation	AR	64,69
miR-886-3p	*SMAD3, FoxO1*	Regulation of TGF-β pathway	AR	64,69
miR-224	*SMAD4*	Regulation of TGF-β pathway	AR	64,69
miR-18a	*CTGF*	TGF-β pathway	AR	68
miR-205	*MICAL2*	Activation of ERK17 pathway	AR	64
miR-375	*JAK2/STAT3*	Prevention of apoptosis of nasal epithelial cells	AR	70
miR-26a	*SMAD2/SMAD3*	Modulation of TGF-β-dependent pathway, Inhibition of NF-kB, promoting Treg cells	AR	68
miR-135a	*GATA-3*	Increased levels of IL-4 and IgE in the nasal mucosa, prevention of mast cells activation	AR	71-73

Abbreviations: AR, allergic rhinitis; BA, bronchial asthma; miRNAs, micro-RNAs.

with regard to airway remodeling, phagocytosis, and other lung functions.[35,42,45] Genes involved in the epigenetic alterations well-documented in these diseases are listed in Tables 2–4.

Life-style changes have been considered the most relevant epigenetic factor able to increase the prevalence of allergy in developed countries. The reduced exposure to pathogens during the first years of life is the critical factor for IgE-mediated pathology. Such Hygiene Hypothesis foresees that, in early life, a failure of the physiological shift of the type 2 response to allergens toward a more protective type-1 profile occurs. The reduced microbial insults with the consequently decreased cytokines promoting the Th1 cell development are favored by the use of vaccines, antibiotics, and cryopreserved foods, as well as reduced promiscuity and increased environmental hygiene.[108-112] Reduced regulatory mechanisms have been also emphasized to explain the Hygiene Hypothesis,[109] which is based on (i) the reduced prevalence of allergy in countries with widespread helminth infestations inducing Th2 response, (ii) the parallel increase in the developed countries of diseases associated

TABLE 3 Some well-documented DNA methylated genes in asthma

Epigenetic modifications	Genes (gene location)	Tissue/fluids	Function	Clinical outcomes	Refs
Hypomethylation	*ALOX12 (17p13.1)*	Blood	Type 2 response	Childhood persistent wheezing	73,74,107
Hypermethylation	*IFN-g, FOXP3 (12q15,Xp.11.23)*	Blood	Type1 response, Treg cell suppression		75,107
Hypomethylation	*IL-13, RUNX3, TIGIT (5q31.1, 1.p36.11, 3.q13.31)*	Blood	Mucus hypersecretion	Childhood asthma	76,107
Hypomethylation	*IL-5RA (3p.26.2)*	Blood	Eosinophil recruitment	Juvenile asthma	77,107
Hypermethylation	*CYP26A1 (10q23.33)*	Blood		Asthma, aspirin intolerance, allergy	78,107
Hypermethylation	*IL-1R2 (2q11.2)*	Blood		Asthma	79,107
Hypermethylation	*ADRB2 (5q31.33)*	Blood		Severe asthma in children	80,107
Hypermethylation	*WNT2 (7q.31.2)*	Blood		Neutrophilic asthma	81,107
Hypermethylation	*IL-2 Site 1 (4q27)*	Cord blood		Severe asthma in children	82
Hypermethylation	*GATA3 (10p14)*	Cord blood		Reduced asthma risk	83
Hypomethylation	*C7orf50, ZAR1 (7p22.3, 4p11)*	Cord blood	High IgE levels		84
Hypermethylation	*AXL (19q13.2)*	Newborn blood spots		Wheezing (more in girls)	85
Hypomethylation	*ALOX15, POSTN (17p13.2, 13q13.3)*	Nasal epithelium	Type 2 response	Childhood asthma	86
Hypomethylation	*TET1 (10q21.3)*	Nasal epithelium		Asthma	87
Hypomethylation	*CDH26, CDHR3 (20q13.33, 7.q22.3)*	Nasal epithelium		Atopy with asthma	88
Hypermethylation	*ARG2 (14p24.1)*	Buccal cells	Decreased FeNO	Asthmatic children	89
Hypomethylation	*ADRB2 (5q31.33)*	Saliva/blood		Reduced dyspnea in Asthmatic children	90
Hypomethylation	*IL-6, NOS2 (7p15.3, 17q11.2)*	Airway epithelium	Increased FeNO	Childhood asthma	91
Hypermethylation	*STAT5A (17q21.2)*	Airway epithelium	Increased Type 1 response, Decreased Eos recruitment		92
Hypermethylation	*PCDH20 (13q21.2)*	Sputum		Asthma in old male adults	93
Hypermethylation	*ORMDL3 (17q12.21)*	Endobronchial Airway epithelium		Asthma in adult people	94
Hypermethylation	*IL-13 (5q31)*	Lung airway epithelium		Asthma	95
Hypomethylation	*ZPBP2 (17q12-q21)*	HapMap lymphoblastoid cell lines		Asthma	96

TABLE 4 Some well-documented histone-modified genes

Epigenetic modifications	Genes	Clinical association	Refs
Downregulation of histone deacetylase complex (HDAC) 2	*Glucocorticoid Receptor*	Severe asthma	97,107
Hyper-acetylation of H3K9, H3K14, H3K16, H3K18, H3K27. Trimethylation of H3K4 and H3K79	*Notch1*	Asthma	98,107
Hypo-acetylation	*LAT*	Asthma	99,107
Upregulation f HDAC2	*SOX2*	Asthma	100,107
Trimethylation of H3K4	*IFN-g*, *IL-17A*, *IL-17F*, *IL-4*, *Foxp3*, *Rorgt*	Asthma allergic diseases	101,107
Acetylation	*IL-13*, *Foxp3*	Asthma	102
Hypo-acetylation	*ORMDL3*	Asthma	103,107
Acetylation of H3K18	*ANp63*, *STAT6*, *EGFR*	Asthma	104
Acetylation of H3K18	*CXCL8*	Asthma	105
Dimethylation of H3K4	*CCR4*, *CCL3*	Asthma	106,107

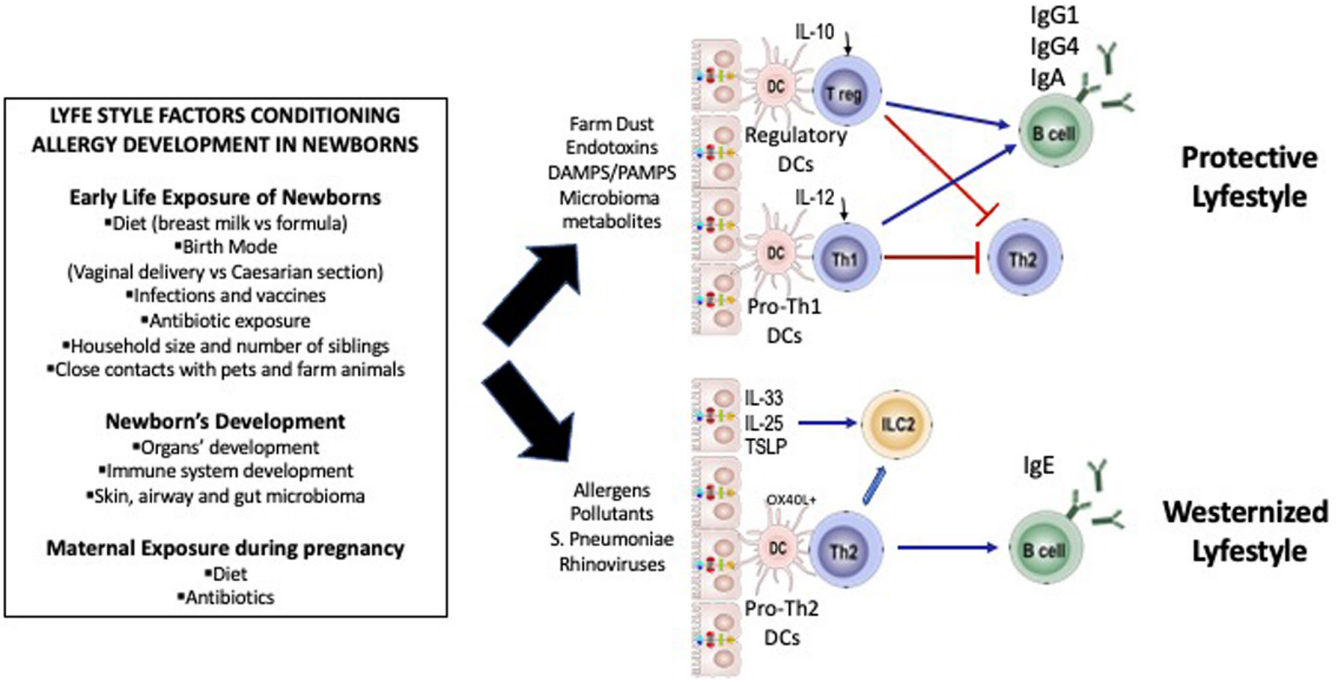

FIGURE 2 Mechanisms of the "Hygiene Hypothesis" responsible for allergy development in newborns. Several factors such as early life exposure of newborns, newborns' development, and maternal exposure during pregnancy to environmental stimuli together with different airway insults may favor a submucosal environment oriented toward a type 1- and regulatory (Protective lifestyle) or type 2- (Westernized lifestyle) response. These latter conditions heavily contribute to allergy onset in newborns. DAMPS, damage-associated molecular patterns, DCs, dendritic cells; ILCs, innate lymphoid cells; PAMPS, pathogen-associated molecular patterns; Th, T helper cells; TSLP, thymic stromal lymphopoietin

with a Th1 response (i.e., Type I diabetes and Crohn's disease), and (iii) the ability of microbial stimuli to induce high levels of regulatory cytokines.[109] Figure 2 summarizes the main mechanisms of conditioning allergy development in newborns.

3 | EFFECTOR AND REGULATORY T CELLS PLAY A MAJOR ROLE IN BA AND OTHER ALLERGIC DISORDERS

Effector and regulatory T cells are usually referred to as immune cells able to favor (T helper [Th] and T cytotoxic [Tc] cells) or inhibit (T regulatory cells [Treg]) the function of other cells involved in allergic inflammation. In addition, other cells not belonging to the T-cell lineage may display effector (such innate lymphoid cells [ILCs], mast cells, eosinophils, and others) or regulatory (immature dendritic cells [iDCs], myeloid-derived suppressor cells [MDSCs], and others) activity at the mucosal level.

Human effector CD4+ Th cells are classified into different subsets on the basis of differentiation signals, cytokine production profiles, and the expression of main regulators of transcription.[113] Th1 cells express the transcription factor T-bet, produce interferon (IFN)-γ and IL-2, and are protective against intracellular pathogens. Th2 cells express the main regulator GATA-3, produce type 2

cytokines, and protect against helminths.[114] The Th17 subset produces IL-17A, IL-17F, and IL-22,[115] expresses the transcription factor RORγt[116] and the surface lectin receptor CD161,[117] and mainly recognize extracellular bacteria and fungi. Both Th1 and Th17 cells are involved in the response to chronic viral and bacterial infections as well as in the majority of autoimmune diseases, whereas Th2 cells associate with allergy and parasitic infections.[118] Finally, Th9 cells produce IL-9 and IL-10, express the main regulator PU1, and are involved in allergic inflammation and tumors, while the Th22 subset synthesizes mainly IL-22, expresses aryl hydrocarbon receptor and associates with mucosal defense, tissue repair, and wound healing.[1,8,9,119] Features of the main Th cell subsets are summarized in Figure 3.

3.1 | Th2 cells

In people with genetic susceptibility for atopy, the first contact with an allergen induces the development of effector T cells with a type-2 profile which has been extensively characterized.[1,8,9] They develop from naïve T cells following a contact (interaction between Notch1 ligand/-Delta4-expressed on DCs and Notch1 on T cells), and soluble signals (IL-4 produced by circulating or tissue eosinophils, mast cells [MCs] or activated NKT cells). Alarmins (IL-25, IL-33, and thymic stromal lymphopoietin [TSLP]) produced by epithelial cells (and subepithelial DCs), are the main contributors to the Th2 cell development.[1,120] Transcription factors STAT6 and cMaf and the main regulator GATA3 are activated by alarmins which also favor the expression of chemokine receptors (CCR3, CCR4, CCR8, and CRTh2) relevant for tissue homing.[119] Once activated, cells with a Th2 phenotype are detectable in the bloodstream or within tissues (CD11a+CD49a+CD69+CD103+T resident memory [Trm2] and CXCR5+T follicular helper cells [Tfh2]).

Trm2 cells survive in inflamed bronchi and influence the local immune response[121] while circulating memory Th2 cells provide systemic host defense.[122-125] In allergic inflammation circulating Th2 and Trm2 cells display distinct nonredundant functions and transcriptional analysis indicates that they share a core of Th2 gene signature but also distinct transcriptional profiles.[126] In the mouse Trm2 cells are able to promote airway hyperreactivity (AHR) and cell homing even when circulating Th2 cells have been depleted[123,125]

IL-4 and IL-13 in addition to the surface signal CD154 (CD40L) favor the cooperation between Tfh2 and mature B cells promoting, at the follicular level, the IgE switch, and the development of allergen-specific IgE-producing plasmablasts migrating into the bone marrow.[127] Then, IgE bind the FcεRI expressed by MCs and basophils.

After the primary response, few memory Th2-lymphocytes, IgE+B cells, and IgE-producing plasma cells persist.[1] At a subsequent exposure, the allergen binds IgE fixed on MC, thus triggering three

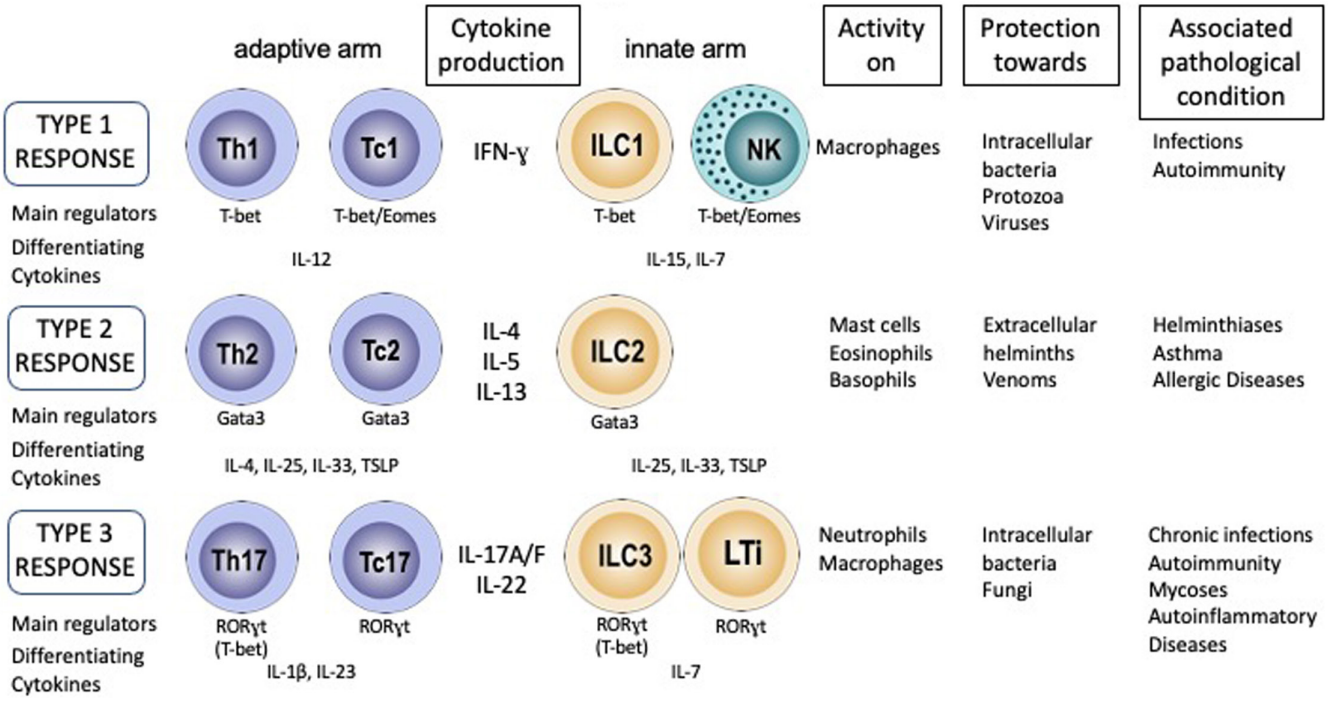

FIGURE 3 Features of innate and adaptive immune cells involved in the three main immune responses. The characteristics of terminally differentiated cells of type 1, type 2, or type 3 immune responses of both innate (ILCs/NK) and adaptive (Th/Tc) arms of immunity are depicted together with main regulators and cytokines promoting cell differentiation. The picture also synthesizes cytokine production, activity on terminal effector cells, protection toward different pathogens, and associated pathological conditions of each type of immune response. ILCs, innate lymphoid cells; LTi, lymphoid tissue-inducer cells; Tc, T cytotoxic cells; Th, T helper cells; TSLP, thymic stromal lymphopoietin

different pathways, PKC, PLA2, and MAP-kinases followed by the release of preformed (histamine, kinins, serotonin, and so on) and newly synthesized mediators such as eicosanoids (leukotrienes, prostaglandins-PG-, and thromboxanes) in addition to several cytokines responsible for immediate reactions and symptoms flare-up.[128]

The persistence of inflammation is due to cells recruited into tissues and their ongoing activation. The first event is the local activation of endothelial cells by different cytokines (IL-1β, IL-4, IL-13, TNF-α, and IFN-α) upregulating the expression of adhesion molecules. The recruitment of blood cells is promoted by chemokines, cytokines, and mediators (histamine and leukotrienes) released from T lymphocytes, MCs, and other resident cells; notably, IL-5, IL-3, GM-CSF, and platelet-activating factor are responsible for eosinophil homing.[129-131]

The expansion of long-lived memory Th2 cells characterizes this phase. Both IL-4 and IL-13 act as IgE-switching factors, while IL-13 induces inflammatory cytokines, hyperplasia of mucus-secreting cells, AHR, and fibrosis. IL-5 is the major chemotactic factor for eosinophil precursors and promotes their amplification and survival, whereas IL-3, IL-4, IL-9, and IL-13 are involved in MC recruitment. Finally, IL-9, IL-13, and IL-31 further induce epithelium damage contributing to worsening AHR.[9] Chronic bronchial inflammation leads to airways remodeling which combines goblet cell hyperplasia, epithelial damage, subepithelial collagen deposition, airway smooth muscle hyperplasia, and increased angiogenesis[132,133]

Th2 cells are not homogeneous effector cells. A Th2 subset specifically recognizing allergens has been identified in allergic individuals exclusively.[134,135] Such pathogenic cells, called Th2A, are terminally differentiated CD27− CD45RB− CD4+ T cells with high expression of CRTH2, CD49d, CD161, and alarmin receptors and strong production of both IL-5 and IL-9.[136] Transcriptome analysis of Th2A cells revealed a distinct pathway during the initial response to allergens. Importantly, reduction in Th2A-cells is a marker of clinical response following allergen immunotherapy (AIT) for pollens or oral immunotherapy for peanuts.[137-139]

The type 2 response, however, cannot fully explain the whole features of allergic inflammation and other cells play a not ancillary role in this process.

3.2 | Th17 cells

Th17 are the new actors involved in some asthma phenotypes. They belong to a lineage different from Th1 and Th2 cells, and usually favor neutrophilic inflammation.[140] The development of Th17 cells from naive T lymphocytes is induced in mice by transforming growth factor beta (TGF-β) and IL-6, whereas IL-21, IL-22, and IL-23 are responsible for their amplification and stabilization. In humans, the induction of Th17 cells mainly depends on IL-1β and IL-23 which are highly produced following inflammasome activation.[116,141] In vitro Th17 cells are poorly sensitive to regulation from Foxp3+Treg cells or soluble TGF-β,[117] suggesting complex crosstalk between Th17 and regulatory cells. Th17 cells are devoted to the recognition of fungal or extracellular bacteria, and, usually, eliminate pathogens not adequately controlled by type 1 or 2 responses.[113,142,143] When activated, Th17 cells produce IL-17A/F, IL-22, IL-6, and TNF-α. IL-17A/F trigger specific receptors (IL-17RA and IL-17RC) broadly expressed on many cell types (fibroblasts, epithelial and endothelial cells, smooth muscle cells, and eosinophils) of the inflamed environment. This favors the release of proinflammatory cytokines (TNF-α, IL-6, G-CSF, and IL-1β) and chemokines (CXCL1, CXCL8, CCL4, and others) promoting neutrophil homing and increased in situ granulopoiesis. These molecules, IL-6 in particular, would be further evaluated as potential biomarkers of the T2 low endotype of asthma. Th17 cells may move into the skin and bronchial mucosa through receptors such as CCR4 and CCR6 which recognize CCL17 and CCL20, respectively. Th17 cells are associated with several different diseases such as infections, autoimmune disorders, and tumors. In asthmatic patients, IL-17A is increased in the lung, induced sputum, bronchoalveolar lavage fluid (BALF), and serum after allergenic challenge. In addition, the severity of unspecific bronchoreactivity and obstruction correlates with IL-17A levels in BALF, whereas polymorphisms of IL-17F correlate with protection from allergic asthma.[144]

3.3 | Unconventional T cells

Among unconventional T cells, γδT cells are likely involved in some pathogenic aspects of allergic inflammation. While Vγ1+ γδT cells favor AHR by secreting type 2 cytokines, Vγ4+ γδT cells decrease AHR via the IFN-γ production.[145,146] In asthmatic patients, airway epithelial γδT cells are prevalently type 2-oriented,[147] whereas in murine models of asthma lung infiltrating γδT cells mainly express the type 3 profile of cytokine production.[146,148]

Similarly, specific invariant NKT (iNKT) cells with a type 2 profile are increased in the blood and BALF of severe asthmatic patients. They express alarmin receptors which, if triggered, favor the secretion of IL-4 and IL-13.[149-152]

Mucosal-associated invariant T cells (MAIT) are resident cells able to recognize microbial-derived riboflavin metabolites restricted to invariant MHC-class I molecule MR1. MAIT quickly responds to endogenous bacterial stimuli or environmental signals by producing type 2 and type 3 cytokines. Recent data in adult and pediatric asthmatic patients indicate that the proportion of MAIT cells in peripheral blood and sputum inversely correlates with the severity of the disease.[153-155]

3.4 | Regulatory T cells

Effector cells of allergic inflammation are under the control of regulatory cells and cytokines, contributing to the expression of different endotypes.[156-158] Memory Foxp3+Treg cells, IL-10- or IL-35-producing T regulatory (Tr1 or Tr35) cells as well as the Breg and Breg35 cells inhibit Th2- (or their subsets) and, to a minor extent, Th17-mediated responses. Similarly, regulatory molecules (IDO

and PGE2) and cytokines (TGF-β, IL-10, IL-35, IL-37, and IL-38) have a strong inhibitory activity on Th2- but mild on Th17 cells.[159,160] Increased proportions of regulatory cells and molecules have been also found after AIT or desensitization procedures to biologics in patients suffering from IgE-mediated drug adverse reactions.[161-165] The excess of regulatory mechanisms may be in turn responsible for the exhaustion and depletion of effector cells as observed in the pauci-leucocytic asthmatic phenotype.[166]

Based on the prevalence of the two major types of effector T cells, endotypes of BA have been distinguished into "type 2" (or T2 high) and "non-type 2" (or T2 low) asthma.[13,17,167,168] Type 2 high (type 3 low) endotype is commonly, but not exclusively, induced by allergic inflammation, characterized by the presence of eosinophils in the lung. However, type-2 eosinophilic asthma may also exist in the absence of allergic sensitization, such as, for example, in late-onset eosinophilic asthma.[139] The type 2 low (type 3 high) endotype includes heterogeneous conditions which share the feature to be unrelated to allergic and/or eosinophilic inflammation, as found in neutrophilic asthma and pauci-granulocytic asthma.[169] The latter types are mainly sustained by type 1 and type 3 immune responses, with high- or low neutrophils. Finally, in the mixed granulocytic endotypes of asthma (neutrophilic plus eosinophilic), both type 2 and type 3 immune responses are involved. Even though these patterns generally develop independently, they can coexist in the same patient, mainly because of the time length of the disease and the plasticity of immune cells.[170]

4 | EPITHELIAL BARRIER, ENVIRONMENTAL, AND INNATE LYMPHOID CELLS CONDITION THE TYPE AND SEVERITY OF INFLAMMATION

The analysis of candidate genes for different asthma endotypes indicates that innate immunity- and steroid resistance-associated genes are linked to the more severe disease with a parallel decrease in the expression of genes related to adaptive immunity.[171] Indeed, factors released from damaged epithelia like alarmins and damage-associated molecular patterns (DAMPs) trigger macrophages, innate lymphoid cells (ILCs), and other environmental cells and induce a T-cell independent inflammation resembling adaptive immunity.[171]

4.1 | Epithelial barrier

The airway epithelium is a physical barrier that, when activated by external agents, releases molecules active on submucosal cells.[172,173] The bronchial epithelium is exposed to a cascade of materials[174] and its dysfunction is a common feature of asthma, due to the increased exposure of tissues to inhaled allergens and air pollutants.[175-177] The high sensitivity/permeability of epithelium to environmental triggers and oxidative stress signals reduces the threshold of epithelial damage,[178] further promotes allergic sensitization, affects immunological responses, and modifies the diversity of asthmatic microbiota.[179-182]

Dysfunctional epithelium may lead to airway remodeling through a mechanism of impaired wound repair and excessive proliferation. Damaged epithelium secretes IL-13, TGF-β,[183,184] vascular endothelial growth factor, metalloproteinases, and osteopontin,[185,186] which, in turn, activate and transform the underlying mesenchymal cells into fibroblasts.[187] This epithelium-fibroblast signaling pathway, called epithelial-mesenchymal trophic unit, may explain the dissociation between inflammation and airway remodeling.[188] IL-4, IL-17A, and amphiregulin from ILCs, Trm cells, MC, and eosinophils in addition to TGF-β from macrophages and DCs induce the collagen synthesis by fibroblasts favoring the airway remodeling and basement membrane thickening.[189]

Epithelial cells may be pre-committed to T2 high (so-called E2)- or T2 low (so-called E1)-like phenotypes by different airway stimuli (allergens or pollutants, as example). The molecules differently synthesized by E2 and E1 cells affect the immune responses at the mucosal level as favoring the development and the expansion of Th2/ILC2 or Th17/ILC3 cells, respectively (Figure 4).

E2 cell activation by allergens or pathogen-associated molecular patterns (PAMPs) induces the release of pro-inflammatory molecules favoring type 2 inflammation. The production of alarmins TSLP, IL-25, IL-31, and IL-33 contributes to the local expansion of Trm2 and ILC2, while chemokines, such as CCL2, CCL5, CCL7, CCL8, CCL11, CCL24, and CCL26 favor the recruitment of eosinophils and other inflammatory cells.[189,190]

E1 epithelial cells can be triggered by several signals like smoke, pollutants, oxidants, endotoxins, drugs, hypoxia, DAMPs and PAMPs, fungi, and viruses. After that, they release chemokines (CXCL2, CXCL8, CCL17, and CCL20) and cytokines (IL-1β, IL-12, and IL-23) recruiting and amplifying DCs, ILC3, Th17, Th1, and unconventional T cells (γδT, MAIT, iNKT with type 3 profiles). Some cytokines with antiviral activity (IFN-γ, IL-2, IL-17A/F, TNF-α, IL-12, IL-18, and IL-36) induce resistance in not-infected phagocytic cells. Neutrophils are recruited by CXCL8 produced by the majority of IL-17-triggered resident cells, and when activated by IL-12 and IFN-γ, can release pro-inflammatory cytokines contributing to infection containment, hyperthermia, and recruitment of further phagocytic cells.[190] The history of allergen- or pathogen-derived stimuli can leave some kind of memory in neutrophils, now known as "trained immunity".[191,192]

In addition to E1- or E2-priming signals from epithelial cells, other mechanisms may contribute to the local shift toward a type 3 (Th17/Tc17/ILC3) response from an original type 2-oriented (Th2/Tc2/ILC2) inflammation of the lung. As an example, the hyperproduction of PGE2 inhibits type 2-response while improving type 3.[192] Secondly, the airway microbiota shifts eosinophilic vs neutrophilic endotype.[193,194] Finally, the excess of eosinophils induces Charcot-Leyden crystals (formed by galectin 10) able to activate inflammasome whose cytokines amplify the type 3- at the expense of the type 2 response.[195]

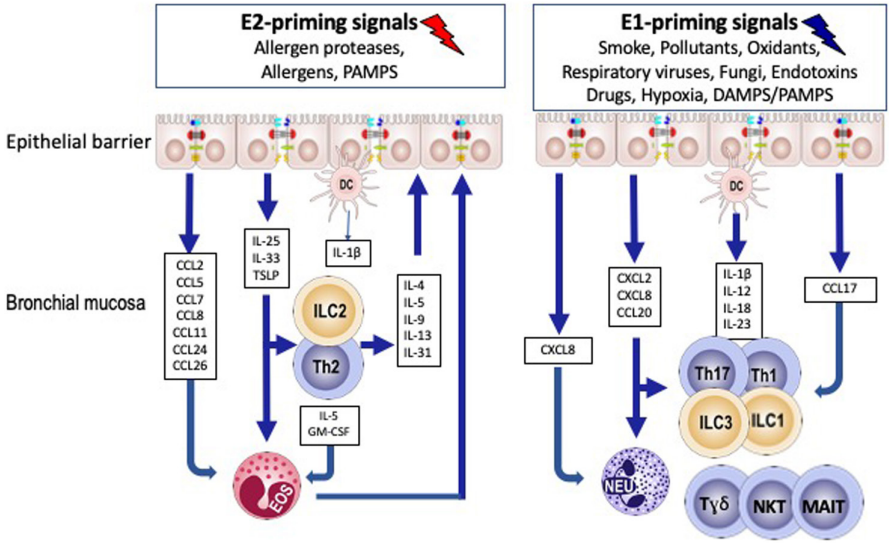

FIGURE 4 E2- and E1-mediated epithelium signals conditioning type 2 or type 3 tissue immune responses in respiratory allergy. Epithelial cells are primed by two distinct groups of airway stimuli able to induce the development and the maintenance of T2 high- or T2 low-phenotypes. A cascade of two different sets of molecules (including cytokines, chemokines, other growth factors, defensins, and others) is synthesized by E2 or E1 cells with the effect to influence mucosal immune cells and direct toward type 2 or type 3 responses, respectively. DAMPS, damage-associated molecular patterns; EOS, eosinophils; ILCs, innate lymphoid cells; MAIT, Mucosal-associated T cells; NEU, neutrophils; NKT, Natural Killer T cells; PAMPS, pathogen-associated molecular patterns; Th, T helper cells; TSLP, thymic stromal lymphopoietin

4.2 | Innate lymphoid cells

ILCs are newly described, predominantly hematopoietic, tissue-resident effector cells. They are involved in lymphoid tissue formation, tissue remodeling after damage, homeostasis of stromal cells, and protection from pathogens.[196] Based on the expression of their specific transcription factors, surface markers, and cytokine secretion, helper ILCs are classified into four groups (ILC1, ILC2, ILC3, and lymphoid tissue-inducer cells -LTi) mirroring the functional profiles of adaptive CD4+ Th1/Th2/Th17 cells. ILC2 and ILC3 are involved in asthma pathogenesis, ILC2 favoring eosinophil and ILC3 neutrophilic prevalence[197,198] (Figure 3).

Alarmins play a pivotal role in ILC2 activation starting allergic inflammation.[198,199] Activated ILC2 express GATA3/cMaf and produce IL-5 and IL-13 with low IL-4. However, atopic patients display circulating ILC2 producing a higher level of IL-4 and IL-13 than healthy donors.[200] ILC2 also releases amphiregulin, a member of the EGF family, favoring fibroblasts activation and airway remodeling.[201] When activated, human ILC2 expresses CD154 for a long time and secrete IL-4/IL-13 favoring polyclonal IgE production by B cells.[200] A high proportion of ILC2 has been found in tissues of patients with all atopic disorders.[202-205] The number of ILC2 is two logs higher in nasal polyps than in the bloodstream.[200] Increased proportions of ILC2 have been detected in blood and sputum of patients with severe- compared to mild asthma.[206-208] IL-5/IL-13-producing ILC2 are expanded in severe eosinophilic asthma and following allergen challenge,[209] suggesting bidirectional crosstalk between ILC2 and other cells as DC and Th cells, which amplify type 2 response.[210-212] Lung ILC2, which expresses the IL-4Rα chain, can be triggered by Th2-derived IL-4/IL-13 followed by the activation of the STAT6 signaling pathway.[213-216] IL-4 secreted by basophils may also induce the recruitment/proliferation of ILC2 in murine inflamed tissues.[215,216] Notably, not controlled-asthma is associated with higher ILC2 proportions than well-controlled disease, suggesting a relationship between ILC2 and disease severity.[217,218]

There are limited reports on ILC3 and LTi cells in asthma so far. The ILC3-mediated production of IL-17A may contribute to explain some different alterations: (i) IL-17-associated severe asthma, (ii) neutrophilic asthma, and (iii) asthma exacerbations and airway remodeling mainly due to neutrophil infiltration.[219] Although fewer in number, ILC3 are high producers of type 3 cytokines (IL-17A, IL-22, and GM-CSF).[220] Furthermore, the development of AHR and inflammasome activation in obesity-related asthma in mice is related to IL-17A-producing ILC3.[221] A high proportion of IL-17A$^+$ILC3 cells has been found in the sputum and BALF of severe asthma.[221,222] Along with this, ILC3 gene signatures are enriched in total RNA from patients with adult-onset non-eosinophilic asthma.[223]

In conclusion, ILCs are relevant partners in an inflammatory environment that promotes chronic respiratory diseases, potentiating both type 2 and type 3 responses (Figure 3).

Figure 5 details the phenotype and function of the different subsets of innate and adaptive effector and regulatory cells contributing to the T2 high- and T2 low- endotypes of asthma and allergic disorders.

4.3 | Other environmental effector cells

Resident cells are immune cells with a circulating counterpart (such as Trm, MAIT, γδT, and iNKT cells) with tissue tropism, whereas

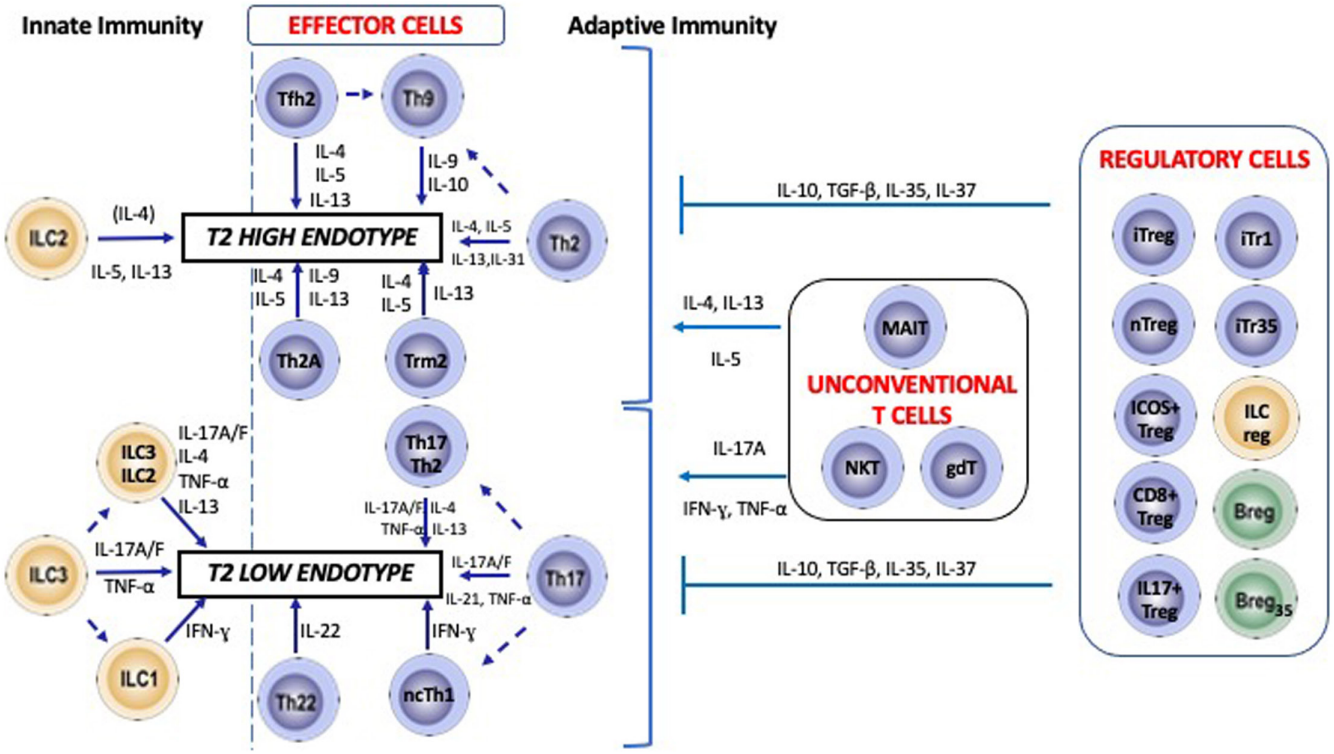

FIGURE 5 Effector and regulatory ILCs and T cell subsets involved in allergic inflammation. The figure synthesizes the complex network of cells and molecules conditioning the development of T2-high and T2-low endotypes. Allergic inflammation is essentially due to the activity of innate and adaptive effector cells and of unconventional T cells (such as MAIT, NKT, and γδT cells) counterbalanced by a large panel of lymphocytes with regulatory function (iTreg, nTreg, ICOS+Treg, CD8+Treg, IL-17+Treg, iTr1, iTr35, Breg, Breg35, and ILC-reg) producing suppressive cytokines. Breg, B regulatory cells; Breg35, IL-35-producing Breg cells; ILC-reg, regulatory ILCs; iTr1, inducible T regulatory 1 cells; iTr35, IL-35-producing inducible T regulatory cells; iTreg, inducible regulatory T cells; MAIT, mucosal-associated invariant T cells; ncTh1, non-conventional Th1 cells; NKT, natural killer T cells; nTreg, natural regulatory T cells; Tfh, follicular helper T cells; Th, T helper cells; Trm, resident memory T cells

environmental cells are tissue non-immune cells such as epithelial, endothelial, smooth muscle and muciparous cells, fibroblasts, and others. The environmental compartment is a privileged target of type 2 or type 3 cytokines produced by Th- and ILC subsets, and in turn, stimulates the release of pro-inflammatory cytokines and chemokines. For instance, smooth muscle cell hyperplasia and hypertrophy, described in severe asthma, are due to the chronic stimulation exerted by LTs, PGD2 TGF-β1, IL-1, IL-6, CCL2, and CCL3 secreted from environmental cells.[133,224]

Goblet cells hyperplasia and mucus hypersecretion induced by MUC5AC and MUC5B gene activation are the effects of this chronic cascade of stimuli.[225] IL-13, which is the major inducer of mucus production, maintains inflammation also stimulating exhaled nitric oxide (FeNO) release from epithelial cells.[226]

Tissue eosinophils establish a vicious circle directly or indirectly enhancing type 2 responses through cytokines, chemokines, and the release of granule proteins. For instance, eosinophil-derived neurotoxin promotes DC migration/activation which further amplifies memory of Th2 cells.[227] In parallel, eosinophils damage the airway mucosa through the release of basic proteins, oxygen free radicals, and lipid mediators. Chemokines like CCL2, CCL5, CCL7, CCL11, and CCL26 produced by the damaged epithelium recruit eosinophils through CCR3, a receptor also shared by basophils and Th2 cells.[228] The activated epithelium, through the overproduction of IL-33 and TSLP, favors the formation of eosinophil extracellular traps which may indirectly activate lung ILC2[227] and whose number is high in severe inflammation.[227-231] A similar vicious circle is maintained by neutrophils in T2 low asthma where they release proteases, contribute to oxidative stress, and release neutrophil extracellular traps (NETs) which, in turn, induce local inflammasome activation, Th17/ILC3 expansion, and further promote neutrophil recruitment.[232]

5 | THE FLEXIBILITY OF TISSUE EFFECTOR CELLS AFFECTS THE TYPES OF ALLERGIC INFLAMMATION

Thirty years ago we showed for the first time that not only naïve but also fully polarized memory T cells in humans display high flexibility in response to external signals.[233] Based on a huge of confirming results,[234-236] we now know that Th2 or Th17 cells cannot be considered terminal lineages but rather flexible cells with a high degree of plasticity (Figure 6). For instance, molecules such as IL-12 can epigenetically modulate both Th2 and Th17 responses toward

a pro-Th1 direction, even though the progeny can maintain some features of the original cells.[116,117,237,238,239,240] Th17-derived Th1 cells have been defined as "non-classical Th1" or, alternatively, "Th1 stars." These cells were found in the BALF of children with severe asthma and the Th1 signature was associated with both the presence of IFN-γ+IL-17+ and IFN-γ−IL-17+ T cells and high serum levels of IL-23, this latter cytokine being crucial for the differentiation and proliferation of Th17 cells.[241] Th1 cells may seldom associate with a T2 high endotype upon treatment with biologicals shifting type 2- into type 1 profile.[242] Importantly IL-4 itself can induce in vitro the expression of type 2 cytokines by clonal Th17 cells.[243] Such a new subset of memory Th2/Th17 effector cells exerts a strong pathogenic effect on the lung by promoting the exacerbation of chronic asthma in mouse models.[244] Increased dual memory Th2/Th17 cells have been found in the periphery and in the BALF of a proportion of severe asthmatic patients.[245]

Moreover, in the presence of TGF-β, Th2 cells, can lose their ability to produce IL-4 or IL-5 but maintain IL-9 and IL-10, giving rise to new functional Th9 cells exhibiting strong pro-inflammatory properties.[246] In addition, IL-9 itself is able to induce the synthesis of IL-17A by T and non-T cells.[247] Some reports indicate that both Th9 and Th17 cells play an essential role in the chronicity of IgE- or non-IgE-mediated asthma and in tissue remodeling. In particular, Th17 cells are prone to expand into chronically inflamed tissue, because they do not require IL-2 for their differentiation and are poorly affected by down-regulating signals provided by Treg cells, regulatory cytokines (TGF-β), and membrane PD-L1.[248] Further, both Th2/Th17 and Th9 cells would be resistant to steroid effects because of the up-regulation of the transcription factor MEK1, thus resulting as more pathogenic.[245,249]

Finally, the presence of IL-12 plus IL-27 and the interaction Notch1L-Notch1 makes the IL-10 gene suitable for activation in all polarized Th subsets.[250] Indeed, IL-10-producing Th1 cells are frequently observed upon antigen hyperstimulation which is responsible for the exhaustion of T cell functions, as it can be observed in AIT, in chronic administration of biologics, and in cancer[251-255] (Figure 6).

The same plasticity of memory Th cells is also found in other tissue-resident cells such as Trm-, Tfh-, γδT, NKT, MAIT, and Treg cells.[256,257] ILCs are highly plastic upon environmental signals, and this could be likely due to the abundance of cytokine receptors on their surface able to mediate switching effects from each other ILC subset.[258,259] Actually, steroid-resistant ILC3/ILC2 dual cells, as well as IL-10-producing ILC2 (so-called ILC2-reg) would play a role in steroid-resistant asthma and in AIT.[163,260,261]

6 | PLASTICITY OF EFFECTOR CELLS AND ENVIRONMENTAL SIGNALS AFFECT THE DIFFERENT ENDOTYPES AND THE RELATED ASTHMA PHENOTYPES

The type and strength of signals from inflamed tissue, which may vary over time, are able to activate innate and adaptive cells, thus favoring their reciprocal cross-talk and plasticity.[262-264] The pathogenic effector cells of allergic inflammation are highly flexible in response to molecules from the inflamed tissue and may shift to more heterogeneous and aggressive profiles. Taking into account both the flexibility of effector cells and the chronicity (usually years) of the airway inflammation, a crucial question is whether they both are responsible for the different phenotypes described in allergic disorders.

As discussed so far, at least three main variables may condition the immunological scenarios of chronic inflammation in asthma: (i) signals deriving from the mucosal barrier and submucosal DCs; (ii) strength of regulatory signals exerted by cells and molecules, and (iii) activity of signals from environmental non-lymphoid cells. All these variables may be responsible for at least four scenarios characterizing asthma endotypes as depicted in Figure 7.

When the mucosal barrier and the related DCs are exclusively stimulated by E2-priming signals, and intact regulatory mechanisms with poor or no tissue cytokines are present, effector cells will be oriented towards the type 2 response as seen in the T2 high (type

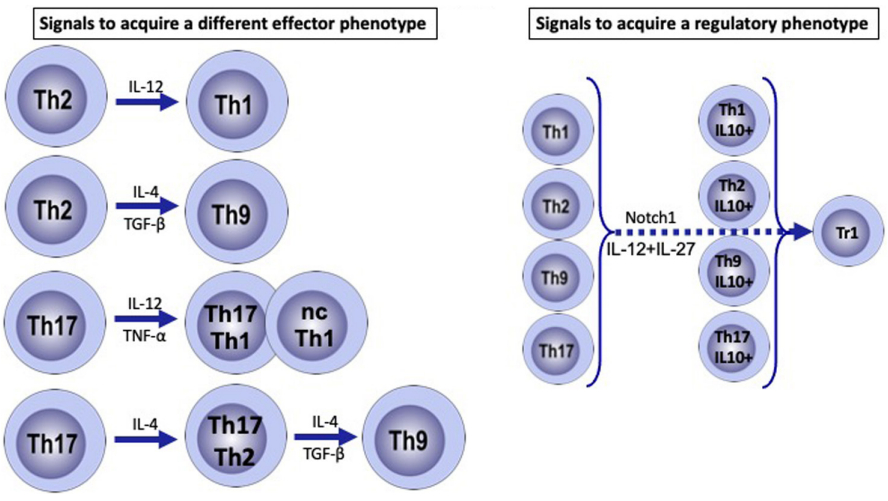

FIGURE 6 In vitro plasticity of polarized mature Th cells upon signals from inflamed lung tissue. The cytokines prevalently produced by APC (with the possible contribution of contact signals) condition the final phenotype of effector or regulatory T cells. Terminally differentiated T cells, as well as ILCs, are particularly susceptible to such external signals which can shift phenotype and function of the original cells toward new and unconventional cellular profiles. iTr1, inducible T regulatory 1 cells; ncTh1, nonconventional Th1 cells; Th, T helper cells

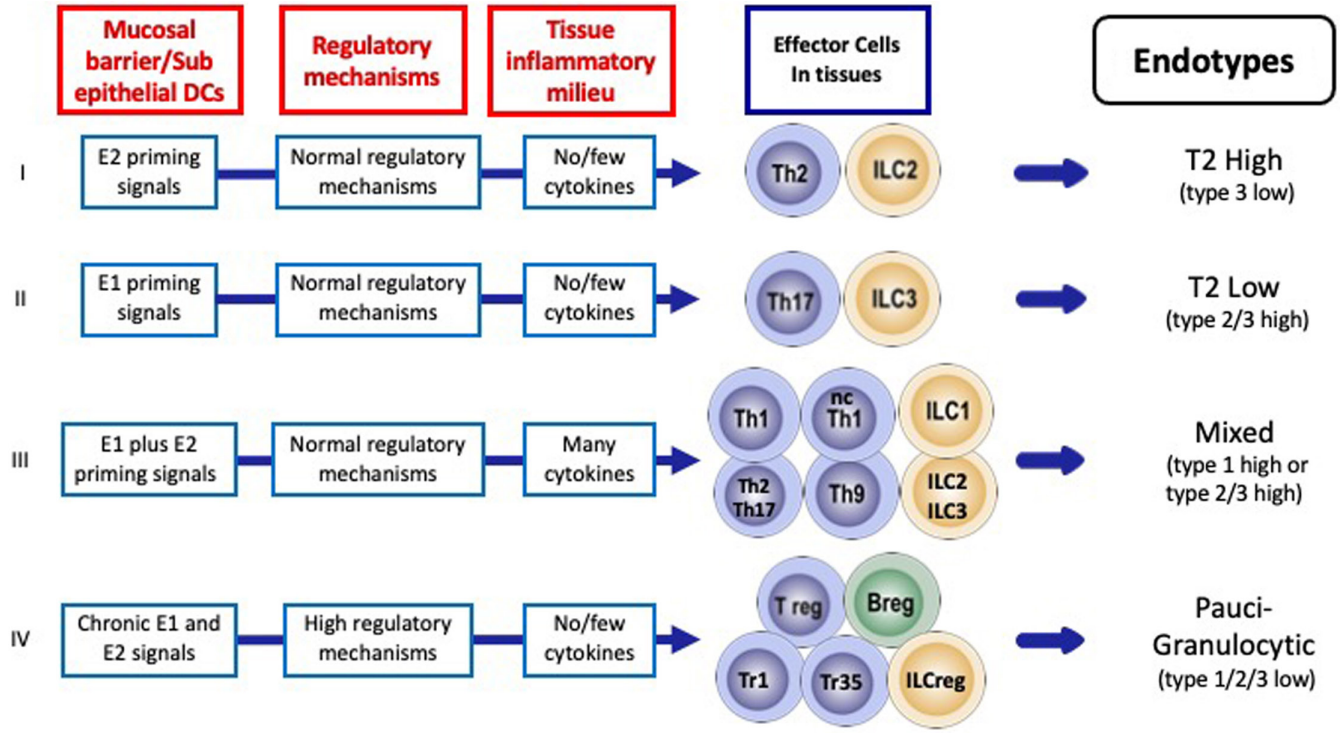

FIGURE 7 Mechanisms involved in the modulation of resident effector ILCs and T cells into the main functional profiles characterizing asthma endotypes. At least three variables may affect the immunological responses in asthma chronic inflammation: (A) signals deriving from the mucosal barrier and submucosal DCs, (B) strength of regulatory signals exerted by cells and molecules, and (C) effects of signals from non-lymphoid cell compartments. These variables, differently associated, may generate at least four scenarios of inflammation defining asthma endotypes: T2 high (or type 3 low). T2-low (or type 3 high), mixed (type 1, 2, 3 high), and pauci-granulocytic (type 1, 2, 3 low). Therapeutic regimens or intercurrent environment modifications may favor reciprocal interchanges in endotypes. Moreover, a particular endotype may remain unaltered since the beginning of the disease or may progress toward differently oriented responses on the influence of local signals. Breg, B regulatory cells; ILC-reg, regulatory ILCs; iTr1, inducible T regulatory 1 cells; iTr35, IL-35-producing inducible T regulatory cells; ncTh1, non-conventional Th1 cells; Th, T helper cells; Treg, regulatory T cells

3 low) endotype. Vice versa but similarly, when the mucosal barrier and the related APCs are exclusively stimulated by E1-priming molecules and normal regulatory mechanisms and few or no environmental cytokines are present, the effector cells will be oriented towards the type 3 response mirrored by the T2 low (type 3 high) endotype. As a fact, such type 2- and type 3-oriented profiles are really rare, especially in long-lasting diseases. Actually, the so-called mixed endotype (type 2 and 3 high) is far more common and established when mixed E1- plus E2-priming signals associate with intact regulatory mechanisms and high cytokine production from the microenvironment, thus conditioning the presence of several different effector cells: Th17/Th2, not classical Th1, Th9, ILC1, ILC2/3, and others. Finally, when ongoing E1- and E2-signals are followed by overactivation and exhaustion of most of the effector cells and regulatory mechanisms are efficiently active, effector cells are replaced by few regulatory cells (i.e., iTreg, Breg, Tr1, Tr35, and ILCreg) such as in the pauci-granulocytic (types 2/3 low) endotype (Figure 7). These four endotypes reflect the clinical phenotypes of inflammatory airway diseases proposed by Barnes PJ et al[11]; within each endotype, the different proportions of effector cells may condition further subclinical patterns[18] (Figure 3). In the T2-high endotype, for instance, the prevalence of Th2 on ILC2 cells features a distinct pattern with high IgE levels, pluri-sensitivities, few eosinophils in the blood and sputum, mild severity observed in the "early onset allergic asthma." Vice versa, when ILC2 predominates on Th2 cells, high numbers of eosinophils in the blood/sputum, normal IgE levels, and high severity characterize the different types of "adult-onset eosinophilic asthma".[265-268] The pure T2-low endotype is always counterbalanced by a high number of neutrophils in BALF and sputum, together with normal eosinophil counts, normal to low IgE levels, and high clinical severity as seen in "non-eosinophilic neutrophilic asthma", "obesity-associated asthma," or "late onset non-allergic asthma of the elderly".[269,270] Furthermore, in the mixed endotype a spectrum of different phenotypes can be hypothesized, as based on the expansion of a defined subset of effector cells with respect to the others. The type 1 predominance, involving Th1 cells or non-classic Th17-derived Th1 lymphocytes, Tc1 or ILC1 cells, is observed in "virus-induced asthma" and in "smoking/pollutants associated asthma.[271] On the other hand, unusual effectors such as Th9, dual Th2/Th17 or ILC2/3 cells associate with "severe steroid-resistant asthma." Finally, the pauci-granulocytic endotype may be frequently coupled with some "children's idiopathic asthma," "brittle asthma," "exercise-mediated asthma," and other rare phenotypes[266] (Figure 8).

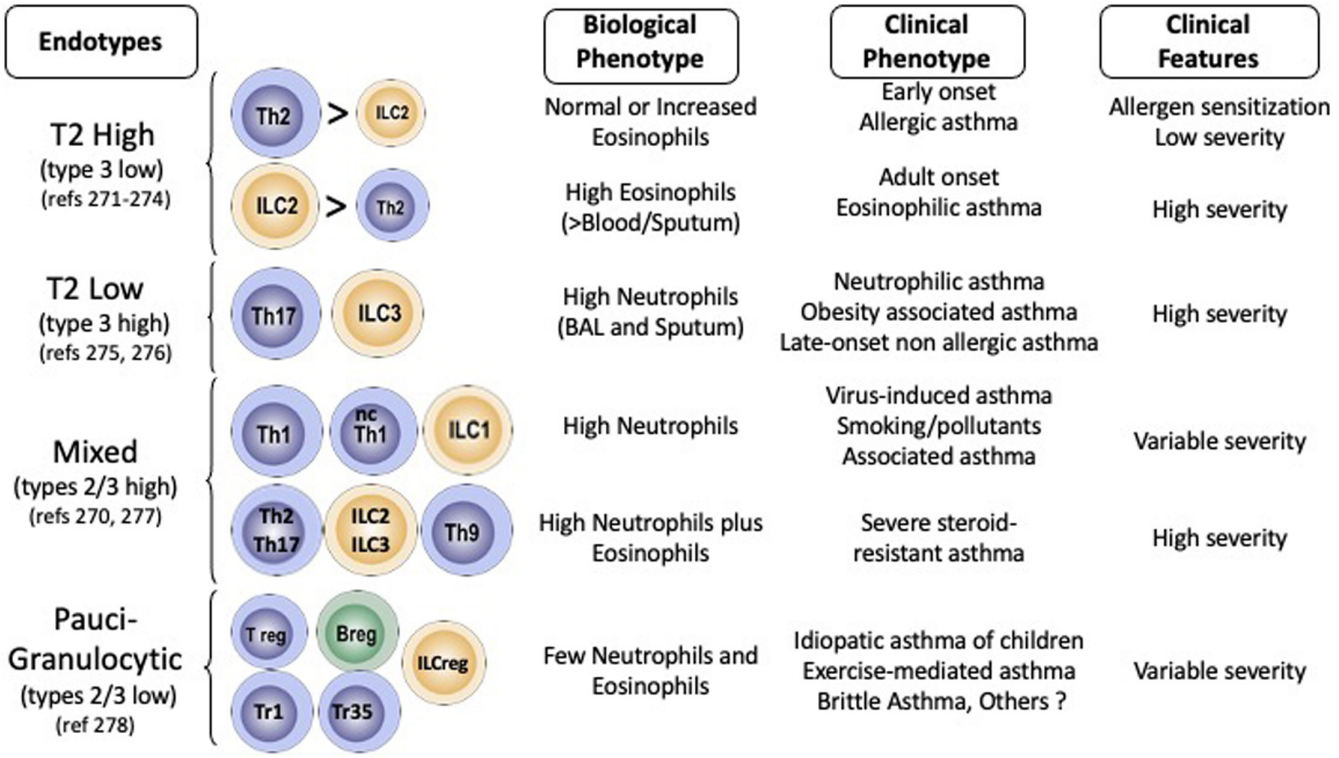

FIGURE 8 The tight association of each pathogenic endotype/sub-endotype with a defined phenotype of asthma. The four endotypes reported in Figure 7 reflect the clinical phenotypes of inflammatory airway diseases as proposed by Barnes et al.[11] Inside each endotype, the different proportions of effector cells may result in further subclinical patterns (as for instance, in the T2-high endotype). Each endotype (or sub-endotype) is linked to eosinophil or neutrophil prevalence in BALF or sputum, the degree of disease severity, or additional clinical features. Thus, all the conceivable endotypes or sub-endotypes can be related to the majority of the known asthma phenotypes. BALF, bronchoalveolar lavage fluid; Breg, B regulatory cells; ILC-reg, regulatory ILCs; iTr1, inducible T regulatory 1 cells; iTr35, IL-35-producing inducible T regulatory cells; ncTh1, non-conventional Th1 cells; Th, T helper cells; Treg, regulatory T cells

It is indeed possible that, as a long-lasting disease, therapeutic regimens themselves or intercurrent modified environment conditions might favor reciprocal interchanges in endotypes. And, finally, it is questionable whether a particular endotype is present since the beginning of the disease or, instead, is progressively and differently oriented by local signals. Both scenarios are equally probable because of the high plasticity of effector cells.

Importantly, several recent studies, clearly indicate that asthma endotypes/sub-endotypes are also shared by other allergic diseases.[22,272,273,274] T2-high inflammation is a major feature of AR and CRSwNP. Penetration of allergens through the nasal mucosa triggers a T2-dominant inflammatory cascade with eosinophilia and IgE production.[275,276] A T2-low inflammation, mainly characterized by the presence of neutrophils in the nasal mucosa[277-279] can be triggered by infections or chronic irritation; these latter events can dysregulate innate immunity, activate the IL-17 pathway, and recruit neutrophils,[280-285] Notably, CRSwNP are usually phenotyped as eosinophilic- and CRSsNP as neutrophilic disorders, respectively.[286] On the basis of cytokines, eosinophils, and IgE levels, CRS can be endotyped as non-type T2 (or T2-low), moderate T2 (mixed), and severe T2 (T2-high).[273,287,288] According to geographical location (so-called "region-types"), the eosinophil-dominant T2-high endotype is more frequent in Western-countries whereas the neutrophilic endotype prevails in Asians. CRSsNP usually recognizes non-eosinophilic mechanisms with prevalent ILC3/Th17 cells.[289,290] Notably, the response to fungi and extracellular bacteria infections, frequently associated with CRSsNP, is a prerogative of Th17 cells.[291]

All the same, AD is characterized by a highly heterogenous endotype repertoire with the activation of the diverse T cell phenotypes (Th1, Th2, Th17, and/or Th22 cells) together with the compromise of the epidermal barrier and lipid and tight junction abnormalities.[292,293] A T2-high vs a T2-low inflammation was suggested for AD endotyping,[21,22] even though several other sub-endotypes encompass children vs adults, ethnic origin and region-types, disease stage (chronic vs acute), IgE levels, and filaggrin expression have been proposed.[272]

Even though more heterogeneous, some FA can display endotypes similarly to other allergic disorders.[294] Four endotypes are described: (i) Alpha-gal- and red meat allergies which display a classical T2-high profile.[295,296] (ii) Oral allergy syndrome due to cross-reactivity between some foods and pollens exerting a T2-high response.[297] (iii) Food protein-induced gastrointestinal endotype (as in food protein-induced enterocolitis syndrome)[298,299] related to a type 3/type 1 (T2-low) immune response.[300] (iv) EoE with a typical eosinophilic endotype,[301] although displaying phenotypic and

endotypic heterogeneity.[302-305] As a fact, a T2-low endotype also exists[306] in a limited number of EoE patients sharing symptoms with the classical disease, strong familial aggregation but the absence of eosinophilic infiltration.[307,308] Based on the prevalent T2-high/T2-low inflammation, Shoda and coworkers[309] have proposed three potential endotypes of EoE.[310]

The features of endotypes and phenotypes in AR, CRS, AD, FA, and EoE are summarized in Table 5.

Based on the previous immunopathologic view of allergic inflammation, the next challenges will be the suitable biomarkers and novel therapeutic targets for each endotype.

Several biomarkers have been studied in allergic diseases, but only a few are readily available for clinical use in T2-high profile asthma and indicated to choose the most suitable therapy, as circulating/sputum/BALF eosinophils, FeNO, serum IgE, and periostin levels. Following several posthoc analyses of the clinical trials of biologicals targeting type 2 inflammation,[311-314] the European Academy of Allergy and Clinical Immunology (EAACI) recently reviewed all the currently available biologic therapies together with the required biomarkers to better identify the target patient.[315]

For instance, blood eosinophils count is a reliable marker of response to the anti-IL-4R α-chain monoclonal antibody dupilumab

TABLE 5 Endotypes and related phenotypes of allergic diseases

			Tissue immune response				
Allergic disease	**Phenotype**	**Endotype**	**Type-1**	**Type-2**	**Type-3**	**Th22**	**References**
Allergic rhinitis	Allergic/local rhinitis	T2	–	++++	–	NA	275-285
	Infectious rhinitis	Non-T2	++	–	+++	NA	
	Idiopathic rhinitis	Non-T2	–	–	–	NA	
	Other rhinites	Mixed	++	+++	+++	NA	
Chronic rhino-sinusitis	CRSwNP	T2	+/–	+++	+/–	NA	273,286,287,288
	CRSsNP	Non-T2	++	+/–	+++	NA	
	CRSw/sNP	Mixed	++	+++	+++	NA	
	CRSwNP (North America)	T2	+	++++	+	NA	289-291
	CRSwNP (Europe)	T2	+	++++	+/–	NA	
	CRSwNP (Asian/China)	Mixed	++	++	++	NA	
	CRSwNP (Australia)	Mixed	+	+++	++	NA	
Atopic dermatitis	Extrinsic	T2	–	+++	-	+++	21,22,272,292
	Intrinsic	Non-T2	++	-	+++	–	
	Early phase	T2	–	++++	–	–	
	Late phase	Non-T2	++	++	++	++	
	AD in infancy	Mixed	–	+++	+++	++	
	AD in elderly	Non-T2	–	–	+++	+++	
	Extrinsic AD in Europeans	T2	+	+++	+	+++	
	Extrinsic AD in Asians	Mixed	+/–	+++	+++	++++	
	Extrinsic AD in Afro-Americans	T2	–	+++	–	++	
Food allergy	α-Gal allergy	T2	–	+++	–	NA	294-301
	Food-pollen and oral allergy	T2	–	+++	–	NA	
	Food protein-induced enterocolitis	Non-T2	++	+/–	+++	NA	
	Other food allergies	Mixed	++	+++	+++	NA	
Eosinophilic esophagitis	EoE 1 (atopy, steroid sensitivity, and normal endoscopy)	T2	–	+++	+/–	NA	302-310
	EoE2 (pediatric onset, steroid-refractory, and inflammatory)	Mixed	+	++	++	NA	
	EoE3 (non-atopy, adult onset, and fibrostenosis)	Non-T2	++	–	+++	NA	

Abbreviation: NA, not applicable.

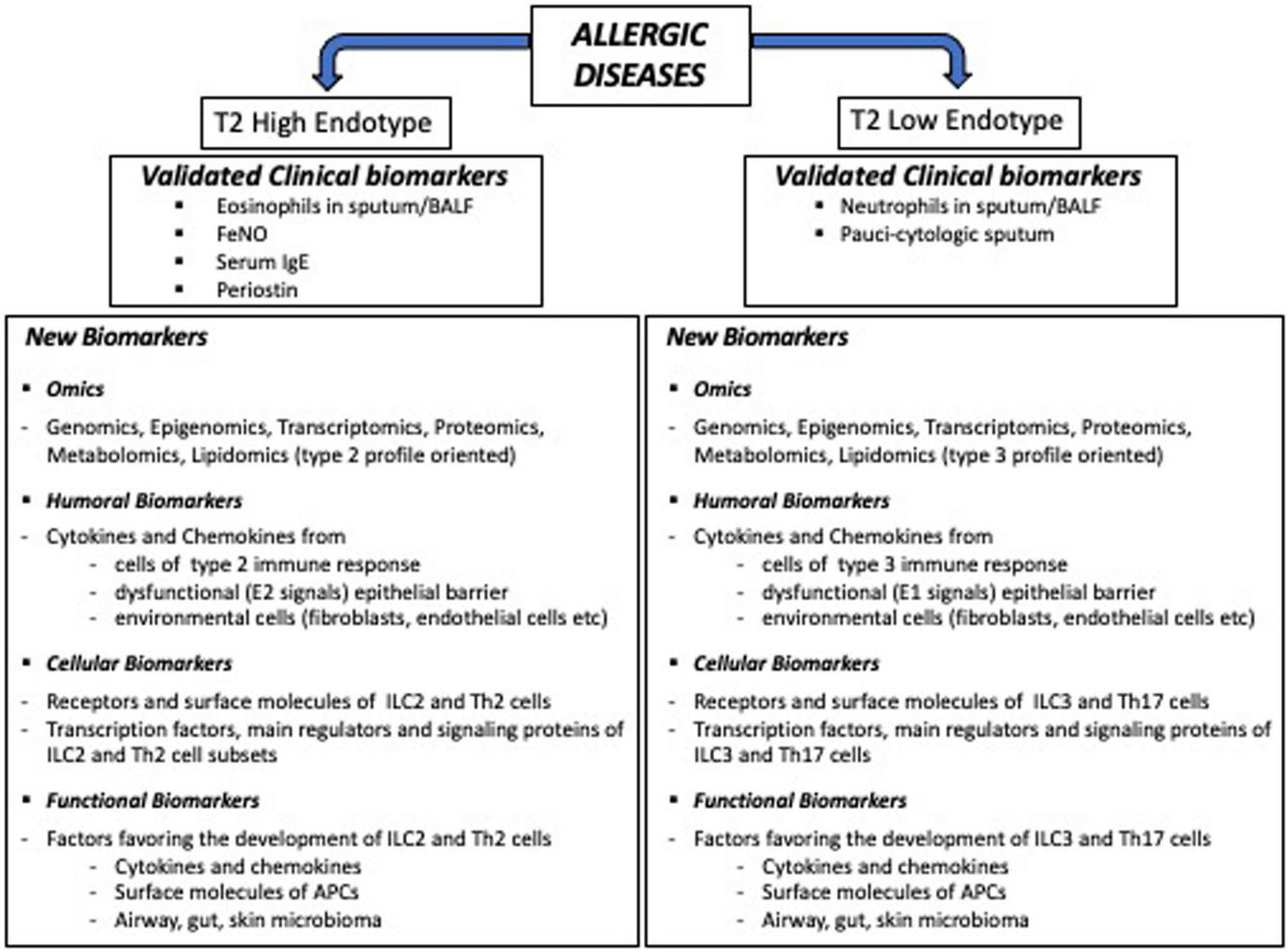

FIGURE 9 New potential biomarkers of asthma and allergic diseases based on the pathogenic mechanisms underlying T2-high and T2-low endotypes

in patients with severe eosinophilic- or corticosteroid-dependent asthma even though a good response to the drug may also be expected in cases of low circulating eosinophil counts and high FeNO levels. Blood eosinophil counts ≥150/μl was recommended for anti-IL-5 therapy with a good likelihood of response. Even if eosinophil counts ≥260/μl and FeNO levels ≥19.5 ppb were suggested for a good response, the anti-IgE therapy is not prescribed according to the levels of eosinophils and FeNO.[316] Anyway, currently available biomarkers are of limited value for true precision medicine. Indeed, the T2-related biomarkers are commonly present in the majority of the previously described phenotypes of asthma,[10,271,317] and thus, it is urgent to identify novel biomarkers inside the dominant inflammatory mediators driving disease pathogenesis. They must be easily detectable molecules related to the different effector cells which characterize the described endotypes/sub-endotypes. They must be sought among cytokines and chemokines, receptors, non-signaling surface molecules, transcription factors, miRNAs, or signaling factors. Soluble and surface molecules favoring the plasticity of ILC or T cells and epithelium- or monocyte/macrophages-derived cytokines, costimulatory proteins, and glycans might be additional factors useful to be evaluated. Furthermore, exosomes derived from activated ILC or T cell subsets should be studied as possibly carrying molecules and surface proteins favoring the plasticity of effector cells. EAACI position paper emphasizes the opportunity of a "multi-omic" (genomics, epigenomics, transcriptomics, proteomics, metabolomics, and lipidomics) stratification as a tool to overcome asthma complexity of adequate biomarker identification[315] (Figure 9).

As novel therapeutic targets, some molecules which are crucial for the effector cells of the previously defined endotypes may be suitable, exemplified by omics, activation signals, shifting molecules, surface or cytosolic receptors, and signaling molecules. In this context, caution is needed and some immunological basic notions carefully revised: (i) the redundancy and pleiotropism of some cytokines, (ii) the possible opposite effects elicited by signaling receptors shared by different cells, (iii) the decoy activity of some receptors, and (iv) the pathways redirecting to other (and opposite) pathogenic arms of inflammation, like from the type 2 to the type 3 response.

The most effective to quickly and adequately define new predictive biomarkers and therapeutic targets is the processing of big data coming from International Registries for mild as well as severe asthma.

BOX 1 Conclusive bullet points

- In allergic inflammation, the pathogenic effector cells of innate and adaptive immunity exhibit type-2 or type-3 profiles.
- External stimuli activate bronchial epithelium which in turn releases molecules with high impact on the function of tissue effector cells.
- The plasticity of resident effector cells in response to environmental signals is the prerequisite to explain the multiple endotypes of asthma and other allergic diseases.
- Variability in the epithelial response, tissue regulatory mechanisms, and activity of microenvironmental cells allows delineating four different pathogenic scenarios as responsible for the principal endotypes of bronchial asthma.
- Different types of the immune response characterize each one of these endotypes which, in turn, corresponds to an individual phenotype of asthma.
- This unifying view of the pathogenesis of bronchial asthma may also be extended to other allergic disorders displaying similar endotypes.
- The availability of highly effective personalized therapy for bronchial asthma and other allergic diseases urgently requires to define specific biomarkers for each endotype.
- Such a view overcomes the concept of fixed endotypes to move to the "patient endotype."

7 | CONCLUSIONS

New pathogenic mechanisms suggest that allergic inflammation is due to complex interactions involving effector cells with type-2 and type-3 profiles. A huge amount of different stimuli activate the mucosal epithelium which, in turn, releases molecules impacting the function of the resident immune and environmental cells. These variable conditions modify tissue innate and adaptive cells, providing selective homing of eosinophils or neutrophils. The high plasticity of resident ILCs and T cells is the prerequisite to fully explain the multiple endotypes (or sub-endotypes) of asthma. The notion that effector cells are flexible and easily affected by external signals allowed the broad use of biologics interfering with pathogenic mechanisms of inflammation. The variable conditions with regards to the type of epithelial response, the tissue regulatory mechanisms, and the function of environmental cells allow hypothesizing different pathogenic scenarios for the principal endotypes. The immune response as the base of each endotype corresponds to a precise phenotype of asthma. This unifying integrated pathogenic view may be also true for other allergic disorders displaying similar endotypes. The next challenges will consist of the definition of specific biomarker(s) for each endotype to reach an early diagnosis and establish the best target(s) for the most effective personalized therapy (Box 1). In conclusion, our proposal wants to overcome the concept of fixed endotypes to move to a "patient endotype," which takes into account also a series of clinical variables, including the history of the disease, the number of exacerbations, concomitant infections, and previous/present therapeutic regimens.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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