

**REVIEW**

Shaping the diversity of Th2 cell responses in epithelial tissues and its potential for allergy treatment

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Th2 cells have evolved to protect from large helminth infections and to exert tissue protective functions in response to nonmicrobial noxious stimuli. The initiation, maintenance, and execution of these functions depend on the integration of diverse polarizing cues by cellular sensors and molecular programs as well as the collaboration with cells that are coopted for signal exchange. The complexity of input signals and cellular collaboration generates tissue specific Th2 cell heterogeneity and specialization. In this review, we aim to discuss the advances and recent breakthroughs in our understanding of Th2 cell responses and highlight developmental and functional differences among T cells within the diversifying field of type 2 immunity. We will focus on factors provided by the tissue microenvironment and highlight factors with potential implications for the pathogenesis of allergic skin and lung diseases. Especially new insights into the role of immunometabolism, the microbiota and ionic signals enhance the complexity of Th2 cell regulation and warrant a critical evaluation. Finally, we will discuss how this ensemble of established knowledge and recent breakthroughs about Th2 immunobiology advance our understanding of the pathogenesis of allergic diseases and how this could be exploited for future immunotherapies.

Keywords: Th2 cells · allergy · sodium chloride · metabolism · immunotherapy

Introduction

CD4⁺ Th cells choreograph adaptive immune responses by their secretion of cytokines, by their migration properties and their collaborative interaction with other cell types. Th cells can be categorized into distinct phenotypic and functional subsets [1]. Their responses are tailored to the specific elimination of diverse pathogens [2, 3]. The dualism of Th1 and Th2 cells was originally formulated 30 years ago but has now been replaced by a concept that embraces further Th cell heterogeneity and plasticity. Th1 and Th2 cells target intracellular pathogens and large nonreplicating pathogens such as helminths, respectively. To aid in this

heterogeneity Th17 cells are specialized in fungal clearance [3, 4], while Treg cells exert immunosuppressive functions [5]. Other Th cell subsets, such as Th9, Th22 and Th-GM-CSF cells, which exert effector functions in the skin or central nervous system, have more recently emerged on the scene and await further dissection of their functions and regulatory networks [6–9]. In addition, mixed Th cell differentiation states occur as a result of T cell plasticity [10].

Th2 cells, which are the focus of our review, are thought to have evolved in response to helminth parasites. Helminth infections represent a global health burden with more than a billion people infected [11]. Non-infectious settings are also associated with Th2 cell responses. Th2 cells have been shown to be beneficial for neonatal lung development, angiogenesis, and thermogenesis, which is supported by an overall Th2 cell bias in murine neonates [12–14]. Together, barrier protection and tissue

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remodeling seem to be common denominators of type 2 biased Th cell responses. These processes can be exploited by Th2 cells for anti-helminthic host defense while at the same time limiting collateral tissue destruction. However, if the regulation of Th2 effector functions leaves the boundaries of well-orchestrated checks and balances, overexuberant, or off-target effects of Th2 cell responses might result in allergies covering the range of atopic diseases from eczema to allergic asthma.

The incidence of allergic diseases has been increasing over the past 50 years as a result of genetic and, in particular, rapid environmental adaptation [15]. Th2 cells represent major determinants in the pathogenesis of allergic diseases. Although their regulation has been studied extensively for more than 30 years, new factors and tissue-specific cues have recently enhanced our understanding of Th2 mediated allergic pathologies. Recent technological advances in multidimensional analysis of T cells at the single cell level have further enabled investigations into the heterogeneity of Th2 cell responses [16–19]. Tissue specific adaptation responses have revealed the existence of resident versus recirculating Th2 cells with implications for asthma and possibly other allergic diseases [20]. This opens up new avenues for therapeutic strategies in the modulation of Th2 cells and thus the treatment of systemic as well as tissue restricted allergic diseases.

Recent scientific highlights that advanced our understanding of Th2 cells, in particular their induction, regulation, heterogeneity, and tissue specific adaptation will be critically discussed in this review with respect to their impact for allergic disease pathogenesis and their potential for therapeutic targeting.

Induction of Th2 cell responses

Despite extensive prior work on the molecular regulation of Th2 cells, the priming requirements are still ill defined. IL-4 is commonly accepted as the key Th2 cell polarizing cue for naïve Th cells [21]. So far, the cellular origin of IL-4 that induces Th2 cell priming remains unclear. Because Th2 cells also produce IL-4 as their signature cytokine, it has been suggested that Th2 differentiation could be a default process in the absence of skewing cytokine conditions and even driven by autocrine IL-2 in response to antigenic T cell activation [22]. Basophils, which can provide IL-4, have previously been suggested to initiate Th2 cell polarization in mice, an idea that has largely been abandoned due to poor MHC class II expression [23–25]. DCs are needed for optimal antigen presentation but are not thought to be producers of IL-4 [26, 27]. DCs have nevertheless been shown to be relevant for the induction of Th2 cell responses and to exert their polarizing property by costimuli such as OX40L and Notch ligand Jagged 1, instead. Notch signaling, which has multiple roles for T cell development and function, has also been demonstrated to promote Th2 cell polarization via induction of GATA-3 in a mouse model [28, 29]. The subset of cutaneous CD11b⁺CD301b⁺PDL2⁺ DCs preferentially express these molecules and, accordingly, has been demonstrated to be a potent Th2 inducer in mice [30, 31]. Still, new data question whether it is necessary for Jagged1 and Jagged2 to

be expressed by DCs for Th2 cell generation [32]. More recently, group 2 innate lymphoid cells (ILC2) cells have been identified as rich sources of IL-4. Leukotriene D4 was shown to stimulate IL-4 secretion by ILC2s, which was sufficient to potently drive Th2 differentiation *in vitro* in an IL-4-dependent manner [33]. Leukotrienes have also been shown to drive Th2 cell responses *in vivo* in response to specific allergens and in allergic skin inflammation [34, 35].

Signaling strength represents another determinant of Th cell polarization. While strong TCR mediated signals preferentially induce Th1 cell responses, weak stimulation via the TCR, and low antigen presentation favors a Th2 cell response in mice [36]. However, also very high doses of antigenic peptides have been reported to favor the Th2 cell differentiation program, contradicting previous reports [37, 38]. Although the initial source of the Th2 polarizing cytokine IL-4 still remains ill defined, other cytokines, which are mainly derived from epithelial cellular sources of barrier organs (e.g., thymic stromal lymphopoietin (TSLP), IL-25, and IL-33), have been shown to influence Th2 cell polarization as well as diversification [39]. TSLP is produced by epithelia that are exposed to different insults. Its receptor is expressed on naïve Th cells and can drive the differentiation of a distinct pro-inflammatory murine Th2 cell population characterized by IL-13 expression if systemic TSLP levels are sensed in lymphoid organs [40]. TSLP has also been shown to support Th2 cell responses via suppression of IL-12 secretion by DCs. This property can be co-opted by particular helminths rendering TSLP redundant for the development of Th2 cell responses [41].

Tissue-derived cytokines orchestrate Th2 cell diversification

Another “tissue checkpoint” of Th2 cell differentiation is IL-25 (also known as IL-17E). IL-25, which is mainly produced by tissue epithelial cells in mice [42], can promote Th2 cell differentiation by enhancing NFATc1 and JunB expression. This potentiates early IL-4 expression and the expansion and cytokine production of effector Th2 cells in mice and patients suffering from allergies [43, 44]. The alarmin IL-1 α , which can be released by keratinocytes [45], can also potentiate Th2 cell responses in an autocrine T cell dependent feedback loop [46, 47]. Likewise, IL-33, which represents another tissue derived source of a Th2 potentiating factor, has been described to enhance Th2 cell responses and tissue homeostasis [48–50]. Considering that expression of its receptor ST2 occurs independently of IL-4 but dependently on GATA-3, IL-33 signaling is thought to occur during later steps of murine Th2 cell differentiation, where it increases IL-5 and IL-13 production [51]. IL-33 polarization of antigen stimulated naïve murine and human T cells leads to IL-5 upregulation in the absence of IL-4. This is independent of GATA-3 and STAT6 but MAPK and NF- κ B dependent [52]. Clearance of gastrointestinal helminth infections requires IL-13 production by Th2 cells, which is also promoted by IL-33. Lack of EGFR, which mediates IL-13 expression by forming a signaling complex with its

ligand amphiregulin and the IL-33 receptor T1/ST2, abrogated IL-13 production, and thus host resistance in mice [53]. Although EGFR expression is TCR-activation dependent and thus antigen-specific, the induced ability to respond to IL-33 amplified the IL-13 response in an antigen-independent and thus innate-like manner [53]. Together, this demonstrates that these tissue-derived cytokines diversify the Th2 cell response in terms of differential cytokine expression profiles for further specialization purposes.

T cells co-opt NLRP3 for regulation of type 2 immune responses

NLRP3 is the most studied member of the family of nucleotide-binding oligomerization domain-like receptors (NOD-receptors) and an integral component of the inflammasome complex, which cleaves IL-1 β to exert innate danger signaling and cell death by pyroptosis [54, 55]. Surprisingly, it was found in mice that NLRP3 regulated the Th2 program by directly binding to the il4 promoter and by facilitating its transactivation via IRF4 [56, 57]. This was independent of its role in inflammasome activation. Accordingly, NLRP3 expression in Th cells was shown to be necessary for asthma induction in a mouse model [56]. Whether these recent insights into the transcriptional regulation of Th2 cells translate into novel therapeutic options remain to be seen, considering the recent identification of specific NLRP3 inhibitors in the context of inflammasome driven autoinflammatory diseases [58].

T follicular helper cells as drivers of type 2 immunity

T follicular helper cells (Tfh) drive humoral hallmarks of type 2 immunity [59, 60]. In addition, they have been identified as cellular collaborators for the induction of Th2 cells. IL-4 committed Tfh cells were shown to be precursors of allergen-specific Th2 cells [61, 62]. They are formed upon exposure to house dust mite allergen in a mouse model [61]. Due to their CXCR5 expression, Tfh cells are attracted to the germinal centers of lymph nodes where they support proliferation and differentiation of B-cells into plasma cells and where they provide critical help for antibody maturation [63, 64]. By their ability to produce substantial amounts of IL-4, Tfh cells reinforce a Th2 permissive cytokine environment and might therefore further encourage the induction of Th2 cells. During parasitic helminth infection, murine Tfh cells have been shown to maintain type 2 immunity through IL-4 secretion and to drive the primary IgE response [65]. The requirements for IL-4 production by Tfh cells themselves remain less well understood and differ from those of Th2 cells. Notch signaling has recently been shown to be required for Tfh cell generation but to be dispensable for Th2 cell differentiation in settings of helminth infections, highlighting one bifurcation checkpoint between these two cellular players of type 2 immunity [66].

Metabolic control of Th cell responses

Th cell responses are determined by their metabolic microenvironment. Th cells share a similar immunometabolism with respect to their engagement of the glycolytic machinery and mitochondria as compared to Treg cells or their naïve T cell precursors [67]. Still, insights are emerging that also delineate Th2 cells from other Th subsets. The kinase mTOR has a central role as a sensor of nutrients. It serves as a core of two signaling complexes, mTOR complex 1 (mTORc1) and mTOR complex 2 (mTORc2), which orchestrate several cellular processes including Th1 and Th2 cell polarization, respectively [68]. mTORc2 can contribute to Th2 cell polarization by inhibiting the negative feedback inhibitor SOCS5, which functions as a suppressor of STAT6 [69]. Loss of mTORc2 signaling results in a failure to generate Th2 cells but preserves the generation of murine Th1 and Th17 cells [70, 71]. mTORc1 signaling is, however, still required since it coordinates multiple metabolic programs in T cells to allow for antigen-triggered activation and exit from naïve T cell quiescence, a prerequisite for subsequent Th2 cell polarization [72]. The upstream signals from the tissue microenvironment favoring mTORc2 over mTORc1 signaling remain poorly defined. The mevalonate pathway, also called the HMG-CoA reductase pathway, that yields into the production of isoprenoids such as cholesterol, has also been shown to have a role on Th1 versus Th2 specification [73]. Statins, which block HMG-CoA within this pathway, have been shown to skew toward Th2, while suppressing Th1 cells. This had beneficial effects in the EAE mouse model of MS [73].

Heterogeneity of Th2 cell responses

The Th2 cell subset is characterized by the secretion of its effector cytokines IL-4, IL-5, IL-13, and IL-9 [74]. The differential integration of the polarizing cues outlined above shapes the overall function of the ensuing Th2 cells and thus creates Th2 cell heterogeneity and additional Th2 cell subpopulations with specialized functions in health and disease (Fig. 1). However, T cells that have received identical signals can also differ in effector cytokine production. This might be due to stochastic events of signal integration followed by uncoupling of concomitant cytokine production. This cytokine heterogeneity can also be due to spatial and temporal segregation of cytokine production. IL-4 and IL-13 have been demonstrated to be coregulated by identical transcriptional programs. Their genomic locus on chromosome 5 in humans and chromosome 11 in mice is under control of the locus control region (LCR) on the Rad 50 gene, which is indispensable for their *in vivo* production [75]. Yet, both Th2 cell signature genes differ in their molecular regulation. Calcineurin dependence, for example, applies to IL-4 but not to IL-13 production in mice [76]. IL-13 positive T cells have been identified that lack IL-4 co-expression. They have been shown to derive from naïve T cell precursors independently of IL-4 producing cells in Th2 cell conditions supplemented with TSLP and constitute a separate pro-inflammatory Th2 cell

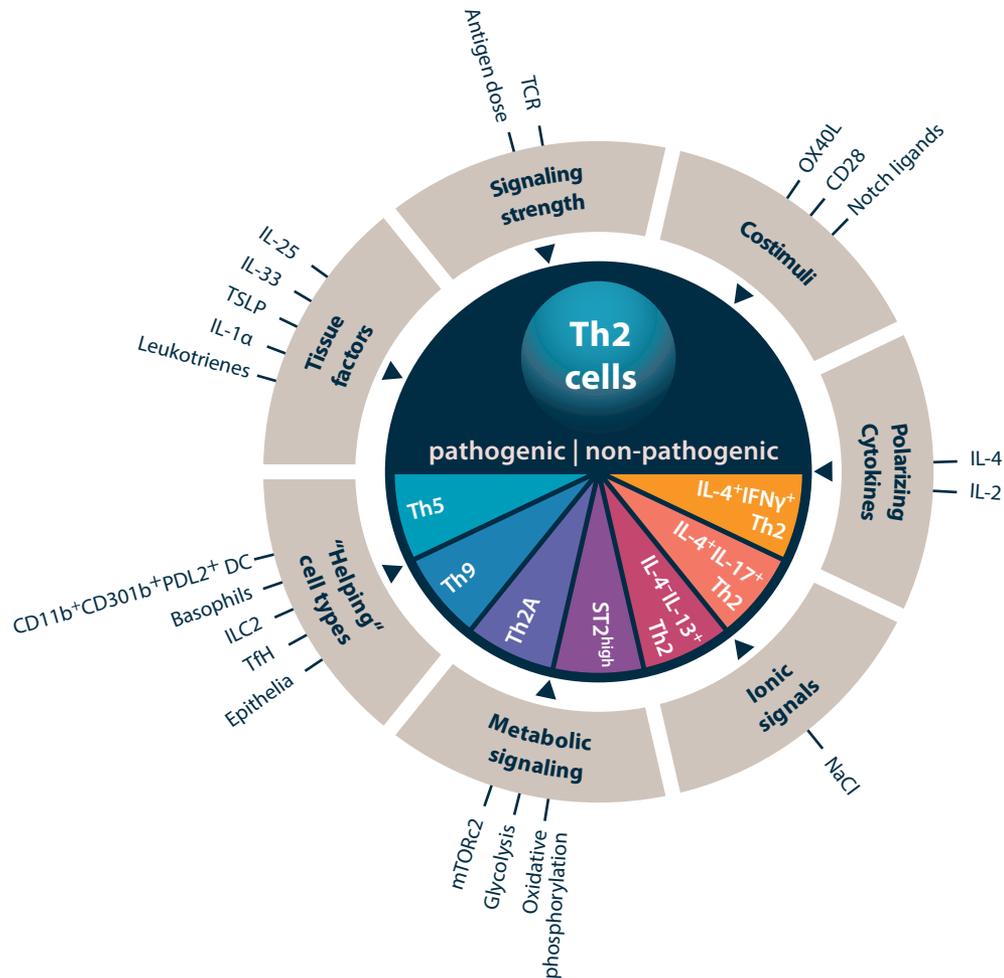


Figure 1. The heterogeneity of Th2 cells is shaped by different signals. Th2 cells can exert pro- or anti-inflammatory functions. They can be categorized into distinct subsets based on the differential expression of cytokines and surface markers (central circle and colored segments). The respective Th2 cell phenotypes and functions are induced by several intrinsic and extrinsic signals (grey areas).

subset in a mouse model [40, 77]. Therefore, Th2 functionalities might arise, which are biased toward one or another signature cytokine. This has further effects on downstream events since IL-4 but not IL-13 can act on naïve T cells for the purpose of Th2 cell polarization and proliferation. Several Th2 mediated allergic symptoms are also differentially regulated by either IL-13 or IL-4. Airway hypersensitivity and mucus metaplasia as encountered in asthma can be blocked by anti-IL-13, but not anti-IL-4 in a mouse model [78, 79].

Single-cell RNA sequencing has revealed production of the steroid pregnenolone by a subpopulation of Th2 cells in vitro and in a helminth infection model in vivo [17]. This steroid hormone producing Th2 cells have previously been masked by bulk transcriptomic analyses. IL-4 promoted, whereas IL-12 suppressed pregnenolone production, in line with its enrichment and absence in the Th2 and Th1 subset, respectively. Pregnenolone exerted immunosuppressive functions in mice, limited ongoing inflammation and could thus equip Th2 cells with a role in the restoration of immune homeostasis [17, 80]. In addition, this property was also

observed in tumor infiltrating Th cells, contributing to a tumor permissive microenvironment [80]. Together, these findings propose a largely overlooked T cell property beyond cytokine production, which is biased toward the Th2 cell subset and shaped in the immunosuppressive tissue microenvironment of chronic helminth infections and tumors.

IL-5 producing Th2-like cells

Similar to the segregation of the Th2 signature cytokines IL-4 and IL-13, observations about IL-5 production, which was independent of other Th2-associated cytokines, suggest the existence of a unique Th5 cell subset in mice [52, 81]. IL-5 producing T cells exacerbated allergen-induced airway inflammation in WT as well as IL-4 KO mice. This demonstrated that IL-5 can mediate allergic disease also independently of IL-4. IL-33 can also induce amphiregulin production by ST2^{hi} memory-type Th2 cells, which are distinct from IL-5 producing Th2 cells and also referred to as

pathogenic Th2 cells [82]. Amphiregulin exerts pathogenic roles in type 2 immunity and contributes to airway fibrosis in asthma through its ability to reprogram eosinophils toward an inflammatory state that includes increased production of osteopontin as has been shown in polyps from patients with eosinophilic chronic rhinosinusitis [82]. The IL-33-Th2-amphiregulin-osteopontin axis could therefore represent a potential target for therapeutically counteracting the fibrosis that is associated with chronic allergic disorders but also other fibrotic diseases such as liver fibrosis [83]. Amphiregulin production is, however, not only restricted to Th2 cells. Also, MUs provide a relevant source of Amphiregulin, by which they mediate tissue repair through its downstream TGF- β activation [83].

IL-9 producing Th2-like cells

IL-9 single-producing T cells have been identified and delineated as a unique Th9 cell subset. Their overall function mimics that of classic Th2 cells and explains their association with allergic skin and lung inflammation [84]. Th9 cells exert effector functions targeted at the elimination of helminths independently of IL-4 [7]. PU.1 was one of the first transcription factors to be associated with IL-9 induction in the Th9 cell subset in mice and humans [85, 86]. BATF and IRF-4 cooperatively contribute to Th9 cell development [87]. CNS-25 acts as an enhancer upstream of the *il9* gene binding most IL-9 promoting transcription factors, as could be shown in mice [88]. TL1A, which represents a member of the TNF superfamily, promotes Th9 differentiation, and function through induction of transcriptional BATF3 expression in mice and humans [89]. The transcription factor peroxisome proliferator-activated receptor- γ (PPAR- γ) regulates IL-9 but not other Th2 signature cytokines and therefore defines a subpopulation of IL-9 expressing T cells within the human Th2 cell pool [90]. The subset status of Th9 cells still remains a matter of debate, since these putative Th9 cells display features overlapping with classic Th2 cell regulation. The Th9 phenotype is displayed, in particular, upon activation of Th2 cells, which is accompanied by transient downregulation of IL-4, IL-13, and IL-5 but upregulation of IL-9, thus reflecting a functional state of Th2 cells [90]. Further studies of their epigenetic identity as well as their ontogeny by lineage tracing could help to resolve this dispute.

Blurring borders among Th1, Th2, and Th17 traits

Th2 cells can simultaneously display the identities of distinct Th cell subsets. Subpopulations of circulating human T cells have been identified that express both IL-4 as well as the Th17 cell signature cytokine IL-17. These cells have been attributed specific roles in asthma [91]. IL-17 coproducing mouse Th2 cells caused increased recruitment of eosinophils, neutrophils, and lymphocytes into the airway as compared to classical Th2 or Th17 cell subsets [92]. They have also been shown to be resistant to immunosuppressive

treatment with dexamethasone in asthmatic patients in contrast to classic Th2 cells [93]. Defects in the key transcription factor FoxP3 in murine Treg cells result in the reduction of Treg cell regulatory functions and induce a Th2-like phenotype, highlighting the plasticity among T-cell lineages [94]. Despite extensive evidence for the reciprocal molecular regulation of Th1 and Th2 cells, hybrid IL-4 and IFN- γ positive T cells exist that resist reprogramming into either classic Th1 or Th2 cells in humans and mice [95, 96]. IL-4/IFN- γ coexpression can, however, also result from secondary restimulation of classic Th1 or Th2 cells in skewing microenvironments due to cell intrinsic plasticity [95]. Epigenetic remodeling plays a major role in T cell plasticity. The balance between the trimethylation and acetylation of H3K9 is regulated in a lineage-specific manner at key Th1 and Th2 gene promoters and correlates with silencing or activation, respectively [97]. Enhanced plasticity of both Th1 and Th2 cells was observed in mice when *Ezh2* function, which catalyzes histone methylation as a component of the Polycomb Repressive Complex 2, was lost, suggesting that it was relevant for subset stability [98].

Differential expression of surface markers delineates Th2 cell heterogeneity

Surface markers also provide phenotypic heterogeneity paired with functional specialization to T cells. The expression of chemokine receptors, which equip T cells with distinct migration properties, is coregulated with functional adaptation of T cells [99]. Several chemokine receptors have been associated with the Th2 cell subset including CCR3 [100], CCR4 [101], CCR8 [102], and the prostaglandin D2 receptor CRTH2 [103]. The differential expression of CXCR3, CD62L, or CCR8 identified Th2 cells with enhanced effector functions in a murine model of allergic inflammation. Terminally differentiated Th2 cells termed Th2A cells, which coexpress CD49d and CD161 but are negative for CD27, have recently been identified in humans. They are considered pro-allergic and strongly confined to atopic individuals [104]. Although CD161 has been considered a signature surface marker for human Th17 cells as well as their precursors [105, 106], its expression on Th2 cells has previously also been associated with IL-5-producing effector T cells in settings of eosinophilic gastrointestinal disease [107]. This heterogeneity within the Th2 cell subset translates into differential roles in immunopathology and might serve immune monitoring purposes. Murine Th2 cells with CXCR6⁺ST2⁺CD44⁺ surface expression, on the other hand, display specialized functions for the inhibition of helminth fecundity, which could serve biomarker purposes in settings of helminth infections [108].

Taken together, Th2 cell responses are heterogeneous as well as specialized and correlate with distinct functions, molecular regulation patterns as well as surface phenotypes. It should, however, not be overlooked that a division of labor takes place with other specialized cellular collaborators such as Tfh2 as well as ILC2 cells, which also share IL-4 production as an effector mechanism and

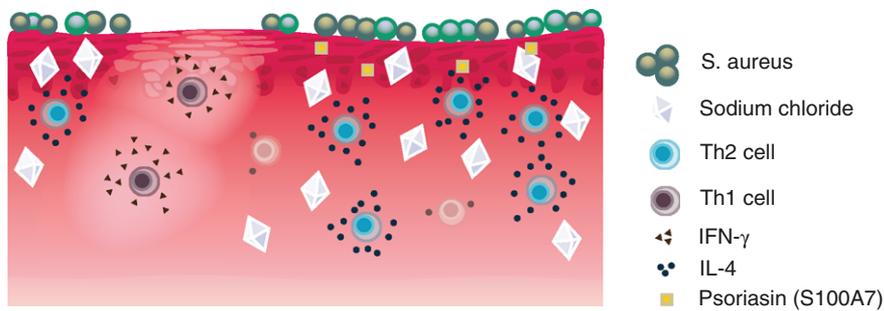


Figure 2. NaCl promotes Th2 cell responses and accumulates in the inflamed skin of atopic dermatitis patients. NaCl upregulates IL-4 and IL-13 expression by Th2 cells, which are crucial for the pathogenesis of atopic dermatitis. The unaffected skin of atopic dermatitis patients contains less NaCl. *S. aureus* is known to outgrow other bacteria in high NaCl concentrations, which could potentially explain the *S. aureus* dominated dysbiosis, a characteristic of atopic dermatitis. How NaCl accumulates in the inflamed skin remains unknown.

result in downstream events for the execution of parasitic expulsion or allergic inflammation [109].

Regulation of Th2 cell responses in peripheral tissues

Tissue specific T cells have previously been considered to be terminally differentiated effector T cells with the ability to recirculate and to home to peripheral tissues. The classic concept of T cell compartmentalization comprising naïve, central, and effector memory T cells has now been complemented by the addition of tissue resident memory T cells (T_{RM}). They express markers of residency such as CD69 and CD103 and persist long-term in their respective tissues where they contribute to fast first-line barrier defense, tissue homeostasis, and possibly other functions that remain to be defined [1]. Most insights into T_{RM} cells have been generated for the $CD8^+$ T cell compartment, but more knowledge into polarized Th cell residency programs is emerging. In a mouse model of house dust mite induced airway inflammation tissue, resident Th2 memory cells were identified and shown to exert pathogenic functions by their secretion of type 2 cytokines independently of recirculating T cells [110]. IL-2 signaling was required for instructing the program of Th2 cell residency and pathogenicity [110]. The maintenance of lung resident Th2 cells is antigen independent but contingent on IL-7 secreting lymphatic endothelial cells that are localized within bronchus-associated lymphoid tissues, as has been shown in mice [111]. Clinical observations support the role of resident Th2 cells in conferring allergic diseases. Lung transplants from mildly asthmatic donor patients transferred clinical airway disease to non-asthmatic transplant recipients. Reciprocally, non-asthmatic lungs conferred disease amelioration to asthmatic patients [112].

The role of ionic checkpoints for Th2 cell polarization

Availability of tissue-specific factors might further shape the heterogeneity and distribution of distinct T cell subsets. Recently, a role for sodium chloride (NaCl) for cytokine independent polarization of human naïve T cells into Th2 cells was identified [113]

(Fig. 2). NaCl has been reported before to have immunomodulatory functions in innate and adaptive immunity [114]. It alters the functionality of immune cells in salt-enriched inflamed tissues and shifts the composition of the intestinal microbiota [114]. In the skin, NaCl has previously been shown to exert immunoregulatory functions on rat macrophages with an impact on blood pressure control [115, 116]. Interestingly, NaCl concentrations were further elevated in skin lesions of atopic dermatitis patients in accordance with the Th2-associated pathogenesis of this disease [113, 117]. It is currently unclear, whether this lesional enrichment of cutaneous sodium is associated with dietary salt intake. Normal sodium concentrations in unaffected skin of atopic dermatitis patients rather suggest localized events as a mechanism of lesional sodium deposition [113]. NaCl exerts Th2 cell polarization and Th2 cell expansion through upregulation of serum- and glucocorticoid-regulated kinase 1 (SGK1), which represents a downstream target of mTOR Complex 2 (mTORC2), as T cell specific deletion of the mTORC2 specific adaptor Rictor abrogates the activation of SGK1 [91]. This links environmental NaCl sensing with metabolic Th2 programming. SGK1 and NFAT5 were shown to upregulate GATA-3 as well as phosphorylation of STAT6 in hypersaline conditions [113]. NaCl can also skew Th1 and Th17 cells to acquire Th2 cell properties on the memory T cell level, thus exploiting the plasticity of non-Th2 cells in favor of type 2 cell responses. These effects on T cells are contingent on the acute presence of elevated concentrations of NaCl and cannot be maintained upon NaCl withdrawal [113]. This is in accordance with a lack of epigenetic imprinting of a NaCl induced Th2 signature in contrast to its effect on epigenetic marks in macrophages [118]. These recent insights revealed NaCl as a so far rather overlooked “ionic checkpoint” for Th2 cell responses in addition to other critical players. It remains to be shown whether therapeutic targeting of NaCl sensing and signaling will have an impact on allergies and other type 2 mediated diseases.

NaCl has recently also been suggested to promote autoimmunity via Th17 cell polarization in mice [119, 120]. It acted in concert with polarizing cytokines to increase IL-17 expression, whereas type 2 responses were induced independently of polarizing cytokines by default [119, 120]. This suggests that the cytokine microenvironment plays a critical switch factor role for the immunomodulatory functions of NaCl. This might allow NaCl to act as a tissue rheostat that can promote different T cell

responses depending on cytokine co-factors in the microenvironment. NaCl also has an impact on Treg cells, as it abrogated their suppressive function [121]. A more recent report, on the other hand, demonstrates that peripherally induced iTreg are completely stable and functional in high salt conditions [122]. It will be interesting to systematically establish the differential distribution of NaCl in human tissues to assess the physiological relevance of NaCl as a so far rather overlooked factor of the tissue microenvironment, considering its impact on T cell responses. In addition, it will have to be assessed whether alterations in tissue NaCl concentrations correlate with T cell mediated human disease conditions and whether this could be modulated by diet. The observation that atopic dermatitis is associated with strongly increased skin sodium deposition might be just the beginning [113].

The role of glucose for Th2 cell regulation

Glucose is a small molecule that easily penetrates into tissues. As early as 1932, skin glucose had been found to correlate with blood glucose levels in diabetic patients [123]. Obesity, which is a high-risk factor for the development of the hyperglycemia-associated metabolic syndrome, is associated with the rising prevalence of allergic diseases [124]. Recently, varying concentrations of glucose have been found in the sweat of atopic dermatitis patients [125]. Thus, glucose seems to be a variable microenvironmental tissue factor with a potential impact on Th2 immunity. Th2 cells have the highest rate of glycolysis among the Th cell subsets, as has been shown in mice [126, 127]. GLUT1 deficient murine T cells display decreased effector cell expansion and reduced Th2 cell skewing in the presence of IL-4 [126, 128]. Loss of the Raptor-mTORC1 signaling axis, which is required to regulate TCR-induced glycolysis, as well as direct inhibition of glycolysis, markedly decrease IL-4 production in mice under Th2 polarizing conditions [72]. Furthermore, Raptor deficiency causes diminished IL-4Ra expression and STAT6 phosphorylation. Hyperglycemia has been found to promote the activation of human mast cells—a major driver and executor of allergic immune reactions [129]. Thus, besides a direct impact of glucose on Th2 cells, high-glucose stimulated Th2 cells might further amplify allergic immune reactions by attracting mast cells into a glucose rich microenvironment [130].

The role of temperature for Th2 immunity

Seasonal temperature drops coincide with a transient intensification of treatment for most asthma and atopic dermatitis patients [131, 132]. Inhalation of cold air has been found to increase immune cell infiltration in the airways of mice [133]. Thermoneutral housing with inhalation air temperatures of 30°C as compared to standard 20°C has been found to lower IL-4 and IL-13 concentrations in bronchial alveolar fluid of mice [134], suggesting promotion of Th2 immune responses upon cold air inhalation. The cold-gated ion channel transient receptor potential cation

channel subfamily M member 8 (TRPM8) increases the expression of the Th2 cytokines IL-4 and IL-13 in human cold-stressed airway epithelial cells [135]. Furthermore, TRPM8-stimulation has been shown to decrease the signature cytokine IFN- γ after cold air inhalation in asthmatic mice, which is reverted upon TRPM8 knockdown [133]. TRPM8 expression can also be found in the epidermis of human skin [136]. As the skin is subject to strong temperature changes, it can be speculated that similar pathways apply to the characteristic exacerbation of atopic skin lesions in low temperatures. On the other hand, TRPM8 stimulation was found to relieve chronic itch in mice, which is a major symptom of AD that can amplify the disease course due to scratching behavior [136]. Thus, cold-stress impacts Th2 immunity on multiple levels with partly opposing effects, which still require further clarification. Reciprocally, cold-stress is also affected by an IL-4 signature as exemplified by alternative macrophage activation through IL-4, which orchestrated thermogenic gene expression and energy expenditure in low temperatures in mice [137].

Th2 cells and the microbiota

Barrier tissues such as the skin or gut are constantly exposed to environmental stressors and densely colonized by the commensal microbiota [138]. The healthy non-inflamed human skin harbors around one million T cells/cm², most of them being of a resident phenotype [1, 139].

Accumulating evidence suggests that those tissue resident T cells display antigen specificities against the commensal microbiota and functions tailored for the tissue-microbial dialogue [140]. *Staphylococcus epidermidis* (*S. epidermidis*) was shown to promote the accumulation of murine ROR- γ ⁺ CD8 and CD4 T cells that acquired GATA-3 coexpression within the tissue as a result of barrier disruption and exposure to the alarmin IL-18 [141]. This licensed *S. epidermidis* reactive T cells to exert type 2 responses and demonstrated plasticity in the context of perturbed tissue integrity. T cell derived IL-13 production promoted wound repair, thus linking antimicrobial reactivity to tissue homeostasis [141]. The gut microbiota has been shown to induce type 3 ROR- γ ⁺ Treg cells and Th17 cells that counterbalance Th2 cell responses. Dysbiosis could therefore promote exacerbated type 2 immunity and allergy [142].

Targeting Th2 cell responses therapeutically in the tissues

Previous and ongoing strategies to suppress Th2 mediated atopic inflammation comprise unspecific paralysis of the immune system by, for example, corticosteroids or T cell targeted approaches by cyclosporin, a calcineurin inhibitor that prevents IL-2 production via NFAT [117]. These systemic drugs display plenty off-target effects and toxicities. Insights into the mechanistic pathways and the cellular crosstalk within the tissue microenvironment have recently translated into more targeted approaches, thereby

mitigating the diverse origin of Th2 cytokines, such as from steroid-resistant IL13⁺ ILC2 cells, where systemic steroid therapy fails to inhibit cytokine production in asthma patients [143]. In particular, the Th2 effector cytokines IL-4 and IL-13 are currently successfully targeted by inhibition of their common receptor IL-4R. Dupilumab, which blocks IL-4R, is the first biological drug approved for atopic dermatitis. It showed good efficacy in randomized, placebo controlled phase 3 clinical trials (SOLO 1, SOLO 2) [144, 145]. Also single cytokine blockade of IL-13 resulted in improvement of atopic dermatitis [146, 147]. Surprisingly, IL-13 blockade did not prove to be effective for the treatment of asthma in two large randomized, double-blind, placebo-controlled, phase 3 clinical trials (STRATOS 1, STRATOS 2) despite its anticipated effects on reducing eosinophilic inflammation, IgE production, macrophage and DC activation as well as airway smooth muscle remodeling. Failure of this treatment modality could potentially be due to lack of action in relevant tissue compartments or redundancy of IL-13-driven responses. In a macaque model of chronic asthma, preliminary efficacy could be achieved using inhalation of IL-13 mAb Fab antibody fragments via a vibrating membrane nebulizer [148]. This implies that immune pathway educated therapeutic strategies should address the compartmentalization of tissue specific immune responses. IL-31 represents another cytokine and a mediator of itch that is preferentially associated with Th2 cell responses in mice [149]. Nemozumab, an anti-IL-31 receptor mAb, proved efficacious in pruritus control in a double-blind, placebo controlled, randomized clinical trial for atopic dermatitis [150]. The JAK and STAT pathway (JAK-STAT) transmits inflammatory signals to the cell nucleus. In experimental models, JAK inhibitors resulted in decreased IL-4 and IL-13 signaling accompanied by improved skin barrier in atopic dermatitis-like skin disease [151]. Oral and topical JAK inhibitors (tofacitinib) also proved efficacious in patients with moderate-to-severe atopic dermatitis that were resistant to conventional treatments [152]. Although JAK inhibitors can also be applied topically to the inflamed skin, more investigations are needed before more widespread use can be advocated [152, 153].

Chemokine receptors could represent another mode of Th2 cell targeting, since Th2 cell responses are associated with characteristic chemokine receptor expression profiles. CCR4 is highly enriched in Th2 cells and might thus serve as another target according to murine studies, in which CCR4 antagonists improved atopic dermatitis-like skin lesions [154].

Tissue-specific dysbiosis is inherent to several chronic inflammatory diseases of the skin, lung, or gut. Atopic dermatitis is characterized by a dysbiosis dominated by *S. aureus* [117]. It has been shown to improve clinically upon “commensal skin transplants” in atopic dermatitis patients, which exerted antimicrobial activities against *S. aureus* [155]. The underlying reason for the dysbiosis remains enigmatic until now. Interestingly, NaCl, which is highly enriched in the affected skin, favors the preferential outgrowth of *S. aureus* at the expense of other species of the commensal microbiota [156] and could therefore, in conjunction with its direct Th2 promoting effects, provide an important common determinant of atopic disease pathogenesis [113]. However, other factors

likely contribute to the dysbiosis. Psoriasin, an antimicrobial peptide, was found to be highly elevated in the inflamed atopic skin. While it suppresses *E. coli* colonization, its presence allows for *S. aureus* persistence, thus contributing to the pathognomonic dysbiosis [157].

Conclusions

The past few years have witnessed an increase of distinct Th cell subsets with specialized functions in host defense and tissue homeostasis. At the same time, it has been acknowledged that the flexibility and plasticity of individual T cell subsets allows for a broad repertoire of effector functions that are instructed by diverse tissue-specific cues. Th2 cells can therefore assume diverse functions depending on their differential expression of prototypic type 2 cytokines, coexpression of signature cytokines of alternative T cell subsets, distinct migration properties, residence versus recirculation programs, and body location. They even display novel features such as steroid production that could be unmasked thanks to enabling technologies that embrace the high-dimensionality of T cells at the single-cell level [17]. Further phenotypes, functions and regulatory checkpoints that characterize type 2 responses in health and disease will probably emerge soon. Although we have focused on Th2 cells, it should not be overlooked that other cellular subsets share similar effector functions such as IL-4 production by Tfh and ILC2 cells despite differential molecular mechanisms. These insights now need to be integrated into therapeutic strategies that are tailored for homeostatic versus pathogenic Th2 cell functions, as well as their tissue compartmentalization and collaboration with other type 2 associated cells.

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Abbreviations: ILC2: group 2 innate lymphoid cell · PPAR: peroxisome proliferator-activated receptor · Tfh: T follicular helper · T_{RM}: resident memory T cell · TSLP: thymic stromal lymphopoietin

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