

Pathogenic T cell subsets in allergic and chronic inflammatory bowel disorders

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Summary

Homeostasis in the gastrointestinal tract relies on a sensitive equilibrium between permissive and protective functions. This is closely reflected in the regulation of the intestinal immune system and especially T cells in the gut. This balance, however, is susceptible to disturbances as demonstrated by pathological conditions like food allergy, celiac disease, or inflammatory bowel disease. In these allergic and chronic inflammatory bowel disorders, luminal antigens get access to the lamina propria where they trigger a dysregulated immune response with crucial involvement of different T cell subsets. We will begin this review with some comprehensive remarks on current concepts on the pathogenesis of these diseases before taking a closer look at the life cycle of intestinal T cells consisting of priming, homing, differentiation and proliferation and apoptosis respectively. Subsequently we will discuss the specific implication of distinct T cell subsets in allergic and chronic inflammatory conditions of the gastrointestinal tract in detail and comment on current and future approaches to targeted therapy in this context.

KEYWORDS

celiac disease, cytokines, inflammatory bowel diseases, food allergy, T cells

1 | INTRODUCTION

The mucosa of the gastrointestinal tract faces the heavy challenge to reconcile different opposing requirements: On a gigantic surface, nutrients, vitamins, and ions have to be transported from the lumen to the tissue, while toxic, allergic or microbial agents from the food or the intestinal flora have to be kept out and coped with or egested. To this end, a sophisticated network of cellular strategies has evolved that effectively realizes these tasks in most cases: A single layer of epithelial cells sealed by tight junctions and covered by a layer of mucins and phospholipids acts as a mechanical barrier but is also equipped with membranous enzymes, channels, and transporters to digest and grant access to dietary products. Moreover, commensal bacteria in the lumen help to digest the food and impede overgrowth of unsolicited species, while specialized Paneth cells in the epithelium

secrete antimicrobial products like defensins to prevent overgrowth or growth of pathogenic bacteria.¹ Below the epithelium, a large variety of different cells occupies the lamina propria and executes different duties: Endothelial cells forming a dense net of blood vessels help to cart off the absorbed food components, deliver oxygen, and allow replenishment of lamina propria cells through gut homing from high endothelial venules.² Innate immune cells like macrophages or dendritic cells surveil their neighborhood for the potential entry of pathogens and concomitantly suppress aberrant immunological responses to the high load of commensal bacteria in the gut. After priming in the gut-associated lymphoid tissue (GALT) and gut homing adaptive immune cells like T and B cells are ready to specifically combat defined pathogens. Although all these cells have different functions, they busily communicate with each other through the secretion of cytokines and direct cell-to-cell contacts resulting in a complex system of checks and balances that secures purposeful digestion and absorption and appropriate reaction to aggressive factors.³

However, the complexity of this network also predisposes to dysregulation. While it works astonishingly well in most individuals, several pathological conditions exist, which arise from defects in the interplay of mucosal cells with each other and luminal agents. Among the most important examples for such conditions are allergic reactions to luminal products, celiac disease, and inflammatory bowel diseases (IBD).^{4–7} Regarding the above depictions, it is obvious that such diseases have a complex pathogenesis with involvement of several cellular players. However, recent research has highlighted the important role of T cells in mediating and orchestrating immunopathogenesis of these disorders.

Thus, this review article will provide a summary on the significance of T cells in allergic and chronic IBD. We will begin with giving an overview of current concepts in their pathogenesis and subsequently review development, trafficking, turnover, and differentiation of intestinal T cells before outlining to date's evidence on particular T cell subsets and their implication in the disorders in focus. Moreover, we will comment on how this knowledge has been and might futurely be translated into clinical practice.

2 | OVERVIEW OF THE PATHOGENESIS OF ALLERGIC AND CHRONIC INFLAMMATORY BOWEL DISORDERS

2.1 | Food allergy

Based on the pathogenesis, food allergy is classified into three distinct groups: IgE-mediated food allergy, cell-mediated food allergy, and mixed IgE-associated/cell-mediated food allergy.⁴ The prevalence of these disorders has been significantly growing in recent years reaching a regionally highly variable life time prevalence of more than 17% in Europe and even exceeding 40% in Eastern Europe.⁸

Antigens possibly eliciting food allergy are present within the food proteins, which amount to 70–100 g daily.⁹ In healthy individuals, however, a combination of digestive reduction of immunogenicity and immunological anergy lead to the status of 'oral tolerance'. In particular, the pH drop in the stomach as well as gastric, pancreatic, and small-intestinal proteases lead to degradation of proteins into single amino acids or oligopeptides and breakdown of immunogenic conformational epitopes resulting in a markedly reduced potential to evoke immune responses.¹⁰ If yet immunogenic epitopes cross the epithelial border and reach the gut tissue, such antigens are physiologically processed by CD103⁺ dendritic cells (DCs),¹¹ which migrate to the GALT, where they induce the priming of antigen-specific and gut-homing regulatory T cells (Tregs).¹² After entry of these Tregs to the gut, they suppress aberrant activation in response to food antigens together with cells of the innate immune system.¹³ Though, early in life and in pathological conditions the gastrointestinal mucosal barrier is in an immature state or leaky, respectively, leading to higher exposure to food antigens. While this might be meant to allow establishment of oral tolerance in the first case, it may also result in immune activation and development of food allergy.¹⁴ If this is the case, in a first step of antigen sensitization antigen-specific Th2 cells secreting high levels

of IL-4, IL-5, and IL-13 are primed by DCs in the GALT,¹⁵ which will be discussed in greater detail below. Moreover, at least in IgE-mediated conditions, B cells undergo an isotype switch and secrete allergen-specific IgE upon breakdown of oral tolerance.¹⁶ The exact mechanisms leading to this switch are still poorly defined but it seems to be facilitated by a Th2 environment.¹⁷ In addition, the Th2 milieu leads to inhibition of suppressive Treg mechanisms,¹⁸ favors the expansion of intestinal mast cells¹⁹ and the infiltration of eosinophils.²⁰ Intestinal mast cells are believed to be the key effector cells of IgE-mediated food allergy. They carry a high-affinity IgE receptor called FcεRI on their surface. Following antigen sensitization and re-exposure cross-linking of membrane-bound IgE on mast cells by the allergen leads to degranulation and release of pro-inflammatory cytokines and mediators like histamine or platelet activating factor with subsequent local symptoms like diarrhea but potentially also systemic signs including urticaria, pruritus, or anaphylaxis.^{4,9,10} Of note, not only sensitization but also this effector phase requires translocation of food proteins in their immunogenic conformation over the epithelial barrier. This is facilitated by the low-affinity IgE receptor CD23 expressed by intestinal epithelial cells (IECs) in response to Th2 cytokines allowing transcytosis of allergen-IgE complexes and subsequent contact with mast cells.¹⁰ It should also be mentioned that sensitization to food allergens via non-oral routes (eg, lung, skin) is also under debate.^{21–23}

Cell-mediated food allergies are known under terms like food-protein induced enteropathy, food-protein induced enterocolitis syndrome or food-protein induced allergic proctocolitis.²⁴ In contrast with IgE-mediated food allergy, their pathogenesis has poorly been elucidated to date. However, systemic IgE against the causing allergens is missing and symptoms are limited to the gastrointestinal tract. Several studies suggested an important contribution of eosinophilic inflammation as well as increased TNF-α and reduced TGF-β responses.⁴

Some examples for food proteins frequently causing food allergy are casein, parvalbumin, profilins, and prolamins occurring in milk, fish, fruits, and cereals respectively.²⁵

2.2 | Celiac disease

Celiac disease, also called gluten-sensitive enteropathy, is believed to originate from an interplay of individual genetic variables with the antigen gluten and additional environmental factors.²⁶ The by far most important genetic aspect is that virtually all patients with celiac disease are carriers of either the major histocompatibility complex (MHC) II alleles HLA-DQ8 or HLA-DQ2. Additionally, single nucleotide polymorphisms in several other genes, many of them related to T cell function, have been associated with an increased risk for celiac disease.²⁷ However, only a small portion of people with HLA-DQ2 and HLA-DQ8 develops pathology highlighting the involvement of environmental factors in disease pathogenesis. Changes in the intestinal microbiome, infections in early life, breast feeding practices, and early exposure to gluten belong to the most suspicious influencing variables.^{5,26} Ultimately, disease onset is effectuated by a pathogenic immune response to gluten proteins, mainly gliadins and glutenins, which are present in most cereals. These proteins are particularly resistant to

digestion, thus potentially reaching the lamina propria of the small intestine in an immunogenic form. Moreover, these proteins are rich in glutamin and prolin, which are substrates of the enzyme tissue transglutaminase that deamidates these amino acids resulting in negative charge and stronger binding to HLA-DQ2 and -DQ8 molecules of antigen presenting cells.²⁶ Upon presentation of these antigens to naïve T cells in the GALT, mainly Th1 cells are primed that home to the small intestine and initiate inflammation there. Furthermore, the production of antibodies to tissue transglutaminase and gluten by B cells is prompted.⁵ In addition, a second pathway with important contribution of innate immune cells exists that leads to activation of CD8⁺ T cells attacking the epithelium: DCs, macrophages and also epithelial cells recognize certain gluten peptides²⁸ with pattern recognition receptors (PRRs) resulting in the release of IL-15. This cytokine triggers the development of mainly CD8⁺ intraepithelial lymphocytes (IELs) with a cytotoxic profile that mediate epithelial apoptosis.²⁹

These mechanisms finally lead to a typical picture of villus atrophy and crypt hypertrophy with ensuing symptoms like diarrhea, abdominal pain, malabsorption, and related extra-intestinal disorders due to deficiency in vitamins, nutrients, or trace elements.³⁰

2.3 | Inflammatory bowel diseases

In comparison to food allergy and gluten sensitive enteropathy, the antigens leading to IBD are much less well-defined. Crohn's disease (CD) and ulcerative colitis (UC) are the main entities of IBD.^{6,7} They are characterized by chronic-relapsing flares of intestinal inflammation resulting in abdominal pain, diarrhea, and rectal bleeding. While UC only affects the large intestine, CD can affect any part of the gastrointestinal tract with the ileocecal transition as predilection site. Similarly, both diseases share some of their potential extraintestinal manifestations and intestinal complications like uveitis, arthralgia, or colitis-associated colorectal cancer, but differ in the frequency of others like primary sclerosing cholangitis or toxic megacolon, which are more often found in UC, while fistulae and stenosis are a hallmark of CD. Such similarities and differences are also reflected in the pathogenetic concepts, which assume that there is considerable overlap in the development of IBD in general, but also specific features exclusive for CD and UC.

A multitude of factors that are interconnected in a complex network are believed to contribute to IBD pathogenesis. Among the most important are the individual genetic predisposition, environmental and behavioral factors, the intestinal microbiome, the intestinal epithelial barrier and—most vitally in this context—the immune system of the gut. In brief, a whole bunch of genetic variations in a large number of genes have been identified as risk factors for IBD. Many of them concern cytokines, transcription factors or receptors expressed by the adaptive immune system (eg, IFN- γ , IL-10, IL-23R, STAT4, IL2RA) or factors associated with the processing and presentation of luminal antigens by cells of the innate immune system (eg, NOD2, IL12B).³¹ Similarly, the availability of hygienic sanitary conditions or the use of antibiotics influence the individual risk for IBD, most probably through affecting the composition of the intestinal flora. Moreover, smoking,

diet and the use of non-steroidal anti-inflammatory drugs have been linked to the predisposition for IBD.³² Several groundbreaking studies from the last two decades support the notion that the microbiome with its myriads of bacteria (and also fungi and viruses) is a major disease-driving player in CD and UC. It is now clear that the biodiversity in the gut of IBD patients is reduced compared with healthy individuals while, conversely, specific strains are selectively enriched and others that are not part of the common commensal flora are present.³³ However, an altered flora can only lead to pathology with an appropriate interaction partner reacting to it. Consistently, evidence suggests that a leaky epithelial barrier in IBD facilitates the access of microbial components to the lamina propria³⁴ with subsequent recognition by the intestinal immune system initiating a dysregulated and undercontrolled inflammatory response that leads to destruction of intestinal structures and promotes further immune cell activation and inflammation.¹

As outlined above the intestinal immune system consists of several cells with different functions. T cells occupy a central position in this system. Accordingly, IBD are characterized by a marked T cell infiltration³⁵ and several key experimental models of IBD crucially rely on T cells.³⁶ Many T cell expressed cytokines are increasingly secreted in both murine experimental colitis and human IBD.^{35,37,38} Finally, most available and potential future therapeutic strategies act by limiting T cell function in the gut,³⁹ further underscoring that these cells are indispensable for disease development and promising candidates to modulate disease.

3 | HOW T CELLS REACH AND STAY IN THE GUT: OVERVIEW OF T CELL TRAFFICKING

Regardless of the disease entity introduced above, pathologic T cell effector functions in the gut require some previous steps that lead to recruitment of antigen-specific T cells to the inflamed mucosa. T cells develop in the thymus and leave it as so called naïve T cells. Such T cells are equipped with a unique T cell receptor and are released to patrol secondary lymphoid organs in search of a potential cognate antigen.⁴⁰ In fact, this means that most naïve T cells will always be naïve T cells, while those that will come across a 'match' in the lymphoid tissue will be activated, will proliferate, and will seed peripheral organs like the gut. This sequence that results in pathogenic T cells reaching the gut in the reviewed conditions includes a number of distinct events: First, naïve T cells home to the GALT. Homing describes the process of extravasation from high endothelial venules (HEVs) to peripheral tissues and briefly involves an initial step of slow rolling of the cell along the vessel wall, subsequent activation with conformational change of membranous receptors, then firm arrest of the cell at the venular wall and, ultimately, trans- or paracellular transendothelial migration.² Naïve T cell GALT homing is controlled by rolling via L-Selectin and $\alpha 4\beta 7$ integrin, which interact with the mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1) that is exclusively expressed on vessels in the intestine, activation by CCL-19 and CCL-21 through CCR7 expressed

on naïve T cells and finally high-affinity adhesion of $\alpha 4\beta 7$ integrin to MAdCAM-1.^{40–43} In the lymphoid tissue of the GALT, naïve T cells get in contact with antigen-presenting cells, more precisely with CD103⁺ DCs that sample the gut tissue (and through extension of dendrites between epithelial cells even the lumen) for evolutionary conserved pathogen-associated molecular patterns (PAMPs) which they detect with PRRs.^{11,44–47} Upon subsequent processing of the associated pathogen, they migrate to the GALT for presentation of the obtained antigens to adaptive immune cells. Once a naïve T cell gets in contact with its cognate antigen and provided that appropriate co-stimulatory signals are present, it is activated and proliferates to a whole antigen-experienced T cell pool with the same T cell receptor.⁴⁸ L-Selectin and CCR7 expression is lost during this process, but, most importantly, CD103⁺ intestinal DCs have the distinct feature to produce retinoic acid from retinaldehyde, which induces the expression of $\alpha 4\beta 7$ integrin and CCR9 on primed T cells.⁴⁹ In conclusion, T cell priming in the GALT leads to the specific generation of large numbers of antigen-specific T cells capable to home to the gut. After such T cells have left the GALT to recirculate in the blood stream, this takes places in intestinal HEVs by rolling through low-affinity $\alpha 4\beta 7$ -MAdCAM-1 interactions, CCL-25-dependent activation via CCR9 and finally firm arrest mediated again by $\alpha 4\beta 7$ -MAdCAM-1 or $\alpha 4\beta 1$ -vascular cell adhesion molecule (VCAM)-1.^{50,51} After transmigration these T cells have then reached their provisional destination and are ready to contribute to immunologic events. However, this is not necessarily the last step in the voyage of an intestinal effector T cell. Sphingosin-1 phosphate (S1P) promotes tissue egress via the S1P receptor⁵² and, similarly, CCR7 on T cells may lead to emigration via lymph vessels.⁵³ On the other hand, TGF- β has been shown to downregulate $\alpha 4$ in favor of αE integrin resulting in $\alpha E\beta 7$ expression and retention of T cells near or in the epithelium through interaction with the corresponding receptor E-Cadherin.⁵⁴

Collectively, T cell trafficking is a tightly controlled process that is an indispensable part of both physiologic and pathogenic T cell action in the human gut. In consequence, T cell trafficking is increasingly targeted in IBD—a strategy that might sooner or later also be translated to other immunologically mediated bowel disorders.

4 | THE FATE OF T CELLS IN THE GUT: PROLIFERATION, APOPTOSIS, AND DIFFERENTIATION

In addition to replenishment by gut homing, intestinal T cell numbers and associated pathological processes are also controlled by the ratio of T cell proliferation and apoptosis.⁵⁵ Proliferation occurs spontaneously or driven by antigens. Feng et al.⁵⁶ showed that spontaneous T cell proliferation in the gut depends on stimulation of DCs by microbial products and subsequent IL-6 production, while proliferation in response to antigens is indispensable for the development of colitis. Consistently, inhibition of the latter form of proliferation leads to reduced disease severity. In particular, CX3CR1^{high}CD11c⁺CD11b⁺ innate cells have been shown to inhibit T cell proliferation through direct cell-cell interaction and thereby beneficially modulate colitis.⁵⁷ Interestingly, IECs

have been demonstrated to have far more functions beyond providing a barrier and transporting nutrients. One of these is a role as antigen presenting cell. In homeostasis, IECs predominantly present antigens to CD8⁺ cells, but in chronic intestinal inflammation IECs also activate CD4⁺ T cells to proliferate,⁵⁸ thus further adding to the variety of mechanisms that increase proliferation of lamina propria T cells in IBD.

The cytokine IL-6 has also been implicated in the regulation of apoptosis in IBD, since it could be shown that its action via both the membranous and the soluble IL-6 receptor (sIL6R) controlled disease activity by conferring resistance to apoptosis to T cells in experimental IBD models. Consistently, T cells from CD patients were also protected from apoptosis by IL-6 signaling via sIL6R.⁵⁹ Later, the role of IL-6 in this context has further been elucidated by a study demonstrating that the transcription factor NFATc2 essentially mediates experimental colitis, which is mechanistically dependent on IL-6 and leads to T cell resistance to apoptosis.⁶⁰ Furthermore, antibodies to the key IBD cytokine TNF- α , which are successfully used for the treatment of IBD patients, were reported to lead to T cell apoptosis in the lamina propria through an indirect mechanism dependent on CD14⁺ monocytes.⁶¹ Similarly, treatment of colitic mice with anti-IL-12 antibodies resulted in apoptosis of mucosal T cells and normalization of IFN- γ levels.⁶² This appears to be a frequent mechanism of action of currently used therapeutic compounds in IBD since thiopurins like azathioprine and 6-mercaptopurine have also been shown to induce T cell apoptosis in the lamina propria through a complex mechanism involving the small GTPase Rac1.⁶³ Overall, the picture emerges that antigen-induced T cell proliferation and apoptotic resistance of T cells induced by central mediators of IBD like IL-6, IL-12, or TNF- α lead to the obvious expansion of intestinal T cells and subsequent overwhelming pro-inflammatory signaling in these disorders.

But not only quantity is important, there are also qualitative differences between T cells in the gut and, most importantly, in the overall composition of the T cell department in the healthy intestine and in specific pathological conditions. Concerning IBD, CD is considered a Th1/Th17 disease, while UC is characterized by a slightly atypical Th2 profile together with Th17 and Th9 characteristics.^{1,35,37} Food allergy is clearly associated with Th2 signaling²⁵ and gluten sensitive enteropathy is dominated by Th1 signaling and CD8⁺ cytotoxic lymphocytes.⁶⁴ These T cell subsets are particularly characterized by the transcription factors governing their differentiation and the effector cytokines they secrete afterward. Commitment to a specific T cell subset is controlled by the surrounding cytokine environment and subsequent or predisposing transcription factor expression (Table 1).

The first lineages described were CD4⁺ Th1 and Th2 cells. The first step in Th1 development seems to be binding of IL-27 released by DCs to the IL-27 receptor on naïve T cells. Next, the transcription factors STAT1 and STAT3 are induced and upregulate expression of the key Th1 transcription factor T-bet⁶⁵ while repressing the Th2 transcription factor GATA3. At the same time, expression of the $\beta 2$ -chain of the IL-12 receptor is initiated enabling subsequent IL-12 signaling in T cells, which results in STAT4 phosphorylation. Then, STAT4 drives the expression of IFN- γ , the signature cytokine of Th1 cells. IFN- γ signaling via STAT1 further amplifies this cascade⁶⁶ as does CD40L expression

TABLE 1 Characteristics of CD4⁺ T cell subsets. Specific subsets of CD4⁺ T cells are induced by a specific cytokine environment during priming. Subsequently, distinct transcription factors are activated and lead to a particular cytokine profile of differentiated T cell subsets

CD4 ⁺ T cell subset	Key inducing cytokine(s)	Key transcription factor(s)	Key secreted cytokine(s)
Th1	IL-27, IL-12	T-bet, STAT4	IFN- γ
Th2	IL-4, IL-33	GATA3, STAT6	IL-4, IL-5, IL-13
Th9	IL-4, TGF- β	PU.1, IRF4, STAT6	IL-9
Th17	IL-23, IL-6, TGF- β	ROR γ t, IRF4, Batf, STAT3	IL-17, IL-22, IL-26
Th22	IL-6, TNF- α	AHR	IL-22
Treg	TGF- β , RA	Foxp3	IL-10, TGF- β , IL-35

IL, interleukin; IFN, interferon; RA, retinoic acid; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; TNF, tumor necrosis factor.

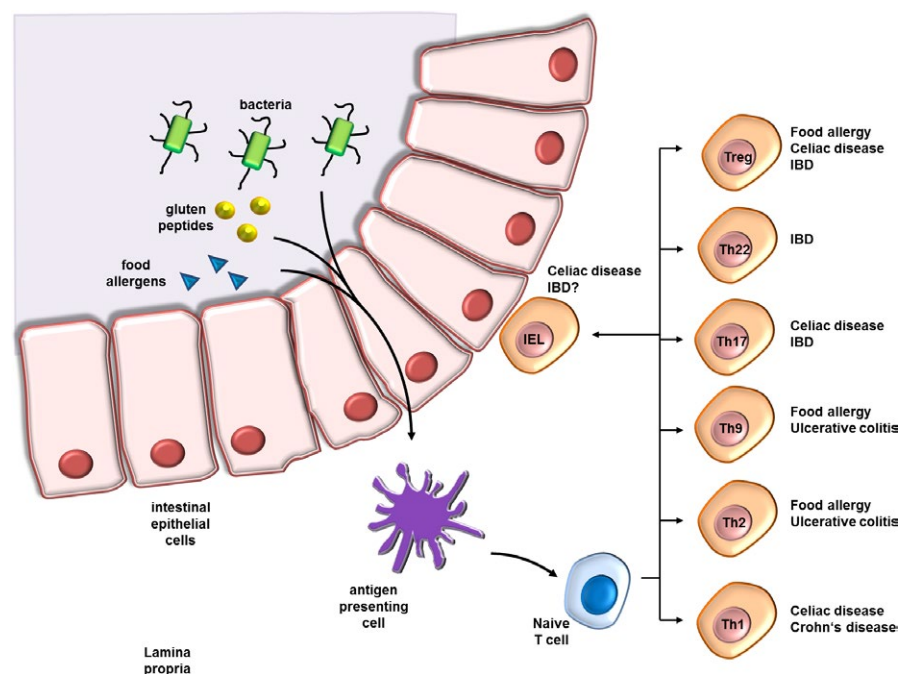
on T cells that prompts monocytes to secrete additional IL-12.⁶⁷ Th2 cell differentiation is induced by IL-4-dependent upregulation of the transcription factors GATA3 and STAT6, which lead to secretion of IL-4, IL-5, and IL-13 by Th2 cells.^{50,68}

Due to opposite development and functions (see below) Th1 and Th2 cells have long been considered to represent a dichotomy of T helper cell function. However, recent reports have significantly refined this view as novel subsets have been identified and considerable plasticity between these subsets has been uncovered. Particularly, Th17 cells have been identified. Their development is initiated by the IL-12 family member IL-23 together with other cytokines like IL-6, IL-1 β and TGF- β leading to expression of the transcription factors ROR γ t, Batf, and IRF4, ultimately driving Th17 cells to secrete IL-17A, IL-17F, and IL-22.^{69–71} Moreover, the IL-9 secreting T helper cell subset of Th9 cells has been described that develops upon signaling of IL-4 together with TGF- β and expression of the transcription factors PU.1, STAT6, and IRF4.^{72–75} Additionally, Th22 cells were discovered, which are induced by IL-6 and TNF- α driving the upregulation of the transcription factor AHR and leading to the secretion of IL-22 without concomitant IL-17 production.⁷⁶ Finally, Tregs have to

be mentioned. This T cell population differs from the so far listed effector cell subsets in that it acts anti-inflammatorily and limits immunologic responses by suppressing the activity of pro-inflammatory T cells. Two different Treg subgroups have to be discriminated^{77–79}: naturally occurring Tregs (nTregs), which are primed in the thymus under the influence of IL-2, and induced Tregs (iTregs) that arise in the periphery upon antigen contact in the presence of TGF- β and gut-specific additional factors like retinoic acid (RA) and butyrate.⁸⁰ Development of both populations is controlled by the transcription factor Foxp3, which leads to the secretion of anti-inflammatory cytokines like IL-10 or TGF- β and the upregulation of membranous receptors or ligands like glucocorticoid-induced tumor necrosis factor receptor (GITR), cytotoxic T lymphocyte-associated protein 4 (CTLA4), or galectin-1 that serve to dampen inflammation by directly interacting with target cells.^{81–84}

While these T cell subsets are best described for CD4⁺ cells similar subsets also exist in the CD8⁺ department (Tc1, Tc2, Tc9, Tc17, Tc22).⁸⁵ The specific contribution of the mentioned T cell subsets to the pathogenesis of allergic and chronic IBDs will be discussed in detail in the following section (Figure 1).

FIGURE 1 Simplified overview of T cell subsets in the pathogenesis of allergic and chronic inflammatory bowel disorders. Antigens translocated over the intestinal epithelial barrier are processed by antigen-presenting cells and presented to naïve T cells in the gut-associated lymphoid tissue. Upon recognition of antigens by the cognate T cell receptor and appropriate co-stimulation naïve T cells differentiate to a variety of antigen-experienced T cells depending on the surrounding cytokine environment (Table 1). Upon recirculation and gut homing they exert their specific functions in the lamina propria. Postulated implication in the pathogenesis of food allergy, celiac disease, inflammatory bowel disease in general, or ulcerative colitis and Crohn's disease in special is indicated. Th, T helper cell; IEL, intraepithelial lymphocyte



5 | T CELL SUBSETS IN ALLERGIC AND CHRONIC INFLAMMATORY BOWEL DISORDERS

5.1 | Th1 cells

Th1 cells do not play a major role in the pathogenesis of food allergy. To the contrary, they are suppressed by the overwhelming Th2 activity found in these disorders leading to a notable Th1/Th2 imbalance. In consequence, several therapeutic strategies currently under investigation aim at promoting Th1 signaling to restore the Th1/Th2 equilibrium to cure the disease.⁸⁶ These are mainly immunomodulators mimicking PAMPs to activate antigen presenting cells to induce Th1 cells. Most prominently, several agonists of toll like receptors (TLRs), a specific class of PRRs, have undergone successful preclinical and early clinical testing in several allergic diseases.⁸⁷

In celiac disease, however, Th1 cells are believed to be a core pathogenetic player and an upregulation of Th1-related cytokines like IFN- γ or transcription factors like T-bet is well-established.^{88–90} As already brought up above, IL-15 is another important cytokine in the pathogenesis of this chronic inflammatory disorder. In addition to its function on IELs it has also been shown to support the generation of Th1 and also Th17 cells in gluten sensitive enteropathy.⁹¹ DCs in the mucosa of patients with celiac disease were shown to secrete higher levels of IL-18, a cytokine further propagating Th1 development.^{92,93} Moreover, IL-21 was proposed to additionally promote Th1 differentiation by upregulation of T-bet and IFN- γ expression.⁹⁴ Another study showed that gluten free diet leads to reduction of IFN- γ expression but no changes in the expression of Th1-related transcription factors like STAT1 suggesting that the increased readiness to generate Th1 cells might be a result of genetic predisposition rather than gluten exposure.⁹⁵ In addition to orchestrating other inflammatory cells in the mucosa in celiac disease, Th1 cells have also been proposed to directly mediate tissue destruction by induction of matrix metalloproteinase secretion via IFN- γ , thus leading to destruction of structural components of the intestinal wall.^{64,96} Altogether, the central role of Th1 cells in celiac disease is beyond question. However, specific strategies for therapeutic targeting are missing so far. While the standard therapy of gluten free diet *inter alia* leads to termination of new Th1 cell priming, investigational strategies indirectly impede Th1 generation by inhibiting gluten access to the lamina propria and its further processing there. Furthermore, inhibition of T cell gut homing by anti- $\alpha 4\beta 7$ antibodies has been proposed as a strategy implicitly targeting Th1 cells.⁵

Similarly to celiac disease, Th1 cells are key drivers of CD. One of the first experimental findings in this regard was that in the T cell transfer model of colitis IBD is clearly associated with a Th1 profile and disease could be ameliorated by blockade of IFN- γ .⁹⁷ Colitis induced by the hapten 2,4,6-trinitrobenzene sulfonic acid (TNBS) also displayed Th1 characteristics and could be cured by treatment with anti-IL12.⁹⁸ Genetic mouse models with specific deletion of Th1-associated molecules provided further insight in modulation of CD pathogenesis by these cells: Transfer of STAT4-deficient T cells to lymphopenic mice resulted in milder disease than transfer of STAT4-competent

counterparts accompanied by lower and higher IFN- γ expression respectively. Strikingly, transfer of IFN- γ -deficient cells did not result in disease protection,⁹⁹ suggesting that Th1 cells may use alternative effector pathways and anticipating later results from clinical studies.¹⁰⁰ Consistent results were reported in a study using STAT4-transgenic mice that developed more pronounced colitis with increased Th1 signaling compared with controls.¹⁰¹ Moreover, deficiency and overexpression of the transcription factor T-bet resulted in protection and aggravation of experimental colitis respectively.⁶⁵

The translational value of these studies has been confirmed by numerous investigations showing that Th1 cytokines and transcription factors are significantly increased in the mucosa of CD but not UC patients.^{35,65,102} There is direct evidence that these cells contribute to tissue injury in the mucosa of affected patients.¹⁰³ It was thus logical to develop therapeutic strategies to target Th1 cells in CD. Antibodies to IFN- γ as a key effector cytokine were tested in phase I and phase II trials. Although some biological effects could be observed no significant differences in clinical parameters were noted in comparison to placebo-treated patients.^{100,104} In contrast, ustekinumab, an antibody to IL-12p40, the common β -subunit of Th1-driving IL-12 and Th17-driving IL-23, has meanwhile demonstrated efficacy in large phase III trials and has thus been approved for clinical use.¹⁰⁵

5.2 | Th2 cells

As outlined above, Th2 cells are a main feature of allergic bowel disorders. Though not directly implicated in the responsible effector mechanisms, which mainly rely on B cell-secreted IgE and mediators and chemokines released from mast cells, they have crucial functions in mediating the pathology of gastrointestinal allergy by counteracting oral tolerance and facilitating the mentioned downstream mechanisms.

It is still not fully clear, what events lead to breakdown of tolerance with sensitization to food allergens and allergen-specific Th2 responses. In murine models, oral administration of antigens normally leads to oral tolerance and, thus, models of intestinal allergy typically involve the additional administration of an adjuvant like cholera toxin that breaks tolerance.⁹ In such a model it was shown that the adjuvant cholera toxin leads to upregulation of the OX40 ligand (OX40L) on DCs and neutralization of OX40L with anti-OX40L antibody is accompanied by decreased induction of Th2 cells.¹⁰⁶ Similarly, in a model using the adjuvant staphylococcus enterotoxin B, upregulation of T cell immunoglobulin-domain and mucin-domain (TIM)-4 on DCs could be identified as a crucial mechanism controlling the differentiation of Th2 cells in response to ovalbumin challenge.¹⁰⁷ Although cholera toxin or staphylococcus enterotoxin play no evident pathophysiological role in the mediation of human disease, these findings suggest that specific regulation of membrane ligands on antigen presenting cells like DCs by so far unknown factors might affect subsequent priming of naïve T cells in the GALT and lead to Th2 skewing of resulting T cells. Interestingly, the cytokine IL-33, which is produced by epithelial cells in the gut, was proposed to be such a factor that could drive DCs to induce Th2 cells. In contrast with IL-25 and thymic stromal

lymphopoietin it was a non-redundant mediator of food allergy to house dust mite and peanut as could be shown in experiments with knockout mice for the IL-33 receptor ST2. Moreover, it was demonstrated that upregulation of OX40L by IL-33 might be responsible for this finding.¹⁰⁸ Of note, genome-wide association studies in the allergic model disease asthma have identified the IL-33 gene to be clearly associated with disease predisposition.¹⁰⁹

Recently, the cytokine IL-9 has been linked to food allergy. Important initial studies showed that IL-9 is essential for the experimental induction of both intestinal and systemic anaphylaxis after oral allergen exposure since IL-9- or IL-9 receptor-deficient mice were protected from anaphylaxis and IL-9 transgenic mice were predisposed to intestinal anaphylaxis.^{110,111} However, it was unclear which cells were secreting IL-9. In addition to evidence suggesting that Th9 cells are an important source of this cytokine (see below), Chen et al.¹¹² reported that IL-9 is produced by multifunctional mucosal mast cells, whose development was dependent on Th2 cells. Moreover, Th2 cells have been proposed to be implicated in the IL-25-dependent induction of IL-13 production by type 2 innate lymphoid cells (ILCs) as secretion of this hallmark cytokine of allergy in response to IL-25 derived from the epithelium was markedly increased in mice with Th2 amplification after repeated allergic challenge.¹¹³ Another recent interesting report showed that both in murine models of food allergy and in human patients Tregs may acquire an altered phenotype with Th2-like features in response to signaling via the IL-4 receptor leading to a reduced potential to limit mast cell functions and highlighting a possible induction mechanism in the pathogenesis of food allergy.¹¹⁴

Th2 involvement in food allergy has also been demonstrated in human disease. For instance, plasma levels of Th2 cytokines like IL-4 and IL-13 were markedly increased in a pediatric cohort with proven food allergy¹¹⁵ suggesting that the above mentioned findings from mouse models may be translated to human gastrointestinal food allergy. To date there is no established therapy for food allergy that specifically targets Th2 cells. Yet, major focuses of translational research in this area are immunomodulatory approaches to revert the Th2-dominated immunological profile back into balance with Th1 cells as discussed above.¹¹⁶

While there seems to be no significant contribution of Th2 cells to celiac disease and CD, their central role in UC is undisputed. Experimentally, it was shown almost 20 years ago that colitis induced in mice by the hapten oxazolone closely resembles UC, is characterized by an excessive Th2 profile and can be treated by antibodies to IL-4.¹¹⁷ Later, this was amended by the finding that the Th2 cytokine IL-13 released by NK-T cells is also essential to the model.¹¹⁸ Experiments with STAT6-deficient mice revealed a protection of these animals from oxazolone colitis and thus further confirmed that Th2 cells mediate pathology.¹¹⁹ A very recent report extends this finding to the Th2 transcription factor GATA3 by demonstrating that GATA3-deficient animals develop less severe colitis in acute oxazolone colitis and chronic TNBS colitis,³⁸ which has been shown to display Th2 characteristics as well.¹²⁰ This is fitting to the finding that GATA3-transgenic mice develop particularly severe experimental colitis.¹²¹ Mechanistically, Th2 cells have been proposed to negatively affect intestinal epithelial

barrier function by triggering IEC apoptosis and pore formation by claudin-2 while impeding intestinal epithelial restitution.¹²² Th2 induction via the epithelium-derived cytokine IL-33¹²³ has gained increasing attraction in recent years and was also demonstrated to be relevant in experimental colitis: Mice deficient in ST2, the receptor for IL-33, were protected in different experimental models and administration of IL-33 resulted in impairment of the epithelial barrier.¹²⁴ In contrast, IL-33 was suggested to be protective in a chemically induced chronic colitis model.¹²⁵ In UC but not in CD patients, IL-33 was elevated in the inflamed mucosa and, moreover, anti-TNF- α treatment modulated IL-33 expression.¹²⁶ Further research is therefore needed to clarify the role of this axis in both experimental and human IBD.

Increased expression of Th2 markers in UC has been reported in several studies^{35,122,127} although results for IL-13 were not consistent in all reports.¹²⁸ Consequently, huge efforts to translate these preclinical data into clinical therapy have been undertaken. However, two phase II trials with different antibodies to IL-13 did not show convincing effects,^{129,130} thus demonstrating once more that human disease is much more complex than animal models and suggesting that targeting downstream cytokines might be bypassed by compensatory mechanisms. Therefore, targeting upstream molecules might be more promising and, indeed, hopes can be placed in a so called DNAzyme against GATA3 which was effective in murine models³⁸ and is currently tested in a clinical pilot trial.

5.3 | Th9 cells

Due to its close relation to Th2 cells, a contribution of Th9 cells to allergic diseases in general and food allergy in special was suspected early after the identification of this independent T cell subset. Although specific evidence for food allergy is rare so far, essential functions of Th9 cells have been demonstrated in experimental asthma models. In particular, the transcription factors PU.1 and IRF4 were shown to be essential for pathology.^{74,75} Moreover, adoptive transfer of Th9 cells led to even higher mast cell accumulation than the transfer of Th2 cells.¹³¹ A similar role in food allergy is strongly suggested by the finding that the IL-9 gene is the most differentially expressed gene in peanut allergic children compared with non-allergic counterparts.¹³² Further mechanistic studies in animal models are thus required to clarify the nature of these cells in food allergy.

Quite a number of such studies have already been performed in IBD to date. In an investigation taking advantage of the oxazolone colitis model in PU.1-deficient mice, disease protection conferred by the absence of Th9 cells was demonstrated and mechanistically linked to protective functions of IL-9 for epithelial barrier integrity.³⁷ This was later confirmed by the use of IL-9 deficient mice in the TNBS colitis model¹³³ and through administration of anti-IL-9 antibody in DSS colitis.¹³⁴ Consistently, IL-9 expression in T cells and IL-9R expression in IECs from UC patients was found to be significantly elevated.¹³⁵ Recently, IL-9 was also detected in the serum of IBD patients.¹³⁶ IL-9 is therefore considered a potential target for future therapy in UC patients.¹³⁷ Interestingly, Th9 cells seem to express especially high levels of α E β 7 integrin favoring their epithelial

retention in the gut and suggesting that these cells might be a main target of the anti- α E β 7 antibody etrolizumab currently investigated in phase III trials.⁵⁴

5.4 | Th17 cells

When it was discovered in 2000 that the IL-12 subunit p40 was also part of the new cytokine IL-23,¹³⁸ several established pathogenetic concepts had to be reinterpreted since a significant part of the evidence on IL-12 and Th1 cells had been generated by the use of antibodies to IL-12p40, thus not discriminating between the two cytokines. Consistently, several features previously attributed to IL-12 and Th1 turned out to be rather associated with IL-23 and Th17 cells.¹³⁹

Several reports have shown that, in addition to the discussed implication of Th1 cells, celiac disease is characterized by Th17 signaling.^{140,141} However, detailed investigations of their pathogenetical contribution are largely missing so far and their precise role as well as the function of their secreted cytokines in celiac disease still need to be determined.⁶⁴

In IBD, the appearance and function of Th17 cells seems to be especially linked to the communication of the intestinal flora with the intestinal immune system since it was shown that specific bacteria led to the induction of Th17 cells in the gut.¹⁴² Consistently, our group could show that epithelial translocation of bacteria in the terminal ileum resulted in the induction of Th17-driving IL-23.¹⁴³

Several functions have been attributed to Th17 cells. On the whole they are believed to be pro-inflammatory and disease-driving as sophisticated T cell transfer experiments showed that ROR γ t-deficient mice are protected from disease.¹⁴⁴ Moreover, genetic deletion of the upstream Th17 transcription factor IRF4¹⁴⁵ or the receptor for the inducing cytokine IL-23 in T cells¹⁴⁶ resulted in amelioration of disease. However, different suggestions have been made regarding the precise role of the cytokines mediating these effects. While the above mentioned study demonstrated redundant pathological functions of the signature cytokines IL-17A and IL-17F,¹⁴⁴ another report even favored protective functions of IL-17A.¹⁴⁷ Moreover, Th17 cells also secrete IL-22, which is considered rather anti-inflammatory based on experiments demonstrating protection from disease by IL-22.¹⁴⁸ However, there also exist IL-22 secreting Th22 cells (see below) and protective IL-22 signaling might therefore not be a major feature of Th17 cells. In addition, Th17 cells secrete the pro-inflammatory cytokine IL-26, which has been shown to directly affect the intestinal epithelium and lead to lower proliferation as well as higher secretion of pro-inflammatory mediators.¹⁴⁹

To further complicate the situation, plasticity between different T cell subsets is increasingly acknowledged in pathogenetic concepts of disease and especially concerns Th17 cells. In particular, this T cell subset shows transition to Th1 cells.¹⁵⁰ Indeed, T-bet- and STAT4-dependent plasticity toward Th1 cells has been shown to be essential for disease development in a T cell transfer model of colitis¹⁵¹ and regarding the important role of TGF- β for differentiation and sustaining of Th17 commitment Tregs have been shown to control the balance

between Th17 and Th17-derived Th1 cells.¹⁵² Moreover, polarization toward Th17 and Tregs is both controlled by TGF- β leading to plasticity between these T cell subsets as well.^{153,154} Collectively, so far evidence strongly supports the notion that Th17 cells are indispensable for the pathogenesis of colitis although some ambiguity in mechanistic details remains.

This is reflected by the finding that Th17 cell-related cytokines and markers are increased in the lamina propria of IBD patients^{145,155,156} with both UC and CD. However, Th17-specific therapeutic approaches, namely a trial with secukinumab in CD, an anti-IL-17A antibody, failed to demonstrate efficacy.¹⁵⁷ As already mentioned clinical testing of ustekinumab in CD was by far more successful and is meanwhile approved for clinical therapy. Although it is not clear to what extent the effect of this antibody is due to blockade of Th1 and Th17 cells, this demonstrates that Th17 are an important target in IBD and further research as well as alternative treatment strategies might result in development of additional therapies.

5.5 | Th22 cells

Th22 cells secrete IL-22, but in contrast with Th17 cells they do not secrete IL-17, thus justifying their position as independent T cell subset.⁵⁰ While there are so far no clues for a major role of Th22 cells in food allergy or celiac disease, a growing body of research suggests an implication in the pathogenesis of IBD. Based on reported results the prevailing view is that Th22 cells counteract inflammation through secretion of IL-22 since protective functions of IL-22 have been demonstrated in independent studies.^{148,158} However, the effect of IL-22 may vary depending on the model used regarding a study in which IL-22 was rather pro-inflammatory in experimental colitis.¹⁵⁹ Yet, mechanistic investigations also favor a protective role for IL-22 as it has been shown to activate STAT3 in epithelial cells leading to enhanced epithelial wound healing.¹⁶⁰ Consistently, the expression of the Th22 transcription factor AHR and the number of IL-22 secreting CD4⁺ cells are reduced in the inflamed mucosa of IBD patients^{161,162} and experimental disease could be ameliorated by administration of an AHR agonist.¹⁶¹ Though, it has also to be considered that similar to Th17 cells Th22 cells seem to display plasticity, in particular toward a Th1 and Th17 phenotype.¹⁶³ Taken together, these findings suggest that promoting Th22 signaling in human IBD might beneficially affect patient outcome, while they also underscore the need for further dissection of their exact function at the same time.

5.6 | Treg cells

It has already been mentioned above that regulatory T cells are vital for the induction of oral tolerance toward food allergens. In turn, Treg dysfunction is a hallmark of sensitization and reaction to food allergens but might also be of therapeutical value due to their anti-inflammatory properties. In particular, mice that lack iTregs spontaneously develop allergic inflammation in the gastrointestinal tract that is marked by excessive Th2 signaling.¹⁶⁴ Another important study demonstrated that iTregs are especially responsible for the maintenance

of oral tolerance and prevention of sensitization, while the control of effector functions was independent of Tregs and rather required IFN- γ signaling.¹⁶⁵ Moreover, there is evidence that Th2 cytokines like IL-4 directly reduce the frequency of allergen-specific Tregs and, thus, promote the development of allergy.¹⁶⁶ In turn, Tregs can control Th2 effector signaling, a process that is—in contrast with control of Th1 or Th17 responses—mechanistically dependent on the Wiskott-Aldrich syndrome protein (WASP) and might thus explain the frequent presence of IgE-mediated food allergy in patients suffering from Wiskott-Aldrich syndrome.¹⁶⁷

In view of the fact that a considerable portion of pediatric food allergy patients 'outgrow' their allergy, another report favors the notion that Tregs may also serve to acquire tolerance after previous sensitization, since the transfer of Tregs from mice tolerant to ovalbumin to sensitized mice prevented anaphylaxis and reduced IgE and IL-4 expression.¹⁶⁸ In addition, Burton et al.¹⁶⁹ showed that disruption of IgE effector functions leads to the emergence of Tregs and subsequent desensitization. Similarly, oral immune therapy and immunomodulatory substances proposed for treatment of food allergy were shown to act via Treg induction.^{170,171} Enhancing the function of Tregs might therefore be a promising goal for further translational research in gastrointestinal allergy.

The T cell infiltrate in the small intestinal mucosa of celiac disease patients contains an expanded Treg population compared to controls.¹⁷² Yet, they are not able to control inflammation. Several pieces of evidence indicate that this is due to impaired suppressive functions on the one hand and resistance mechanisms of effector T cells on the other hand. For instance, IL-15, a central cytokine for celiac disease as mentioned above, has been shown to confer resistance to effector cells in a PI3K-dependent mechanism.¹⁷³ Moreover, not only lamina propria lymphocytes but also IELs did not respond to Tregs from celiac disease,¹⁷⁴ whereas the *in vitro* administration of the suppressive Treg cytokine IL-10 impaired gliadin-specific T cell activation.¹⁷⁵ Modulating the function of Tregs and their interaction with effector T cells in celiac disease is therefore also considered a target for future therapy but necessitates previous elucidation of causalities in experimental models.⁵

Although regulatory T cells are not only found in increasing numbers in the gut of IBD patients but—in contrast in celiac disease—are also functional, they are still not able to control pathogenic T cells. Most probably this is due to an even more prominent expansion of effector T cells resulting in a disturbed Teff/Treg ratio.¹⁷⁶ However, if iTregs are co-transferred in the T cell transfer model of colitis they are efficiently able to suppress colitis,¹⁷⁷ leading to the notion that adoptive transfer of expanded Tregs in humans might be an auspicious treatment strategy.¹⁷⁸ The suppressive function of Tregs in IBD has been clearly associated with their secretion of IL-10 and TGF- β .^{179,180} In the healthy state, TGF- β -dependent negative regulation of T cell activation is mediated through intracellular signaling via Smad2 and Smad3. It was convincingly shown that in IBD, however, elevated levels of Smad7 lead to disruption of this signaling cascade.¹⁸¹ Later explorations in experimental colitis confirmed these findings¹⁸² and provided the rationale for clinical testing of mongersen, an antisense-oligonucleotide to

Smad7. In a recent phase II trial, this compound showed tremendous beneficial effects in CD.¹⁸³ Although these findings need confirmation in larger trials with longer observation periods, they substantiate the hopes that this strategy might be a breakthrough regarding the efforts to fortify Treg activity and function in IBD.

It has already been mentioned that Tregs also employ other mechanisms than IL-10 and TGF- β . IL-35 is another suppressive cytokine released by Tregs, whose role in IBD has only recently been elucidated. It could be shown that IL-35-deficient mice developed spontaneous signs of colitis and IL-35-deficient T cells were potent inducers of colitis upon transfer to lymphopenic hosts. Moreover, administration of recombinant IL-35 ameliorated experimental colitis. All these findings were related to a reduction of Th1 and Th17 signaling by IL-35.¹⁸⁴ In addition, membraneous receptors like CTLA-4 have been demonstrated to mediate the suppressive function of Tregs in colitis.⁸⁴

5.7 | CD8⁺ T cells

IELs, which are mainly CD8⁺ T cells, are a hallmark of celiac disease and are thought to directly contribute to villous atrophy by induction of IEC apoptosis. Consistently, it was shown that lots of perforin and Fas ligand expressing IELs are present in the epithelium of active celiac disease patients correlating with the number of apoptotic IECs.¹⁸⁵ Once more, IL-15 appears to be prominently implicated in their function since it is an essential factor promoting proliferation, cytotoxicity, and cytokine production of IELs.²⁹ In addition, IL-15 triggers gliadin-dependent expression of MICA molecules on the small intestinal epithelium in celiac disease. MICA acts as receptor for NKG2D on IELs, which recruits these cells into close contact with epithelial cells, activates them and finally leads to IEL cytotoxicity toward the epithelium.¹⁸⁶ IELs expressing NKG2 were found to be markedly enriched in samples from celiac disease patients.¹⁸⁷ Finding a way to specifically modulate the presence or function of these cells might thus aid to treat celiac disease.

Although they are a major T cell subset, CD8⁺ T cells have only rarely been specifically addressed in the context of chronic colitis. The available evidence, however, supports the notion that CD8⁺ T cells have important implications in disease pathogenesis through direct cytotoxicity and immunomodulatory action. Their numbers in the mucosa of IBD patients are increased.¹⁸⁸ Moreover, dinitrobenzene-sulfonic acid induced colitis was demonstrated to be essentially dependent on CD8⁺ but not CD4⁺ T cells¹⁸⁹ and transfer of CD8⁺ T cells to lymphopenic recipients resulted in intestinal pathology that was comparable to CD4⁺-induced colitis in severity.¹⁹⁰ Moreover, the CD8⁺ subset also contains anti-inflammatory subsets that are able to suppress colitis.^{191,192} Cytotoxicity of CD8⁺ cells toward IECs is believed to be a central mechanism of CD8⁺ cells influencing colitis.¹⁸⁹ Strikingly, one study reported that it was possible to forecast the course of IBD by CD8⁺ but not CD4⁺ T cell gene expression profiling.¹⁹³ Regarding our recent finding that the blockade of α E β 7 by anti- β 7 antibodies mainly affects CD8⁺ T cells⁵⁴ it will be interesting to see whether this has implication on the course of clinical disease.

6 | CONCLUDING REMARKS

The landscape of T cell subsets in allergic and chronic IBDs has experienced considerable diversification in recent years. While—from a clinical point of view—this might sometimes be perceived to unnecessarily complicate pathogenetic concepts for such disorders, one should not underestimate the translational potential of sophisticated approaches to explain disease development. It is evident that particularly the latest advances are not always perfectly fitting into the pre-existing picture and some current views might have to be readjusted following future findings, but regarding the discoveries on T cell subsets made one or two decades ago, it is impressive to see what novelties they have facilitated regarding clinical therapy. Above all, the anti-IL12p40 antibody ustekinumab has been recently approved and the anti-Smad7 oligonucleotide Mongersen seems highly promising in this regard. At the same time, it must not be forgotten that by far more approaches failed or did not produce as convincing results as expected, eg, anti-IFN- γ , anti-IL17A, or anti-IL-13 strategies. However, this is most probably owed to the inevitability that neither rodent immunology reflects human immunology nor experimental colitis models fully reflect human IBD. Further research on pathogenic T cell subsets will thus compulsorily lead to further innovations that fall through at some stage of the translational process, but it is also very likely that others will succeed and increase our options to successfully treat patients with allergic and IBDs.

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