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The Concept of Pathogenic T_H2 Cells: Collegium Internationale Allergologicum Update 2021

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T helper-cell subsets · Pathogenic T_H2 cells · T_H2A cells · Allergic inflammation · Type 2 immunity

Abstract
T helper (T_H) cells have evolved into distinct subsets that mediate specific immune responses to protect the host against a myriad of infectious and noninfectious challenges. However, if dysregulated, T_H-cell subsets can cause inflammatory disease. Emerging evidence now suggests that human allergic disease is caused by a distinct subpopulation of pathogenic T_H2 cells. Pathogenic T_H2 cells from different type-2-driven diseases share a core phenotype and show overlapping functional attributes. The unique differentiation requirements, activating signals, and metabolic characteristics of pathogenic T_H2 cells are just being discovered. A better knowledge of this particular T_H2 cell population will enable the specific targeting of disease-driving pathways in allergy. In this review, we introduce a rational for classifying T_H cells into distinct subsets, discuss the current knowledge on pathogenic T_H2 cells, and summarize their involvement in allergic diseases.

Introduction

In the body of adult humans, memory T cells are the most abundant lymphocyte population [1]. Among them, $CD4^+$ memory T helper (T_H) cells make up the largest fraction, acting as crucial mediators of the immune system. Once activated by a cognate antigen, they migrate to follicles to provide help B cells and peripheral organs to fight infections by initiating the appropriate type of effector cell functions [2]. Confronted with a myriad of different infectious challenges, T_H cells have evolved into specialized subsets, characterized by distinct migratory properties, proliferative capacities, cytokine profiles, and transcription factors. These specialized T_H cell subsets exert distinct and crucial functions in health and disease. Our ever-growing understanding of human T_H cell biology has significantly contributed to the development of effective therapies for inflammatory and neoplastic diseases [3, 4].

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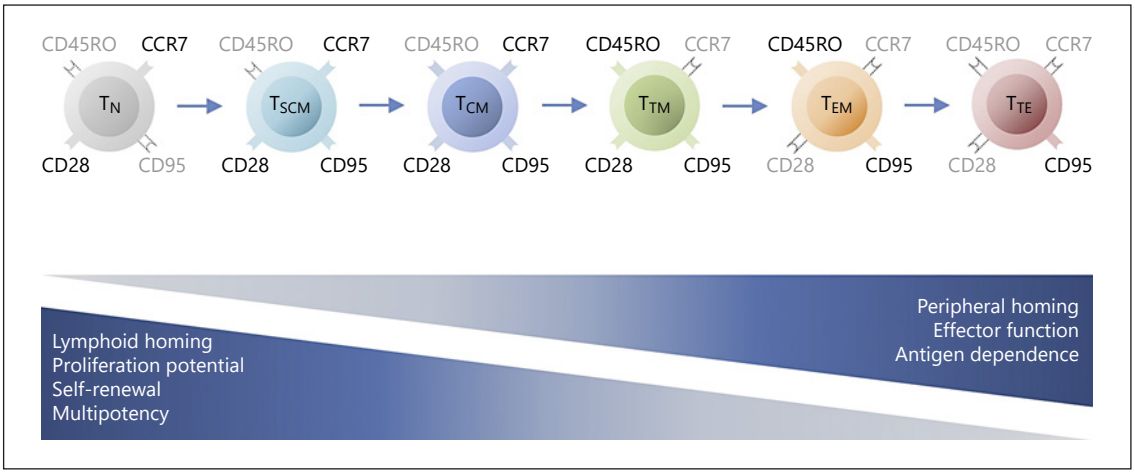

Fig. 1. Classification of T cells based on differentiation. A progressive loss of T cell stemness occurs during differentiation. The differentiation process starts from T_N, with maximal potential for proliferation, self-renewal, differentiation, and lymphoid homing, and culminates in T_{TE}, with maximal potential for tissue homing and effector functions. Each subset represents memory T cells with increasing levels of differentiation and is classified according to the differential expression of CD45RO, CCR7, CD28, and CD95. Black text highlights the expression of the specific markers on the respective cell subset, whereas gray text represents the markers that are not expressed. T_N, naive T cells; T_{SCM}, stem cell memory T cells; T_{CM}, central memory T cells; T_{TM}, transitional memory T cells; T_{EM}, effector memory T cells; T_{TE}, terminal effector T cells. (Adapted from Mahnke et al. [5].)

Heterogeneity of T_H Cells

The Universe of T_H-Cell Subsets

Because of the vast diversity of T_H cells, different paradigms have been formulated to classify T_H cells into subsets. Accordingly, T_H cells have been classified based on their (i) differentiation status, (ii) migratory properties or tissue location, and (iii) functional properties [5]. There is considerable overlap between these classification systems since differentiation, migration, and function of T_H cell subsets are linked. Still, the investigation of T_H cell biology has strongly profited from the conceptual organization of T_H cells into distinct subsets. In particular in the human system, they help understand the quality of memory T cell responses and help dissect the mechanisms of immunity and immunopathology [6]. In the following text, an introduction to these classification systems is presented in greater detail.

Classification of T_H Cells Based on Differentiation

Phenotypic, functional, and transcriptional profiling of T_H cells suggests that human memory T cell differentiation follows a linear progression along a continuum of defined cellular entities (shown in Fig. 1) [7, 8]. The overarching concept is that less differentiated cells give rise to more differentiated progeny in response to antigenic stimulation or – potentially – homeostatic signaling [5]. On the undifferentiated end of the spectrum, naive T cells (T_N) represent antigen-unexperienced cells with maximal potential for proliferation, self-renewal, differentiation, and lymphoid homing. On the other end of the spectrum, terminally differentiated terminal effector T cells (T_{TE}) are highly antigen-dependent T cells with maximal potential for tissue homing and effector functions. In between, stem cell memory T cells [9], central memory T cells (T_{CM}), transitional memory T cells, and effector memory T cells (T_{EM}) represent memory cells with increasing levels of differentiation and progressive acquisition or loss of specific functions. This concept has a number of interesting implications for therapeutic manipulation of T cells. Targeting stem cell memory T cells, for instance, could enhance the efficacy of vaccines and adoptive T cell therapies for cancer and infectious diseases because of their stem cell-like properties [9]. Conversely, T_{EM} with strong but potentially destructive effector functions could be specifically disrupted to treat T cell-driven autoimmunity [10].

Classification of T_H Cells Based on Migration and Tissue Location

With respect to the migratory potential of memory T cells, 3 major subsets are recognized (shown in Fig. 2):

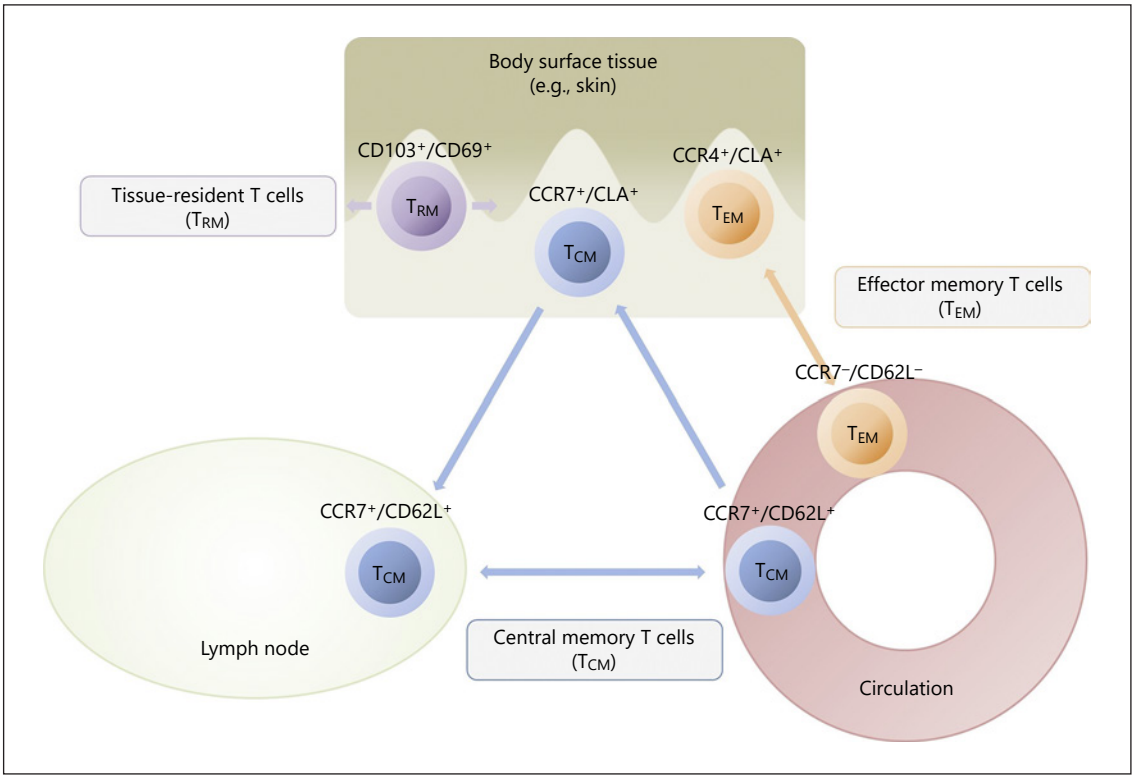

Fig. 2. Classification of T cells based on migration and tissue location. Memory T cells can be classified in terms of its migratory properties into 3 basic subsets: (1) T_{CM} have the ability to migrate between secondary lymphoid organs (lymph nodes), the blood circulation, and peripheral tissues. This migratory capacity is dependent on their expression of lymphoid homing receptors (CCR7/CD62L) as well as peripheral homing receptors (e.g., cutaneous lymphocyte antigen (CLA) for skin-homing). (2) T_{EM} lack the ability to home to lymphoid organs but are poised to home to peripheral tissues efficiently. Accordingly, T_{EM} lack CCR7/CD62L expression but express high levels of tissue homing receptors (e.g., CCR4/CLA for skin). (3) T_{RM} reside in peripheral tissues long term. They express the integrin CD103, which mediates tissue adhesion (via its binding to E-cadherin), and retain markers of persistent activation (CD69).T_{EM}, terminal effector T cells; T_{CM}, central memory T cells; T_{RM}, tissue-resident T cells.

T_{CM} and T_{EM}, both of which are found in the circulation, and tissue-resident T cells (T_{RM}), which reside in peripheral organs [11]. As described previously, T_{CM} and T_{EM} represent different stages of memory T-cell differentiation. However, they also differ with regard to their migratory potential [12]. T_{CM} express the chemokine receptor CCR7 and the vascular addressin CD62L (L-selectin), enabling them to access and enter lymph nodes from blood. On the other hand, T_{EM} lack CCR7 and CD62L expression but express receptors that enable them to enter peripheral tissues [13]. For example, T_{EM} expressing cutaneous lymphocyte antigen (CLA), the ligand for E-selectin present on cutaneous endothelial cells are capable of efficient homing to the skin [14]. Conversely, $\alpha4\beta7^+$ T_{EM} get access to the intestinal tract since they bind to MadCAM-1 expressed on gut endothelia [15, 16]. In contrast to T_{CM} and T_{EM} that migrate between the blood, secondary lymphoid organs, and peripheral tissues, T_{RM} permanently reside in epithelial barrier tissues. Thus, T_{RM} are strategically positioned at the interface between the host and the environment, such as the gastrointestinal tract, the respiratory tract, and the skin [17–19]. There, T_{RM} provide frontline immune protection against pathogen challenge [17, 20–22]. Importantly, T_{RM} differ not only in their location from other memory T-cell subsets but also in the expression of a distinct transcriptional program and have a unique cellular metabolism adjusted to the local microenvironment [23].

Classification of T_H Cells Based on Functional Properties

Finally, the heterogeneity of T_H cells can be organized according to functional modules (shown in Fig. 3) [2]. This classification positions each T_H cell subset at the cen-

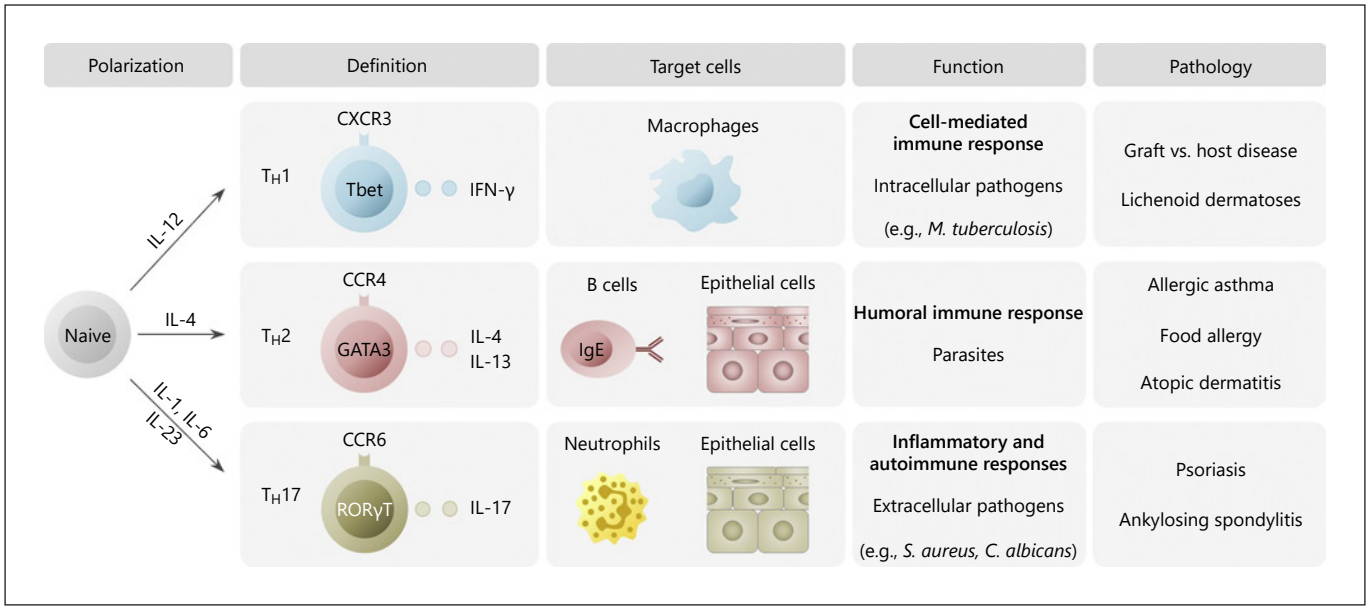

Fig. 3. Classification of T_H cell subsets based on functional properties. A T_H-cell subset is defined by 4 primary properties: (1) the cytokine environment under which it is polarized, (2) the cytokines it secretes itself, (3) the chemokine receptor repertoire it expresses, and (4) the transcription factors that orchestrate its phenotype at the genetic level and act as "master gene regulators". For instance, T_N stimulated by cognate antigen in the presence of IL-4 polarize into T_H2 cells that express IL-4 and IL-13, reside in the CXCR3−/CCR4+/CCR6− population of memory T_H cells, and are phenotypically stabilized by the master transcription factor GATA3. In addition, each T_H cell subset communicates with distinct target cells through which it exerts its functions in immunity and disease. For instance, T_H2 cells induce IgE class switching in B cells via their secretion of IL-4 and induce an antiparasitic state in epithelial cells via secretion of IL-13. When dysregulated, the T_H2 cell subset can induce pathology via the overexpression of these effector molecules and cause allergic disease. (Adapted from Sallusto and Lanzavecchia [2].) T_H, T helper; T_N, naive T cells.

ter of a module which mediates a specific class of immune response. Each module can either exert regulatory function to prevent autoimmunity or promote effector functions against different types of pathogens. The modules encompass, first, the cytokines required to polarize T_H cells into distinct subsets. Second, each module features a T_H cell subset at its center which, in turn, is defined by the cytokines and effector molecules it produces, the transcription factors that orchestrate its phenotype, and the chemokine receptor profiles it expresses. Third, the modules finally define what the main target cells of each T_H cell subset are, for example, what the cellular targets and functional consequences of the cytokines they produce are. Thus, these functional modules integrate aspects of differentiation, migration, and function of T_H cells into a theoretical framework that helps explain how different types of immune responses are regulated by T_H cells. T_H1 cells, for instance, are differentiated under the influence of interleukin (IL)-12, are controlled by the "master" transcription factor T-bet, express the chemokine receptor CXCR3, and – by their secretion of the cytokine interferon γ (IFN-γ) – activate macrophages to kill intracellular microbes. On the other hand, T_H2 cells are polarized by IL-4 and express GATA3, CCR4, and cytokines such as IL-4, IL-5, and IL-13, which mediate immune responses against extracellular parasites through the activation of epithelia and eosinophils. Additional T_H cell modules that have been described include – among others –T_H17 cells [24–26], follicular T_H cells [27–29], and regulatory T cells (T_{REG}) [30–32].

Based on the close relation between the phenotype and function of T_H cell subsets, it is possible to assign antigen specificities to each module. For example, T_H1 cells are enriched for T_H cells that recognized the intracellular microbe *Mycobacterium tuberculosis*, whereas T_H17 cells are enriched for T cells that recognize the extracellular pathogens *Staphylococcus aureus* and *Candida albicans* [33, 34].

This concept of functional modules has proven useful for the study of human T cell responses because it provides a theoretical framework to understand the huge complexity of human adaptive immune responses in both

health and disease [35]. Mechanistic insights into how these T_H modules orchestrate the inflammatory response at the tissue level and how T_H cells interact with resident cells led to the discovery of potent therapeutics for inflammatory diseases [36]. A typical example is the T_H17 module, which – when not properly controlled – leads to destructive tissue inflammation and autoimmunity [37]. Accordingly, inhibition of the T_H17 module is an excellent therapeutic strategy in the treatment of autoimmune and autoinflammatory diseases such as psoriasis and arthritis [3].

Limitations of Classifying T_H Cells into Subsets

Despite its usefulness, classifying T_H cells into rigid subsets has its limitations. Sophisticated single-cell analysis and cell fate tracking revealed the capacity of polarized T_H cells to change their phenotype, repolarize into different subsets, or take on mixed phenotypes [38–40]. This has led to the appreciation that memory T_H cells are adaptable in the face of repolarizing environments, a phenomenon described as T_H cell plasticity. Plasticity is defined as a single T_H cell's ability to adopt characteristics of multiple T_H cell subsets at the same time or at different times during its life cycle [38], as exemplified by the dichotomous nature of T_H17 and peripherally induced T_{REG} [24, 41]. While plasticity is an integral part of T_H cell biology, its conceptual meaning is challenging to embrace. Certainly, generating many functionality associated with different subsets from an individual T_H cell increases flexibility of host immunity. Conversely, it may also render previously protective memory T_H cells, generated during infection, to pathogenic cells with detrimental properties to the host. For instance, it was shown that a T_H17 cell can adopt not only regulatory but also enhanced pathogenic phenotypes depending on the local microenvironment [42, 43]. Thus, when studying T_H cell subsets, it has to be considered that they are more flexible than initially thought. Nevertheless, the concept of functional T_H cell modules provides a useful organizational principle to understand adaptive immune responses in health and disease [38].

Heterogeneity of T_H2 Cells

Functional Heterogeneity of T_H2 Cells

Of the pro-inflammatory T_H cell subsets, T_H2 cells are established as the main T_H cell subset that drives allergic tissue inflammation [44]. Recently, the T_H2 cells that promote allergic inflammation have been further dissected, thanks to single-cell analysis of T cells isolated from inflammatory tissues [45, 46]. These studies have identified a specific subset of T_H2 cells that is intricately linked to allergic pathology. This subset has therefore been termed "pathogenic" ("Tpath2," "peT_H2") [47, 48], "inflammatory" [49], or "proallergic" ("T_H2A") [50] T_H2 cells. Pathogenic T_H2 cells can be distinguished from their "conventional" T_H2 cell (cT_H2) counterparts based on phenotypic and functional attributes, just as their "parent" T_H-cell subsets. Pathogenic T_H2 cells are defined by the expression of distinct chemokine receptors, cell surface molecules, transcription factors, metabolic programs, and cytokine profiles [39, 46–49, 51]. For instance, T_H2 cells expressing the chemokine receptor CCR8 were found to secrete large amounts of IL-5 and cause chronic allergic skin inflammation, suggesting that CCR8 may serve as a surface marker of pathogenic T_H2 cells [49]. At the transcriptional level, pathogenic T_H2 cells were found to express the ligand-activated transcription factor peroxisome proliferator-activated receptor gamma (PPARγ), which appears crucial for their potential to mediate type 2 immunopathology, albeit through yet unknown mechanisms [50, 52]. Metabolically, pathogenic T_H2 cells also use specific pathways as they are capable of synthesizing prostaglandin (PG) D2 owing to the specific expression of the hematopoietic PG D synthase (HPGDS) [48]. Finally, pathogenic T_H2 cells feature a unique functional repertoire by expressing higher levels and a broader range of T_H2 cytokines than their cT_H2 counterparts [50, 52, 53]. Taken together, there is mounting evidence that T cell-mediated type 2 inflammation in both mice and humans is mediated by a specific subpopulation of pathogenic T_H2 cells that can be defined at multiple cellular levels. These specific characteristics and their functional properties are discussed in more detail in the next chapter.

The Core Phenotype of Pathogenic T_H2 Cells

Pathogenic T_H2 cells have been identified in multiple studies of type 2-driven diseases such as allergic asthma or eosinophilic esophagitis (EoE). From these studies, a core phenotype of pathogenic T_H2 cells emerges (Table 1). Although there are minor differences depending on the disease or species that was analyzed, pathogenic T_H2 cells express a core set of defining markers. These markers include chemokine and cytokine receptors, enzymes of PG synthesis and fatty acid metabolism, and cytokines. How these markers contribute to the pathogenicity of T_H2 cells is not known in all instances. However, certain markers such as IL-13 are well-known mediators

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Table 1. Core phenotype of pathogenic T_H2 cells

Category	Gene	Name	Induced by IL-4/TGFβ?	Pathogenic role	Refs.
Cytokine receptor	IL17RB	Interleukin 17 receptor B (IL-25R)	Yes	IL17RB expression enables pathogenic T_H2 cells to sense IL-25, which leads to promotion and maintenance of allergic inflammation in epithelial barrier tissues	[46] [50] [66] [67] [85]
	IL9R	Interleukin 9 receptor (CD129)	No	IL-9R signaling promotes survival, proliferation, and cytokine production in T_H cells and suppressive functions in T_{REG}	[50] [66] [67]
	IL1RL1	Interleukin 1 receptor like 1 (IL-33R and ST2)	No	Binding of IL-33 to IL1RL1 enhances differentiation, expansion, and antigen-independent production of cytokines in T_H2 cells	[46] [50] [66] [85]
Other receptors	TIGIT	T-cell immunoreceptor with Ig and ITIM domains	?	Binds with high affinity to the PVR, which causes increased secretion of IL-10 and decreased secretion of IL-12B and suppresses T-cell activation by promoting the generation of mature immunoregulatory dendritic cells	[50] [66]
	KLRB1	Killer-cell lectin-like receptor B1 (CD161)	?	CD161 ligation enhances TCR-induced proliferation in T_H17 cells. The ligand of CD161 is expressed by epithelial cells of the lung during inflammation, in the skin and on skin-resident T_H cells	[50] [66]
Chemokine receptor	CCR8	CC chemokine receptor 8	Yes	T_H2 cells expressing high levels of CCR8 secrete large amounts of IL-5, causing chronic allergic skin inflammation	[49] [130]
Prostaglandin PW	HPGDS	Hematopoietic prostaglandin D synthase	Yes	Catalyzes the conversion of PGH2 to PGD2, which is produced by pathogenic T_H2 cells upon activation, promoting their proinflammatory effect	[46] [50] [66] [67]
	PTGDR2	Prostaglandin D2 receptor 2 (CRT_H2)	No	Mediates activation, migration, and upregulation of IL-4, IL-5, and IL-13 in T_H2 cells and promotes their ability to sense PGD2	[50] [66] [130]
Cytokines	IL5	Interleukin 5	Yes	IL-5 secretion enables T_H2 cells to promote eosinophilic inflammation and amplify the type 2 inflammation in the tissue	[46] [50] [66] [67] [89] [85]
	IL9	Interleukin 9	Yes	Induces secretion of pro-inflammatory mediators by mast cells which are critical for full type 2 tissue inflammation	[46] [50] [85]
	IL13	Interleukin 13	Yes	In the lung, IL-13 mediates airway hyperresponsiveness, goblet cell mucus production, and eosinophilic inflammation. It is also a potent mediator of tissue fibrosis by regulating production of the extracellular matrix	[46] [50] [89] [85]
	LIF	Leukemia inhibitory factor interleukin 6 family cytokine	No	Pleiotropic cytokine, induces differentiation of myeloid cells and neuronal cells, and regulates mesenchymal to epithelial conversion	[50] [66] [67]

Table 1 (continued)

Category	Gene	Name	Induced by IL-4/TGFβ?	Pathogenic role	Refs.
Fatty acid metabolism	FFAR3	Free fatty acid receptor 3	No	Activation of FFAR3 by SCFAs can increase T_H2 cytokine production and promote allergic inflammation	[46] [50] [66] [67]
Lipid metabolism	PLIN2	Perilipin 2	No	Coats lipid droplets for intracellular storage of lipids. Lipid droplets might serve as a reservoir for AA which can be mobilized for the formation of signaling lipid mediators, such as PGs	[50] [66]
Transcription factors	PPARγ	Peroxisome proliferator-activated receptor gamma	Yes	Controls the expression of genes involved in adipogenesis, lipid metabolism, inflammation, and metabolic homeostasis	[89] [85]

T_H, T helper; AA, arachidonic acid; T_{REG}, regulatory T cells; PG, prostaglandin; IL-9R, IL-9 receptor; PVR, Poliovirus receptor; TCR, T-cell receptor; SCFA, short-chain fatty acids.

of type 2 immunopathology and are expressed at higher levels in pathogenic than in cT_H2s. Since the majority of these markers have been identified by transcriptomic analyses, their expression at the protein level has not been validated in all instances. With these limitations in mind, we summarize in the following text the current understanding of the pathogenic T_H2 cell markers.

Surface Receptors

IL-17 Receptor B. IL-17 receptor B (IL-17RB), in complex with IL-17RA, forms the receptor for IL-25 (IL-17E). IL-25 is expressed by epithelial cells and by innate immune cells, such as eosinophils, basophils, and mast cells [54]. Lung epithelia, for instance, secrete IL-25 after exposure to allergens, whereas mast cells release IL-25 as a result of IgE cross-linking [55, 56]. Binding of IL-25 to its receptor on T_H2 cells promotes T cell expansion, production of T_H2 cytokines, and polarization and maintenance of T_H2 cells [56]. Thus, IL-17RB expression enables pathogenic T_H2 cells to sense the epithelial type 2 alarmin IL-25, which promotes and maintains allergic inflammation in epithelial barrier tissues.

IL-9 Receptor. The IL-9 receptor (IL-9R) consists of the cytokine-specific IL-9R α-chain and the common γ-chain [57]. Activation of IL-9R initiates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, mainly through JAK1 and JAK3, followed by the phosphorylation of STAT1 and STAT5, respectively [58, 59]. While the effect and functional importance of IL-9R signaling on innate immune cells, particularly on intestinal mast cells, have recently been elucidated [60, 61], its effects on human T_H cells remain a contentious issue [57, 62]. IL-9R signaling has been shown to promote survival, proliferation, and cytokine production in human effector T_H cells as well as suppressive functions in T_{REG}. However, data on the in vivo importance of IL-9R signaling in human T_H cells are still scarce [63–65]. The repeated identification of IL-9R as a marker of pathogenic T_H2 cells in humans will likely renew interest in this "old" cytokine receptor and trigger further studies to elucidate its specific role in human T_H2 cell biology [50, 66, 67].

IL-1 Receptor-like 1. IL-1 receptor-like 1 (IL1RL1, ST2, IL-33R) encodes for the receptor of IL-33, a member of the IL-1 cytokine family with critical functions in allergic diseases. IL-33 is expressed by epithelial cells and other mesenchymal cells such as fibroblasts and endothelial cells. Stored in the nucleus, IL-33 is rapidly released upon cell injury and thus functions as a tissue alarmin. IL-33R is expressed by a wide range of innate immune cells (e.g.,

mast cells, eosinophils and group 2 innate lymphocytes (ILC2)) as well as by adaptive immune cells, most prominently T_H2 cells [68]. In T_H2 cells, IL-33R expression is driven by the transcription factors GATA-3 and STAT5 and upregulated after T_H2 cell activation. Binding of IL-33 to its receptor enhances differentiation, expansion, and antigen-independent production of cytokines in T_H2 cells [69]. Therefore, IL-33R expression on pathogenic T_H2 cells further expands their ability to sense type-2-associated tissue alarmins and amplifies their pro-inflammatory potential in allergic tissue inflammation.

T-Cell Immunoreceptor with Ig and ITIM Domains. T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is a member of the Poliovirus receptor (CD155) family of immunoglobin proteins. It is a co-inhibitory molecule expressed by T, natural killer (NK), and T_{REG} cells. Its activation limits autoimmunity and impairs antiviral and antitumor immune responses [70, 71]. In contrast to this regulatory function in cytotoxic T cells, TIGIT has been shown to enhance T_H2 cell function by promoting allergic inflammation and T_H2 polarization [72]. The precise mechanisms and functional consequences of this dichotomous effect on different T cell subsets are still unclear. Hence, whether TIGIT expression on pathogenic T_H2 cells serves to enhance or to control their pro-inflammatory function remains to be investigated.

Killer Cell Lectin-like Receptor B1 (CD161). CD161 is a C-type lectin-like receptor known for its inhibitory role on NK cell cytotoxicity. Its role on T cells, and in particular on T_H2 cells, has not been fully uncovered, although CD161 ligation has been shown to enhance T cell receptor-induced proliferation in T_H17 cells. It might thus promote T_H2 cell function in a similar way [73]. The ligand of CD161 is the C-type lectin domain family 2 member D (CLEC2D). In macrophages, CLEC2D has been recently discovered as cell death sensor detecting histones released during necrosis, contributing to inflammation and immunopathology [74]. Moreover, CLEC2D is expressed by epithelial cells of the lung during inflammation, suggesting that pathogenic T_H2 cells might be activated via CD161 in the setting of allergic lung inflammation [75]. CLEC2D is also expressed in the skin, and CD161 is highly expressed on skin-resident T_H cells, suggesting that CD161 also contributes to type-2-driven diseases of other barrier tissues such as atopic dermatitis (AD) [76].

PG Synthesis Enzymes

Hematopoietic PG D Synthase (HPGDS). HPGDS catalyzes the conversion of PGH2 to PGD2 and, thus, mediates the production of inflammatory prostanoids in cells of the immune system. Consistently, pathogenic T_H2 cells have been shown to produce large amounts of PGD2 upon activation, thereby promoting activation of T_H2 cells, eosinophils, and basophils and expanding the pro-inflammatory effector repertoire [77–79]. Importantly, pathogenic T_H2 cells also express the PG D2 receptor 2 (CRT_H2; see below) and are, thus, capable of amplifying their own activation and effector function via the HPGDS-PGD2-CRT_H2 axis [48, 80].

PG D2 Receptor 2 (CRTH2). CRT_H2 is a G-protein-coupled receptor that mediates activation, migration, and upregulation of IL-4, IL-5, and IL-13 in T_H2 cells [81, 82]. Thus, CRT_H2 endows pathogenic T_H2 cells with the ability to sense and react to PGD2, a pleiotropic mediator in type 2 disease. Inhibitors of CRT_H2 are currently being evaluated in clinical trials of various type-2-mediated diseases, albeit with ambiguous results so far [83, 84].

Cytokines

IL-5. IL-5 is a homodimeric cytokine which induces differentiation, migration, survival, and activation of eosinophils, basophils, and mast cells. IL-5 is among the most specifically expressed genes in pathogenic T_H2 cells as compared to cT_H2s [48, 50, 66, 67, 85]. Functionally, prominent IL-5 secretion broadens the effector repertoire of pathogenic T_H2 cells, enabling them to promote eosinophilic inflammation and to amplify and perpetuate type 2 inflammation in the tissue [86].

IL-9. IL-9 is a pleiotropic cytokine that signals through IL-9R (see above). IL-9 has been described to have a wide range of effects on both hematopoietic and nonhematopoietic cells [57]. Given that pathogenic T_H2 cells also express IL-9R, it is likely that IL-9 has important autocrine functions, which are not yet fully understood. However, IL-9 is a key activator and survival factor of mast cells [60, 87], and IL-9 secretion by T_H2 cells is critical for tissue mast cell accumulation and activation [61, 88, 89]. Thus, by their expression of IL-9, pathogenic T_H2 cells are able to induce secretion of pro-inflammatory mediators by mast cells, which is critical for full type 2 tissue inflammation [87]. On memory B cells, autocrine and/or paracrine IL-9 signaling plays a key role for the humoral recall response. It is hence proposed that IL-9 signals the proliferation and subsequent plasma cell differentiation of memory B cells after their cognate interaction with memory T cells [90].

IL-13. IL-13 has crucial functions in parasite immunity and type-2 inflammation. It promotes IgE class switching in B cells and alternative activation of macrophages. In the lung, IL-13 mediates airway hyperrespon-

siveness, goblet cell mucus production, and eosinophilic inflammation. Finally, IL-13 is also a potent mediator of tissue fibrosis by regulating production of the extracellular matrix [91, 92]. In this context, it will be interesting to see whether pathogenic T_H2 cells are also involved in the process of tissue fibrosis and excessive wound healing.

Leukemia Inhibitory Factor. Leukemia inhibitory factor (LIF) is a highly pleiotropic cytokine of the IL-6 family, signaling through the LIF receptor β/gp130 receptor complex. LIF can have opposite effects in different cell types, either stimulating or inhibiting cell proliferation and differentiation, respectively [93]. Of the many functions described for LIF, its action as a neurotropic factor is of particular interest in the context of T_H2 cell function as it might be involved in the propagation of itch, a hallmark of type-2 inflammation of the skin [94, 95]. Further, LIF might be involved in the regulation of cellular metabolism during allergic inflammation, since cytokines of the IL-6 family are important regulators of immunometabolism [96, 97].

Cell Metabolism

Free Fatty Acid Receptor 3. Free fatty acid receptor 3 (FFAR3) encodes a G protein-coupled receptor for short-chain fatty acids (SCFAs) with a chain length of C2–C5 [98, 99]. Interestingly, in multiple studies on both human and murine T_H2 cells, FFAR3 was identified to be specifically expressed on pathogenic T_H2 cells and to correlate with IL-5 levels and tissue eosinophilia [46, 50, 66, 67]. Correspondingly, activation of FFAR3 by SCFA can increase T_H2 cytokine production and promote allergic inflammation in vivo in mice [66]. FFAR3 on T_H2 cells thus enables them to sense SCFAs, a metabolic by-product of commensal microbiota. SCFAs are increasingly implicated in the modulation of the immune system at body surface tissues, where there is an active interface between the microbiome and immune cells [98].

Perilipin 2. Perilipin 2 (PLIN2) belongs to the perilipin family of proteins, which coat lipid droplets for intracellular storage. PLIN2 has been implicated in the mediation of inflammation signals induced by triglycerides [100]. Experimental data on the function of PLIN2 in the immune system are still rudimentary. However, intracellular lipolysis of lipid droplets has been shown to directly induce pro-inflammatory gene expression in macrophages [101]. In addition, lipid droplets in T_H2 cells, promoted by PLIN2, might serve as a reservoir for arachidonic acid which can be metabolized to signaling lipid mediators, such as PGs [102]. This is of particular interest since enhanced PG metabolism is a hallmark of pathogenic T_H2 cells (see above).

Transcription Factors

Peroxisome Proliferator-Activated Receptor Gamma. PPARγ is a ligand-activated nuclear receptor best known for regulating lipid and glucose metabolism in mesenchymal cells such as adipocytes [103]. *PPARG* is one of the most reproducibly identified genes associated with the pathogenic T_H2 phenotype [47, 50, 66, 67, 85]. PPARγ is activated by synthetic ligands such as thiazolidinediones or endogenously by fatty acids and their derivatives. However, specific endogenous PPARγ ligands have been difficult to identify, and thus, the role of endogenous PPARγ activation remains poorly defined [104–106]. When activated, PPARγ dimerizes with retinoid X receptor, binds to PPAR-responsive regulatory elements, and controls the expression of a network of genes involved in adipogenesis, lipid metabolism, inflammation, and metabolic homeostasis [107]. The specific functional role of PPARγ in T_H2 cells is best described in murine cells, where PPARγ has been shown to promote IL-33R expression, thereby enhancing T_H2 cell activation in allergic tissue inflammation. In agreement with these findings, mice with a T_H cell-specific knockout of *Pparg* are protected from allergic lung inflammation and have reduced immunity against parasite infection [52, 53]. In humans, the function of PPARγ in pathogenic T_H2 cells and allergy remains to be defined. Yet, it is tempting to speculate that PPARγ mediates metabolic adaptation of pathogenic T_H2 cells to the harsh environment of inflamed tissue.

Genes Specifically Downregulated in Pathogenic T_H2 Cells

A number of genes have been reported to be specifically downregulated in pathogenic T_H2 cells as compared to cT_H2s. Among them, the transcription factor eomesodermin (EOMES) and the surface receptor CD27 are of particular interest.

Tumor Necrosis Factor Receptor Superfamily Member 7 (CD27). CD27 is a member of the tumor necrosis factor receptor superfamily. CD27 is expressed on various T cell populations and upregulated upon T cell activation. When activated by its ligand, CD70, CD27 signaling promotes clonal expansion, survival, differentiation, and effector function in T cells [108]. Given its ability to enhance T cell function, it is a target for immune checkpoint therapy in cancer [109]. However, highly differentiated memory effector T cells downregulate CD27 (shown in Fig. 1) [5]. Whether negative expression of CD27 in pathogenic T_H2 cells simply reflects their highly differentiated state or whether it is a sign of "exhaustion" and prevents further cell activation, has yet to be explored.

Eomesodermin. The transcription factor EOMES is crucial for embryonic development of mesoderm and plays a central role in promoting cytotoxic effector functions in $CD8^+$ T cells. In T_H2 cells, EOMES represses IL-5 secretion by preventing GATA3 from binding to the IL-5 promotor. Consequently, downregulation of EOMES in pathogenic T_H2 cells, observed in both murine and human studies, allows binding of GATA3 to the IL5 promoter and represents the transcriptional mechanism by which these cells express high levels of IL-5 [47].

In summary, the core phenotype of pathogenic T_H2 cells differentiates them from cT_H2s on 4 levels: First, pathogenic T_H2 express a wider range and higher levels of effector molecules, most notably cytokines. This broadens the spectrum of innate immune cells and stromal cells they can activate during allergic inflammation. Second, they strongly express cytokine receptors for tissue alarmins. This renders them highly sensitive to danger signals from the tissue and facilitating immediate effector responses even in the absence of strong antigen-dependent stimulation. Third, pathogenic T_H2 cells express distinct receptors for chemokines and chemoattractants, granting them strategic access to niches in barrier tissues where they may mediate frontline immune defense or barrier tissue pathology. Fourth, they are endowed with a set of metabolic properties that may affect both their effector repertoire and their metabolic adaptation to the tissue and the inflammatory environment within which they have to function. Our understanding of this aspect of T_H2 cell biology is still nascent, making the study of T_H2 cell immunometabolism an intriguing field for further research.

"T Helper Type 9" Cells: Just Another Name for Pathogenic T_H2 Cells?

In 2008, T helper type 9 ("T_H9") cells were proposed as a novel subset of T helper cells with the ability to secrete high amounts of IL-9 [110, 111]. However, many lineage-defining properties of "T_H9" cells remained unknown, calling the true identity of "T_H9" cells as a bona fide subset into question [112]. Indeed, comprehensive characterization of human IL-9-producing T_H cells revealed that "T_H9" cells are at root T_H2 cells with a set of distinct properties [89]: "T_H9" cells express the chemokine receptor CCR8, secrete – in addition to IL-9 – high amounts of IL-5, and depend on PPARγ for full effector functions. Strikingly, "T_H9" polarization, that is, priming of T_N in the presence of IL-4 and TGF-β, induces higher levels of PPARγ than cTH2 polarization with IL-4 alone. In addition to IL-9 and PPARγ, "T_H9" polarization induces high levels of CCR8 [113], IL-17RB [114], HPGDS [113], and IL-5 [89], all of which are hallmarks of pathogenic T_H2 cells (shown in Fig. 4). Furthermore, genes typically expressed at low levels in pathogenic T_H2 cells, such as IL-4, are downregulated by "T_H9" priming. Taken together, these data suggest that the addition of TGF-β to T_H2 priming with IL-4 represents an important differentiation step toward pathogenic T_H2 cells. However, additional differentiation cues remain to be identified for the induction of the full pathogenic T_H2 phenotype (e.g., IL-33R, FFAR3, and PTGDR2).

Transcriptional Overlap between Pathogenic T_H2 Cells and Skin-Resident T_H Cells

T_{RM} reside long term in nonlymphoid tissues where they provide frontline immune defense [115, 116]. While it became clear that T_{RM} are fundamentally distinct from circulating memory T cells, the precise transcriptome of human skin $CD4^+$ T_{RM} under homeostatic conditions remained unknown. Recently, the core transcriptome of human $CD4^+$ T_{RM} from healthy skin has been defined and revealed an intriguing overlap of the T_{RM} transcriptome with that of pathogenic T_H2 cells [76]. $CD4^+$ T_{RM} were found to be enriched for cytokines (*IL9*), chemokine receptors (*CCR8*), cytokine receptors (*IL17RB*, *IL9R*, and *TGFBR3*), and transcription factors (*PPARG*) that are closely linked to pathogenic T_H2 cells. At the same time, genes typically downregulated in pathogenic T_H2 cells, such as *IL4*, *CXCR3*, *CD27*, and *EOMES*, were also downregulated in $CD4^+$ T_{RM}. While the relevance of this remarkable similarity remains to be understood, it indicates that both T_{RM} and pathogenic T_H2 cells share a tissue differentiation program that is – at least in part – the result of TGF-β signaling and that it represents their adaptation to the tissue environment. Indeed, in murine $CD8^+$ T_{RM}, PPARγ mediates metabolic adaptation to the lipid-rich microenvironment of the skin [23]. Since both T_{RM} and pathogenic T_H2 cells are linked to chronic immunopathologies of barrier tissues, this kinship holds great promise for future therapeutic or even curative strategies.

Pathogenic T_H2 Cells in Allergic and Atopic Disease

Memory T cells are crucial for the maintenance of long-term antigen-specific immunity to previously encountered infections as they are capable of mounting a rapid and effective response program upon re-exposure to pathogens. However, this capacity to respond vigor-

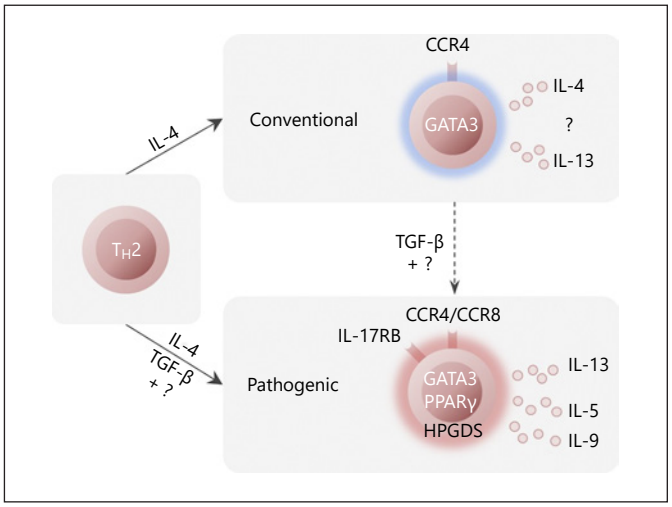

Fig. 4. "T_H9" polarization induces hallmarks of pathogenic T_H2 cells. Polarization of T_N in the presence of IL-4 and TGF-β ("T_H9" priming) induces many – but not all – phenotypic characteristics of pathogenic T_H2 cells. Namely, IL-4 and TGF-β induce expression of CCR8, IL-17RB, PPARγ, HPGDS, IL-5, and IL-9, while expression of IL-4 is downregulated. Additional polarizing signals are likely required to induce the full phenotype of pathogenic T_H2 cells (e.g., expression of IL-33R, CRT_H2, and FFAR3). T_H, T helper; T_N, naive T cells; PPARγ, peroxisome proliferator-activated receptor gamma; HPGDS, hematopoietic prostaglandin D synthase; FFAR3, free fatty acid receptor 3; T_H9, T helper type 9.

ously can have harmful consequences in the context of chronic inflammatory diseases. Exaggerated production of cytokines is tightly linked to the initiation and perpetuation of recurrent episodes of tissue inflammation. In allergic and atopic diseases, T_H2 cells play a central pathogenic role in promoting tissue inflammation [117]. Below, we discuss T_H2 differentiation in allergic diseases and present a summary of the known involvement of pathogenic T_H2 cells in type 2 immunopathology. As an example, we summarize putative differentiation and function of pathogenic T_H2 cells in allergic inflammation of epithelial tissue in Figure 5.

Differentiation of T_H2 Cells in Allergic Diseases

T_N, following their maturation, recirculate throughout the body, migrating within the secondary lymphoid organs such as lymph nodes, where they interact with antigen-presenting cells. When they encounter cognate antigens presented by antigen-presenting cells in the presence of appropriate co-stimulatory molecules, they become primed and acquire the activated phenotype. After priming, T cells migrate through post-capillary venules and infiltrate target peripheral tissues, where the antigen is located, such as skin, lungs, or gut, to exert their function [118].

Allergic inflammatory diseases, as previously discussed, have been found to be characterized mostly by the T_H2 cell immune response. In this context, differentiation from naive $CD4^+$ T cells toward the T_H2 phenotype typically rely on the presence of IL-4 in the local cellular environment. Binding of the IL-4R triggers JAK1/3-mediated phosphorylation and dimerization of STAT6, which translocates to the nucleus inducing the expression of GATA3, the master transcription factor of the T_H2 cell lineage. GATA3, together with the activated form of STAT5, in turn promotes type 2 cytokines expression, like IL-4, IL-5, and IL-13 [119, 120]. However, T_H2 differentiation does not only occur through the GATA3-STAT6 axis, but also proceeds through other "noncanonical" pathways. For example, IL-2 is able to induce IL-4 production via STAT5 activation [121]. Furthermore, there is a number of other transcription factors, including the previously mentioned EOMES, STAT3, c-Maf, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb), and interferon regulatory factor 4 (IRF4) that have been shown to play a role in the early stages of T_H2 cell differentiation [122–124]. The further differentiation into the pathogenic T_H2 phenotype requires the activation of distinct epigenetic and transcriptional programs, which presumably takes place after multiple rounds of differentiation, following chronic antigen exposure. TGF-β, together with IL-4, plays a crucial role in this process, promoting the development of the pathogenic T_H2 signature. Pathogenic T_H2 cells are therefore highly differentiated T_H2 cells, defined by specific properties that result in enhanced effector function, innate responsiveness, and migratory capacity (shown in Fig. 5) [80].

Involvement of Pathogenic T_H2 Cells in Allergic Disease

Chronic Allergic Rhinosinusitis

Chronic allergic rhinosinusitis is characterized by persistent inflammation of the nasal mucosa and nasal obstruction. Symptoms can be severe and difficult to treat. In Western countries, the disease is closely associated with allergic asthma, suggesting a pathogenic link [125]. Indeed, allergen-specific T_H2 cells with a pathogenic phenotype were identified in chronic allergic rhinosinusitis and linked to eosinophilic tissue inflammation [126, 127].

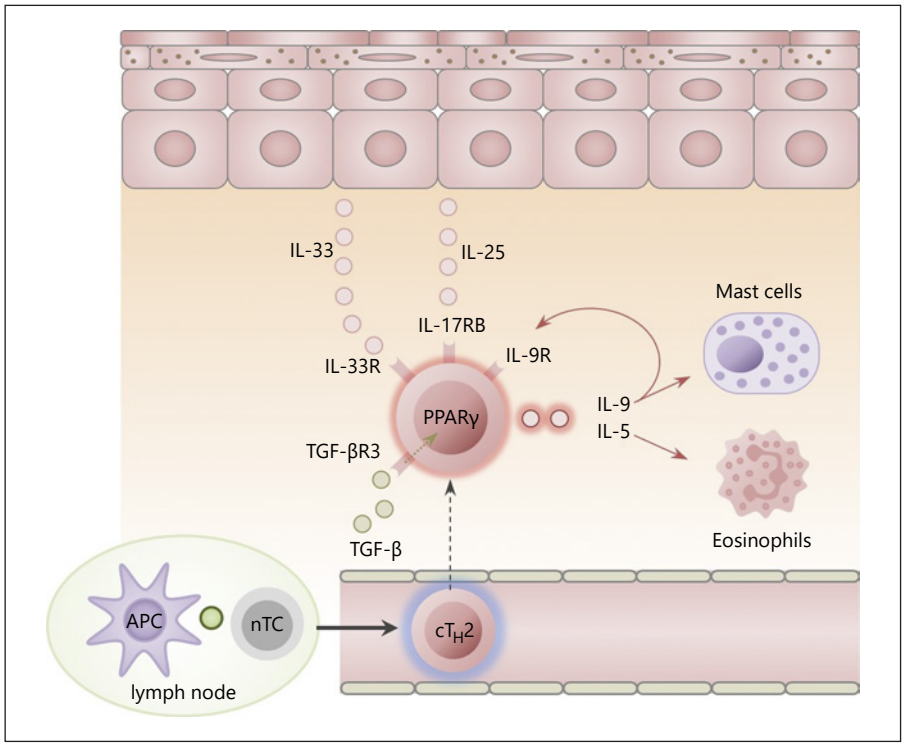

Fig. 5. Putative differentiation and function of pathogenic T_H2 cells in allergic inflammation of epithelial tissue. T_N encounter cognate antigens presented by APCs and differentiate into cT_H2. cT_H2 migrate through postcapillary venules and infiltrate target peripheral tissue (e.g., epithelial tissue). In the peripheral tissue, additional polarizing signals, such as TGF-β are likely required to induce the full phenotype of pathogenic T_H2 cells. Pathogenicity of T_H2 cells likely results from (1) the ability to sense epithelia-derived tissue alarmins like IL-33 or IL-25, (2) the adaptation to the metabolic microenvironment via TGF-β-induced PPARγ expression, and (3) a broadened effector repertoire, including IL-9 and IL-5, to active local innate immune cells, such as mast cells and eosinophils, respectively. T_H, T helper; T_N, naive T cells; PPARγ, peroxisome proliferator-activated receptor gamma; APC, antigen-presenting cell; cT_H2, conventional T_H2 cells.

Allergic Asthma

Allergic asthma is a classic example of a chronic, type-2-driven disease, characterized by inflammation, obstruction, mucus secretion, and hyperresponsiveness of the lower airways [128]. While T_H2 cells have long been implicated in allergic airway inflammation, recent evidence from mice and humans indicates that the disease is specifically driven by pathogenic T_H2 cells [46, 52, 53, 67, 80, 85]. This is further supported by successful clinical application of monoclonal antibodies against IL-5 and IL-13. Moreover, other therapeutics targeting pathogenic T_H2 cells or associated pathways, such as anti-TSLP and anti-IL-33 treatments, are currently being developed in allergic asthma [129].

Atopic Dermatitis

AD is a common chronic inflammatory skin disease and affects both children and adults. AD has a genetic background and is characterized by a disturbed skin barrier and excessive T_H2 mediated inflammation [130]. Clinically, AD presents with eczematous skin lesions and intense pruritus [95]. First, evidence that the pathogenic T_H2 cell subset might be crucially involved in AD came from mouse models in which a specific subset of $CCR8^+$ memory T_H2 cells expressing high levels of IL-5 was found to drive chronic skin inflammation [49]. In accordance with these findings, CCL18, a ligand of CCR8, is overexpressed in lesional skin of AD and correlates highly with disease severity [130]. Furthermore, T_H2 cells expressing IL-5 and HPGDS were also linked to chronic inflammation in AD [80]. Accordingly, blocking of the T_H2 pathway with a monoclonal antibody against the alpha-chain of the IL-4/IL-13 receptor shows high efficacy in severe AD [95]. However, initial clinical trials in which IL-25 or IL-33 signaling were targeted in AD showed ambiguous results. Future studies will have to address whether targeting of other pathways associated with pathogenic T_H2 cells, such as the CCL18/CCR8 axis, are more promising therapeutic targets in AD.

Food Allergy

Food allergy is defined as an immune-mediated adverse reaction to food and has become an increasingly prevalent health problem in developed parts of the world. Mechanistically, it is thought that allergen-specific T_H2 cells drive IgE class switching and the expansion of allergic effector cells [131]. A growing body of evidence suggests that in particular, pathogenic T_H2 cells are the key drivers of food allergy [50]. For instance, IL-5, IL-9, HPGDS, and IL-33 are closely linked to intestinal pathol-

ogy in food allergy in humans as well as in disease models [60, 80]. In the context of established peanut allergy, a study provides evidence that interruption of the T_H2 pathway with a monoclonal antibody against the alpha-chain of the IL-4/IL-13 receptor inhibits IgE recall responses, skews the T_H2 dominant cytokine response, and prevents induction of anaphylaxis [132]. In further support of this scenario, a recent clinical trial with an anti-IL-33 antibody in peanut allergy showed very promising results [133].

Eosinophilic Esophagitis

EoE is a chronic inflammatory disease of the esophagus, mediated by a T_H2 and eosinophil-dominated inflammation and consecutive esophageal dysfunction [134]. EoE patients suffer from a range of symptoms such as dysphagia, chest pain, and reflux [135]. Recent single-cell analysis of T cells isolated from EoE tissue identified a T_H2 cell population that expresses HPGDS, CRT_H2, and IL-17RB; produces prodigious levels of IL-5 and IL-13; and correlates with disease severity [66]. Thus, these data add EoE to the growing list of diseases that are likely mediated by pathogenic T_H2 cells.

Taken together, there is strong evidence that allergic inflammation in various human tissues is mediated by specific T_H2 cells with particular phenotypic and functional properties, thus warranting their classification as pathogenic T_H2 cells. Their importance for disease pathogenesis is supported by a growing number of clinical drug trials in which specific targeting of pathogenic T_H2 cell biology shows beneficial effects [133, 136–138].

Conclusion

Subdividing T_H cell subsets even further into "conventional" and "pathogenic" "subsubsets" might appear like an academic exercise of questionable clinical and conceptual use at first. At the same time, it still represents an oversimplification of the vast diversity and plasticity of T_H cells. Yet, it can serve as a model to understand clinical phenomena and to guide drug development. First, results of early clinical trials suggest that this might be the case, as shown with anti-IL-33 antibodies in human food allergy and in preclinical models of multiple atopic diseases [133, 136–138]. Similar predictions can be made about targeting IL-5/IL-5R [86], IL-25/IL-17RB [139], or, possibly, PPARγ [97]. Therapeutic targeting of the latter may be an elegant way of inhibiting multiple aspects of pathogenic T_H2 cells by interfering with their transcriptional regulation. In mesenchymal cells, PPARγ regulates the expression of a wide range of genes, thereby acting as a "master regulator" of these cells. By analogy, PPARγ might represent the Achilles heel of pathogenic T_H2 cells, and its modulation might normalize multiple pathogenic pathways at once. However, targeting PPARγ specifically in T_H2 cells represents a major pharmacological challenge as PPARγ is expressed in multiple cell types of multiple tissues in which it exerts protective functions [103]. Regardless, a better understanding of the intricacies of pathogenic cells and cT_H2s will improve our understanding of the pathogenesis of allergic diseases and stimulate the development of novel diagnostic and therapeutic tools.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

C.S. has conceived the concept of the review and written the main part of the manuscript. N.L.B. contributed in writing the manuscript, researching the literature, and generating the tables and figures. C.B. has participated in writing, revising, and editing text and figures of the manuscript.

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