T_h17 Cells in Inflammatory Bowel Disease: An Update for the Clinician

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic systemic relapsing-remitting conditions that are thought to be the end result of dysregulated host immune responses to enteric flora.[1] The pathogenesis of IBD is complex. Genome-wide association studies (GWAS) and animal models implicate multiple mechanisms of disease induction and propagation.[2] Indeed, every component of the gut from the enteric microbiome to (host) epithelial and immune cells including antigen presenting cells (APCs) such as dendritic cells and macrophages and T and B cells have all been linked to the pathogenesis of IBD.[2]

In this regard, it has become clear over the last 20 years that the IL-17 producing subset of $CD4^+$ T-cells, termed "T_h17" cells, are strongly implicated in the pathogenesis of IBD.[2–5] This connection has in turn focused intense attention on T_h17 cells, leading to IBD therapies targeting these pathways.[6, 7]

Herein, we review the role of T_h17 cells in the pathogenesis and treatment of IBD, with a focus on clinically relevant avenues including emerging therapies. Our goal is to make this subject accessible while encompassing the most relevant aspects of T_h17 biology. This review is written with the clinician in mind and is aimed at providing an overview of T_h17 cell biology in humans. Much has been written about the fundamental biology of T_h17 cells in mice and humans, and we refer the reader interested in the unadulterated complexity of the subject to any number of outstanding reviews.[8–10]

MUCOSAL BIOLOGY AND T-CELL DIFFERENTIATION: THE BASICS

The immune system is a multifarious system with many interconnected parts. At the very core, it exists to protect the host from overwhelming pathogenic invasions. Consistent with this purpose, regions of the body that are constantly inundated with microbes, such as the skin, genitourinary (GU) and gastrointestinal (GI) tracts, and respiratory system, are also suffused with extensive immune defenses.[11, 12]

The intestinal immune system functions to regulate homeostatic enteric flora but also prevent barrier breach by pathogenic strains while facilitating nutrient extraction. In a simplified and expansive sense, it is composed of the epithelium, innate lymphoid cells (ILCs), APCs, and T and B lymphocytes.[11, 12] Each of these cell types encompasses subtypes that play specialized roles. Not surprisingly, the intestine contains several T-cell subset—most notably, $CD4^+$, $CD8^+$, and γδ T-cells distinguished by expression of distinct T-cell receptors (TCRs).[13] These T-cell subtypes also exhibit a distinct spatial localization with $CD8^+$ and γδ T-cells typically enriched in the intraepithelial compartment, whereas $CD4^+$ T-cells reside primarily in the lamina propria in the basal state.[14] Increasing evidence furthermore suggests that spatial localization may determine T-cell function, as some subpopulations of T-cells are thought to permanently reside in the intestine.[15–18]

The long-term goal of the immune system is to generate adaptive antigen-specific responses that maintain host integrity. Although the process sometimes tips towards autoimmunity, by and large a suitable balance is achieved with high frequency, and fidelity T-cells are armed with a TCR that has specificity for a given epitope. T-cells are termed "naïve" if they have not engaged their cognate antigen via the TCR and are different flavors of "terminally differentiated" if they have undergone this process. Naïve T-cells are quiescent and do not produce effector cytokines like interleukin (IL)-17A, interferon gamma (IFN)γ, or tumor necrosis factor (TNF)α but circulate throughout the blood and lymphatics until they meet their cognate antigen in lymphoid organs.[19] This antigen, presumably a piece of some invading virus, fungi, or bacteria, is presented to the T-cell by the appropriately termed APC (which is usually a dendritic cell or monocyte in this context).[20–22] In addition to presenting the antigen, APCs also produce cytokines, which are broadly determined by the type of antigen and the type of pathogen recognition receptor (PRR) to which the antigen is bound on the APC.[23, 24] Well known PRRs include toll-like receptors (TLRs) and nod-like receptors (NLRs). T-cells will differentiation in this milieu into specific terminally differentiated subsets typified by characteristic "master" transcription factors (TFs) and

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cytokines. Well known T-cell subsets include T_h1, T_h2, T_h17, and T regulatory (T_{reg}) cells. T_h1 cells are induced by IL-12, express the master TF T-box protein expressed in T-cells (TBET), and produce the cytokine IFNγ.[25] Similarly, IL-4 is the lineage driving cytokine for T_h2 cells, which are characterized by expression of GATA3 and production of IL-4, IL-5, and IL-13.[26] Once differentiated, these T-cell subsets then traffic to sites of pathogen invasion including end organs such as the intestine by expressing organ-homing receptors (such as α4β7) to execute "effector" functions.[27]

T_H17 CELL DIFFERENTIATION

The link between IBD and T_h17 cells is predicated on the pathways that induce and maintain T_h17 cells.

Similar to T_h1 and T_h2 cells, T_h17 cells are terminally differentiated cells. T_h17 differentiation and stabilization seems to be more complex than that of T_h1 or T_h2 cells.[28, 29] In addition, the conditions for differentiation of human T_h17 cells may be different than that of murine T_h17 cells; thus murine T_h17 cell biology may not be congruent with that of humans.[8–10, 30] Specifically, the exact combination of cytokines necessary for human T_h17 cell differentiation (both in vitro and in vivo) have not been irrefutably elucidated. Avoiding the grueling details, much of this controversy rests whether transforming growth factor (TGF)β is required for human T_h17 cell differentiation.[9, 30]

Murine T_h17 cells can be differentiated in vitro with the combination of TGFβ and IL-6.[31–33] Interleukin-23 is dispensable for differentiation but absolutely necessary for murine T_h17 stabilization.[34, 35] The case in humans is more controversial. Initial studies using human T-cells reported differentiation of T_h17 cells with IL-1β or the combination of IL-1β and IL-23 without TGFβ.[36–39] This controversy seemed to close when it was noted that the *in vitro* culture media in those reports contained serum and was potentially contaminated with platelets, both of which are sources of TGFβ. Furthermore, the purported naïve T-cells in those studies could have included differentiated T-cells due to the technicalities of how the naïve T-cells were obtained. When these studies were repeated with rigorous removal of TGFβ and with truly naïve T-cells derived from umbilical cord blood, it seemed that TGFβ is indeed necessary for T_h17 cell differentiation.[40] Moreover, optimal induction of T_h17 cells occurred with the combination of TGFβ, IL-1β, and IL-23. High concentrations of TGFβ impaired induction of *RORC*, which encodes the master transcription factor for T_h17 cells, RORγt, suggesting there is an optimal range of TGFβ for induction of T_h17 cells.[40]

However, more recent data have once again called into question the requirement of TGFβ, indicating that TGFβ-dependent pathways generate so-called "nonpathogenic" T_h17 cells that produce the anti-inflammatory cytokine IL-10, whereas TGFβ-independent pathways generate "pathogenic" T_h17 cells typified by production of IL-17A, IFNγ, and Gram-colony stimulating factor (GM-CSF).[41] TGFβ-independent T_h17 cells can be generated by various combinations of IL-1β, IL-23 and IL-6 and exhibit a distinct gene profile and are more pathogenic *in vivo* relative to their TGFβ-dependent counterparts.[41] Adding one more layer to all this, it seems that IL-21 can promote T_h17 cell differentiation via autocrine mechanisms and it may act as an alternative pathway in the absence of IL-6.[42–44] What the relevance all of this to humans is unclear. Interestingly however, humans with IL-6R deficiency have normal numbers of T_h17 cells, while those with IL-21R deficiency have marked reductions, indicating that IL-21 is more important for T_h17 cell differentiation in humans than IL-6.[45, 46]

Transforming growth factor β is required for *RORC* induction but also potently induces *FOXP3*, the master TF for T_{reg} cells. Interleukin-6 is thus thought to function by suppressing *FOXP3* generation and activating the transcription factor, signal transducer and activator of transcription (STAT)3, which strongly tips the balance toward T_h17 cell generation.[8, 10] Indeed, this node between T_h17/T_{reg} differentiation is one reason these cells are often considered together. The STAT3 then further induces *RORC* with subsequent production of IL-17A and upregulation of the IL-23 receptor (IL-23R), thus defining T_h17 cells.[8, 10]

The exact role and function(s) of IL-23 in T_h17 cells biology is likely to be multifaceted. Interleukin-23 is a member of the IL-12 cytokine family and is a heterodimer of the p40 subunit (which is shared with IL-12) and the p19 subunit which is unique to IL-23. It was long held that CD was a T_h1-IFNγ-mediated disease based on evidence of high amounts of IFNγ-producing T-cells in patients with CD and because blockade of the p40 subunit of IL-12 (which drives T_h1 differentiation) ameliorated murine models of autoimmune disease. This paradigm was upended with the discovery that the p40 subunit is shared by both IL-12 and IL-23. Murine models then made it clear that isolated blockade of p19 (and thus IL-23) ameliorated disease in autoimmune models (collagen-induced arthritis, experimental auto-immune encephalomyelitis [EAE], T-cell transfer colitis, IL-$10^{-/-}$ colitis), whereas mice were largely susceptible to disease with p35 blockade (and thus IL-12), proving that the pathogenic component in these models was IL-23 rather than IL-12.[35, 47, 48] Consistent with this, anti-IFNγ therapies have had modest results in CD.[7]

Naïve mouse T-cells do not express the IL-23R, but the IL-23R is induced by *RORC*. It is clear that IL-23 is required for the maintenance of T_h17 cells, as IL-$23R^{-/-}$ mice have substantial loss of T_h17 cells long-term.[34] However in contrast to mice, it seems that IL-23 (in combination with other cytokines) can indeed drive the differentiation of naïve human T-cells toward a T_h17 lineage.[41, 49] The receptor for IL-23 is a heterodimer composed of the IL-12RB1 chain (which is shared with the IL-12R) and the IL-23R. Signaling downstream of the IL-23R is via janus kinase (JAK)2 and tyrosine kinase (TYK)2 and culminates in the activation of STAT3.[8] Thus, it plausibly functions in a positive feedback loop for stabilizing T_h17 cells.[10] One other critical feature of IL-23R signaling is that it seems

to promote the formation of a particularly pathogenic subset termed of T_h17 cells characterized by coproduction of IL-17A and IFNγ.[8, 10] Exactly how IL-23 drives pathogenic T_h17 cells is uncertain. Moreover, how TBET promotes pathogenic T_h17 cells is also unknown. However, IL-17A$^+$IFNg$^+$ T_h17 are more pathogenic in mouse models compared to IL-17A$^+$ T_h17 cells alone.[50–53]

Broadly speaking then, a (vastly) simplified theory of T_h17 differentiation is that specific pathogens preferentially promote the production of T_h17-driving cytokines (eg, IL-1β, IL-6, IL-23) when they bind to PRRs in APCs. Antigen-laden APCs then skew naïve T-cells toward T_h17 differentiation and suppress differentiation of other T-cell subsets in an inflammatory milieu that is already rich in TGFβ. The combination of TGFβ and IL-6 (or IL-21, IL-23, and IL-1β) then results in activation of STAT3 in naïve T-cells, with sequential induction of *RORC* and IL-17A and IL-23R (Fig. 1). Signaling through the IL-23R then creates a positive feedback loop wherein IL-23R-induced STAT3 further stabilizes *RORC* induction and the T_h17 phenotype. Given our clinical focus, we have limited our summary of T_h17 cell differentiation to pathways clearly implicated in human IBD. Genetic regulation of T_h17 cell differentiation is very complex, and there are a myriad of important issues that have been glossed over; for a more extensive and detained analysis on this, we refer the reader to some primary papers.[28, 29]

PLASTICITY OF T_H17 CELLS

Antigen-experienced T-cells are considered to be "committed," meaning that once they specialize in to distinct T_h –lineages, they and their progeny remain within that lineage. Evidence for this paradigm is strong for the earliest discovered T_h lineages, T_h1, and T_h2 cells. However, this paradigm may not hold for T_h17 cells (or T regulatory cells). T_h17 cells in vivo exhibit a propensity to shift over time to a T_h17/T_h1 phenotype characterized by coproduction of IL-17A and IFNγ—or solely to a T_h1 phenotype with cessation of IL-17A production.[54] This feature of T_h17 cells is termed "plasticity." Increasing evidence, largely from in vitro and in vivo murine models of multiple sclerosis and colitis, indicates that these "ex-T_h17" cells are especially pathogenic relative to their purely T_h17 or T_h1 counterparts.[52, 55] Moreover, in murine models, it seems that IL-23 is a key regulator of this division and that T_h17 cell plasticity is dependent on contextual cues (such as locally produced IL-23).[55] Genetic regulation of T_h17 plasticity is complex, is incompletely understood, and may be contextual. Broadly however, plasticity may be related to stability of RORγt expression and epigenetic marks regulating accessibility of TBET, the master TF for T_h1 cells.[56] The exact function and role of T_h17 plasticity in humans in vivo is not definitively known. However, T_h17/T_h1 cells are enriched in human autoimmune conditions including multiple sclerosis, rheumatoid arthritis, and Crohn's disease, which corroborates murine data linking T_h17 plasticity to human IBD.[57–59]

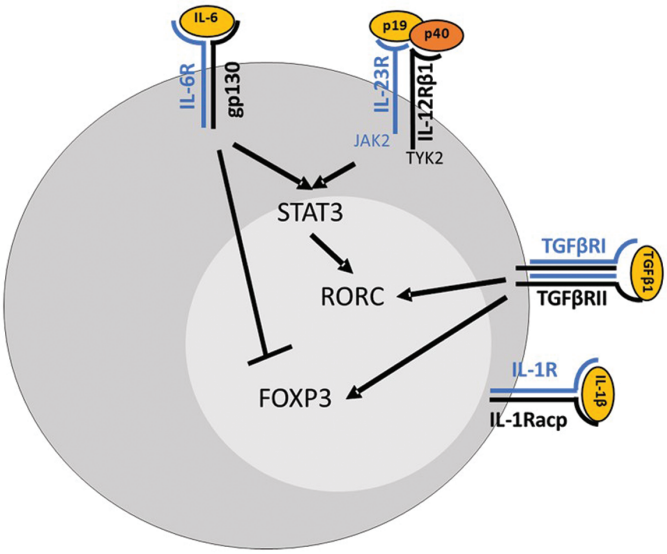

FIGURE 1. T_h17 cell differentiation. Differentiation of T_h17 cells depends on stimulation with IL-6 and TGFβ with induction of RORC and suppression of *FOXP3*. IL-23R signaling then reinforces T_h17 commitment by via-STAT3.

T_H17 CELLS AND THE ENTERIC MICROBIOME

There is a strong link between the microbiome and T_h17 cells. T_h17 cells are enriched in the ileum under homeostatic conditions in humans and in certain strains of mice.[60–64] Homeostatic induction of ileal T_h17 cells in mice is dependent on the microbiota and, in particular, is dependent on strains of bacteria (segmented filamentous bacteria [SFB]) or fungi (*Candida albicans*) that can make contact with the epithelium.[60, 61, 64] In addition, pathogenic strains of bacteria, such as *Citrobacter rodentium* (the murine equivalent of *Escherichia coli*), can also induce T_h17 cells in an epithelial contact-dependent manner.[63, 64] Adding to this link, mice raised under germ-free conditions are immune to colitis in many T_h17-dependent murine models including IL-10$^{-/-}$ and T-cell transfer colitis.[65, 66] Dysbiosis of enteric flora is well known to be a central feature in IBD. Although there is now a substantial body of work linking changes in the enteric microbiome with disease induction, progression, and response to therapy, there is a relative sparsity on of work on the host drivers of this relationship—at least in humans. In this regard, T_h17 cells offer a potential link between dysbiosis in IBD and the pro-inflammatory host response.[67] Though this topic is of considerable theoretical importance, given the paucity of treatments targeting the microbiome, we will not discuss it further here. Instead, we refer those interested to the important primary publications already referenced in this section.

THE LINK BETWEEN T_H17 CELLS AND IBD

T_h17 cells are strongly linked to IBD based on murine model—but perhaps more convincingly by genetic and functional studies in humans.

Genome-wide Association Studies

Over 160 alleles that confer risk for IBD have been identified by GWAS studies. Despite the success of these studies, it is critical to bear in mind when interpreting GWAS studies that they do not in general identify directly causal alleles.[2, 5] Instead, they identify single nucleotide polymorphisms (SNPs) at loci encompassing a potential target gene or, in some cases, genes. Moreover, distinct SNPs in gene regions can have distinct correlation patterns, and it is not uncommon to have multiple protective and risk variants in the same gene region.[68]

Given this caveat, GWAS studies in IBD have nonetheless provided strong evidence linking IBD to T_h17 pathways. Risk alleles in genes specifically in T_h17 pathways include *CARD9*, *IL12B*, *STAT3*, *RORC*, *IL23R*, *JAK2*, *TYK2*, and *CCR6*. Thus, SNPs in T_h17 pathways genes would be expected to impact T_h17 cell generation (*CARD9*, *IL12B*) and intra-cellular events important for T_h17 lineage commitment and maintenance (*STAT3*, *RORC*, *IL23R*, *JAK2*, *TYK2*) or T_h17 cell function (*CCR6*)[2] (Fig. 2). Of these, SNPs in *CARD9* and *IL23R* are of particular importance, as they are in coding regions, and there are multiple risk- and protective-alleles for each gene.[4]

CARD9 is a critical convergence point downstream of fungal PRRs and is necessary to induce *C. albicans*–specific T_h17 responses. Humans with *CARD9* deficiency have substantially reduced T_h17 cells with commensurate susceptibility to *C. albicans* infections.[69] As we have already discussed, IL-23R is expressed by T_h17 cells and is critical for T_h17 cell physiology.

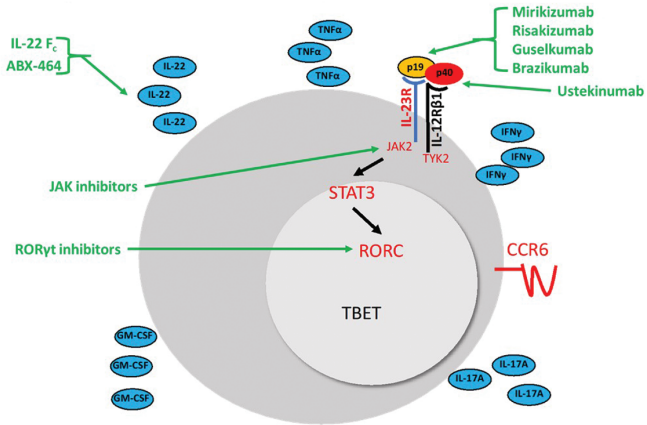

FIGURE 2. T_h17 cells and inflammatory bowel disease risk alleles and treatments. Based on animal models, pathogenic T_h17 cells are thought to express RORC and TBET and coproduce IL-17A and IFNγ. Independent of coproduction of IL-17A and IFNγ, differentiated T_h17 cells produce IL-22, granulocyte colony stimulating factor (GM-CSF), and TNFα and express the receptor CCR6. Differentiated T_h17 cells also express IL-23R, which is a heterodimer composed of IL-23R and IL-12Rβ and recognizes the cytokine IL-23. IL-23 is itself a heterodimer composed of the p40 subunit shared with IL-12 and p19. Several IBD risk alleles are in T_h17 cell pathways (in red; p40, JAK2, TYK2, IL-23R, STAT3, RORC, CCR6) and several approved or pipeline agents for IBD target T_h17 cell pathways (in green).

The risk alleles in *CARD9* are thought to either affect the level of functional *CARD9* protein or to enhance downstream signaling and thus promote T_h17 cells.[70] Similarly, *IL23R* risk alleles are thought to augment IL-23R signaling, thereby promoting T_h17 cells. In contrast, protective alleles of both *CARD9* and IL-23R exhibit reduced downstream signaling with a commensurate dampening of T_h17 cells.[71, 72] The exact functional consequence of SNPs in the other alleles is not clear, but there is some suggestion that the *STAT3* risk alleles cause increased signaling with augmented T_h17 cell responses relative to controls.[73]

In addition, there are risk alleles in loci that are potentially involved in T_h17 cell pathways including *IL1R1*/*IL18RAP*, *IL2*/*IL21*, *PTGER4*, and *IL27*.[2] Loci at *IL1R1*/*IL18RAP* encode the receptors for IL-1β (IL-1R1) or IL-18 (*IL18RAP*), and the loci at *IL2*/*IL21* encodes the cytokines IL-2 or IL-21. *PTGER4* encodes a receptor for prostaglandin E2 (PGE2), and *IL27* encodes the cytokine IL-27. Given that IL-1β, IL-21, PGE2, and IL-27 have all been shown to play a role in the differentiation and function of human T_h17 cells, it is possible that SNPs in these genes may produce disease-associating alternations in T_h17 cells.[8, 74, 75]

Finally, though largely not specific to T_h17 cells, risk alleles have also been found in a variety of genes that are necessary for the genetic regulation T_h17 differentiation (at least in mice) including, *PTPN22*, *KIF21B*, *GPR65*, *IL10*, *IL2RA*, and *TRIB1*.[2] Although these gene products have pleotropic functions affecting multiple cell types, all these genes are activated at some stage in the differentiation of T_h17 cells.[28] Thus, GWAS studies not only link pathways specifically expressed in T_h17 cells to IBD but also implicate a broader array of pathways that may have functional consequences on T_h17 cells.

Functional Studies in IBD

Genome-wide association studies provide a strong link between T_h17 cells and disease susceptibility but do not completely explain variance in IBD, suggesting other factors besides risk alleles are at play in initiating and propagating IBD. In this regard, functional studies of changes in mucosal gene expression and of immune cells populations in IBD reinforce the like between IBD and T_h17 cell biology and provide clues to other drivers of IBD.

Numerous studies have reported elevated expression of T_h17 pathway cytokines including IL-1β, IL-6, IL-17, IL-23, and IL-22 in the intestinal mucosal in active UC and CD relative to inactive regions and healthy controls.[76–79] Moreover, several studies, although from single centers and small, have shown correlations between normalization of mucosal *IL17A* expression with treatment and short- and long-term clinical remission and endoscopic healing.[78, 79] However, elevated expression of these cytokines does not definitively implicate T_h17 cells since these cytokines can be produced by non-T_h17 cells.

More specifically than gene induction data, T_h17 cells are enriched in the intestinal mucosal in IBD and are more responsive to IL-23 in IBD relative to healthy control T_h17 cells, suggesting they

are more pro-inflammatory relative to their healthy control counterparts.[80] Moreover, at least some T_h17 cells in intestine in IBD patients coproduce IFNγ, consistent with a "pathogenic" T_h1/T_h17 phenotype.[57–59] This collectively argues that pro-inflammatory, pathogenic T_h17 cells are enriched in the mucosa in IBD relative to healthy controls. Consistent with this, we recently reported that $CD4^+$ T_{RM} cells, which are a subset of tissue-restricted $CD4^+$ T-cells, are enriched in patients with CD exhibit a T_h17 phenotype and are the major memory T-cell source of TNFα in active CD (and healthy controls).[17] Similar to the data regarding intestinal $CD4^+$ T-cells, peripherally circulating microbial antigen-reactive T-cells in patients with CD skew to a T_h17 or T_h1/T_h17 phenotype relative to healthy controls that exhibit a T_h1 phenotype.[81]

Consistent with this paradigm, inflammatory monocytes are enriched in CD and more avidly produce IL-23 when stimulated with enteric bacteria relative to healthy controls with resultant skewing of T-cells to a T_h17 phenotype in CD.[80, 82] Indeed, humanized gnotobiotic mice with dysbiotic enteric flora from IBD patients have a propensity to develop T_h1/T_h17 cells that are more colitogenic relative to T_h17 cells from mice colonized with enteric flora from healthy controls.[67]

These data are strongest for CD relative to UC, but it collectively indicates a plausible mechanistic link between IBD and T_h17 cell biology. These data also broadly raise the possibility that dysbiotic enteric flora in IBD shift APCs to an inflammatory, pro-T_h17 phenotype with commensurate induction of pathogenic IBD promoting T_h17 cells.

CAVEAT TO T_H17 THERAPIES IN IBD

It is important to remember that although IL-23R is expressed on T_h17 cells and, conversely, T_h17 cells are considered important targets (and perhaps the primary target) of anti-IL-23 agents, many cell types express IL-23R.[83] Notable IL-23R-expressing cells include ILCs and epithelial cells.[84] Thus, IL-23 biology is explicitly not the same as T_h17 biology.[9] Despite this, one could make an excellent argument that the primary targets of therapeutic consequence for anti-IL-23 therapies are T_h17 cells. This is because (1) IL-23R signaling in epithelial cells is considered to have a protective rather than pathogenic role for epithelial host defense and restitution, and (2) there isno clear evidence, as yet, that ILCs are pathogenic in IBD (although there are data correlating changes in disease state and ILC subsets).[84, 85] Adding to the latter, there is intriguing data suggesting ILCs are redundant for host defense in humans.[86] Collectively, this suggests that ILCs are critical for murine physiology but may be redundant in humans.

We should also discuss anti-IL-17A therapies, which failed in CD. These trials were halted early due to either higher rates of adverse events or worsening CD in the treatment arms.[87, 88] These results were surprising given the link between T_h17 cells and IBD and the good efficacy of anti-IL-17 agents in psoriasis. Although trials fail for many reasons, new studies indicate that many of the pathogenic effects of T_h17 cells are IL-17-independent. Indeed, 2 murine studies using distinct models of colitis have shown that IL-17 signaling in epithelial cells is critical for epithelial cell production of antimicrobial peptides (AMPs) and for maintaining tight-junctions, thus promoting epithelial barrier integrity. Moreover, in at least 1 of these studies, IL-23 was pathogenic, whereas IL-17 was protective. Furthermore, though IL-17A is the signature cytokine of T_h17 cells, it is not necessarily what promotes the pathogenicity of these cells. T_h17 cells produce a variety of other cytokines, including TNFα and GM-CSF, which are pathogenic in many models.[35, 89] Consistent with this, it has been demonstrated using GM-CSF fate mapping mice that tissue damage in EAE is specifically due to GM-CSF-producing T_h17 cells, which recruit neutrophil influx.[89] Conversely, IL-17A is produced by multiple cells besides T_h17 cells including ILCs, CD8+ T-cells, and NK-cells.[8, 10]

Another distinct possibility for the failure of anti-IL-17 agents in IBD is the effect of IL-17 on the enteric microbiome. As noted earlier, SFB promote the formation of T_h17 cells. However, T_h17 cells in turn negatively regulate enteric SFB via IL-17-dependent production of epithelial AMPs.[90] Blocking epithelial cell IL-17 signaling in this system leads to the expansion of enteric SFB, which promotes the formation of pathogenic T_h17 cells. Thus, this system of reciprocal regulation of T_h17 cells by SFB, followed by T_h17-produced IL-17-dependent regulation of SFB functions as a negative feedback loop restraining pathogenic T_h17 cells.[90] These data therefore suggest that T_h17 cells may be pathogenic independent of IL-17 and that IL-17 blockade both worsens epithelial restitution after injury and promotes the expansion of pathogenic enteric microbiota. Therefore, these data collectively provide plausible reasons for the discordant efficacy of anti-IL-17 and anti-IL-23 therapies in IBD. Thus, it is collectively clear that T_h17, IL-23, and IL-17 may overlap but are also all distinct, which impacts drug development and efficacy in IBD.

T_H17 TARGETING THERAPIES

Given what we know about the link between T_h17 cells and IBD, the rise of anti-IL-23 therapies, either targeting the shared p40 subunit between IL-12 and IL-23 or targeting the p19 subunit of IL-23 alone, have a sound biological background. In addition, given that IL-23R signaling is via JAK/STATs, it is very likely that JAK-inhibitors, specifically JAK2 inhibitors, will also impact T_h17 cell pathways. Because JAKs are ubiquitously expressed in multiple cell types, we focus here on therapies that specifically impact T_h17 pathways, namely anti-IL-23, anti-IL-23R, and pro-IL-22 agents in the IBD pipeline.

Anti-IL-23 Agents

Ustekinumab

Ustekinumab is a humanized monoclonal IgG1 antibody that binds to and neutralizes p40, the shared subunit of IL-12 and IL-23 (Fig. 2). Ustekinumab is currently the only FDA-approved anti-IL-23 therapy for IBD, having gained approval for CD in 2016. The clinical trial data are published, and much

has been written about the real-world efficacy, including therapeutic drug monitoring and safety data. Phase 3 studies in UC are currently underway and the complete data sets have not been published. However, early results report efficacy for induction, with ~16 % of patients reporting clinical remission at week 8 in the treatment arms (130 mg IV or 6 mg/kg IV) compared with 5% in the placebo group. Moreover, statistically significant fractions of patients who achieve remission with IV induction also maintained remission at week 44 with maintenance therapy of 90 mg SQ every 12 weeks (38%) or every 8 weeks (44%) compared with 24% of those receiving placebo maintenance. Most importantly, ~20% of patients achieved mucosal healing, defined as Mayo endoscopic subscore of ≤1 and histologic healing at week 8 relative to 9% receiving placebo induction, whereas endoscopic healing (Mayo ≤1 alone) was achieved in substantial fraction at week 44 (44% and 51% in maintenance very 12 or 8 weeks, respectively) compared with placebo maintenance (29%).[91]

Mirikizumab

Mirikizumab is a monoclonal IgG4 that binds to the p19 subunit of IL-23 and thus only blocks IL-23 (Fig. 2). A phase 2 study in CD randomizing patients with placebo, 200 mg, 600 mg, or 1000 mg of IV induction followed by open-label treatment was just completed. The primary outcome of endoscopic response, defined as a reduction in the CD simple endoscopic score (SES-CD), was achieved in 11% in the placebo induction group and in 26%, 38%, and 44% of the 200 mg, 600 mg, and 1000 mg induction arms respectively (all significant). Moreover, endoscopic remission, defined as SES-CD of <4 for ileo-colonic disease or <2 for ileal disease without a subscore >1, was achieved in 2% of placebo-treated patients followed by, 7%, 16%, and 20% of drug-treated patients in a dose-dependent manner.[92] Although this seems promising, the numbers in this phase 2 study were largely limited to 30 to 60 patients per arm, and phase 3 studies are actively recruiting.

Data from induction and maintenance portions of a phase 2 study in UC have recently been reported.[93] The induction study compared clinical remission at week 12 with either IV mirikizumab induction of 50 mg or 200 mg with the possibility of exposure-based increases or fixed dosing of 600 mg at weeks 0, 4 and 8. The exactitudes of the variable dosing were not reported in detail, but 23% of patients in the 200 mg exposure-based dosing groups achieved the primary outcome of clinical remission at week 12 relative to 5% of placebo treated patients. Interestingly, there were no statistically significant differences between other groups and placebo despite higher mean doses in the 600 mg arm compared with the 200 mg arm (600 mg vs 260 mg, respectively).[93] Endoscopic healing (Mayo ≤1) was significantly different at lower doses (24% and 31% for 50 mg and 200 mg, respectively) compared with placebo (6%). Similar to clinical remission, however, endoscopic remission in the high dose group (13%) did not did not separate from placebo.[93]

Responders to mirikizumab induction were then rerandomized to either placebo or 200 mg SQ every 4 or every 12 weeks; these results were recently reported. Maintenance dosing every 4 or 12 weeks effectively achieved endoscopic remission (Mayo ≤ 1) in 57% and 48%, respectively. Although this sounds promising, it is incomplete as placebo response rates have not yet been reported.[94] Phase 3 studies in UC are ongoing.

Risankizumab

Risankizumab is a humanized IgG1 anti-p19 antibody that recently reported results of a phase 2 induction study in CD (Fig. 2). Patients were randomized to placebo vs 200 mg or 600 mg IV at weeks 0, 4, and 8, with assessment of the primary outcome of clinical remission (CDAI <150) at week 12. Clinical remission was significantly different between placebo (15%) and 600 mg dosing (37%), but not for 200 mg dosing (24%). There were also significant differences in endoscopic remission between placebo (3%) and the 200 mg (15%) and 600 mg (20%) groups.[95] This study was followed by an open-label extension (OLE) of 600 mg IV every 4 weeks in those who did not achieve deep remission to induction, followed by 180 mg SQ maintenance every 8 weeks for 26 additional weeks in those in clinical remission in the prior group. This redosing strategy resulted in remission in 53% of those not in deep remission after induction and was maintained in 71% at week 52. Additionally, 35% achieved endoscopic remission at week 52.[96] Because this was an OLE, placebo rates were not reported. Phase 3 studies in CD are ongoing. Data from phase 2 studies in UC have not been reported, but phase 3 studies are underway nonetheless.

Guselkumab

Guselkumab is a human IgG1 targeting the p19 subunit; it is currently recruiting for UC for a phase 2a comparing guselkumab monotherapy with guselkumab and golimumab dual therapy and a phase 2 comparing active drug to placebo (Fig. 2). Phase 2 and 3 studies in CD are currently recruiting. Data have not been reported for UC or CD.

Brazikumab

Brazikumab, formerly known as MEDI2070, is a recombinant human monoclonal antibody that selectively binds to the p19 subunit of IL-23A. A phase 2a study in CD was completed, and current recruiting for phase 3 in CD and a phase 2 study in UC is planned (Fig. 2). In contrast to many other studies, patients in the phase 2a CD study are likely skewed to more refractory disease, as failure to at least 1 anti-TNF was an entry criterion. Though the broader study included a blinded 12-week induction period followed by a 100-week OLE, the reported data only cover the first 12 weeks of the OLE. Patients were randomized to brazikumab 700 mg IV at weeks 0 and 4 or to placebo, and assessments of the primary outcome of clinical response (decline in CDAI ≤0) followed at week 8 (induction).

All patients then received 210 mg SQ every 4 weeks for the OLE. There were significant differences in the clinical response between groups at week 12 (49% vs 27% for drug and placebo arms, respectively). Furthermore, response and remission were robust in all groups after open label drug, raising the possibility that drug rescued those previously in placebo arms. Endoscopic data were not presented, and there were not differences in safety between groups.[92]

UTTR1147A

UTTR1147A is a recombinant fusion protein of human IL-22 fused with IgG4 Fc.[97] Mechanistically, the IL-22-Fc fusion protein exhibits a long half-life and signals in epithelial cells (and presumably other IL-22R-expressing cells) to augment epithelial protective factors including AMPs. Preclinical testing has demonstrated efficacy in murine models and safety in healthy volunteers.[97, 98] Recruitment for phase 1 trials in UC and CD and a phase 2 placebo-controlled comparative efficacy trial against vedolizumab in UC are ongoing.

ABX464

ABX464 is a small molecule that promotes the initial interaction with transcription and processing machinery by binding to a complex at the 5′-end of the pre-mRNA transcript. ABX464 is thought to exert its therapeutic effects in UC via this novel mechanism, ultimately resulting in upregulation of macrophage-produced IL-22, with subsequent mucosal protection (Fig. 2).[99, 100] A small but placebo-controlled proof of concept study in UC demonstrated promising results, with clinical remission of 35% with treatment compared with 11% with placebo at 8 weeks.[101] Phase 2 studies are planned.

RORgt Antagonists

Finally, there are several RORgt antagonists that have shown promise in preclinical murine models (Fig. 2).[102–105] As expected based on the central role of RORgt in the regulation and maintenance of the T_h17 lineage, these agents broadly inhibit T_h17 cell transcriptional networks to destabilize T_h17 cells.[102–105] At least some of these agents seem to specifically inhibit T_h17 cells rather than ILCs (which also express RORgt).[102] Moreover, the inhibition of T_h17 cells improved murine models of colitis and suppressed T_h17 cells in vitro in human intestinal tissues.[102]

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