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## Th17 plasticity and its changes associated with inflammatory bowel disease

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### Abstract

CD4 T helper (Th) cell differentiation into distinct T

cell subsets is critical to the normal function of the immune system. Until recently, the paradigm held that naïve T cells differentiated into distinct subsets under the guidance of environmental cues (*e.g.*, cytokines) and that once polarized, these cells were committed to a particular functional state. However, the existence of transdifferentiated T cell populations, which express signature transcription factors and cytokines associated with more than one Th subset, challenges the immutability of T helper subsets and suggests that plasticity is a feature of multifaceted immune responses. How this process impacts immune dysregulation in diseases such as inflammatory bowel diseases (IBD) and the machinery that underlies this process is far from fully understood. Interleukin (IL)-17 secreting helper T (Th17) cells have been heavily implicated in tissue-specific immune pathology including murine models of IBD, human Crohn's disease and ulcerative colitis. Plasticity within this subset is suggested by the existence of IL-17 secreting cells, which, can also secrete interferon- $\gamma$ , the signature cytokine for Th1 cells or, can co-express the anti-inflammatory transcription factor forkhead box p3, a signature transcription factor of regulatory T cells. In this review we mainly discuss evidence for Th17 plasticity, mechanisms, which govern it, and highlight the potential to therapeutically target this process in human IBD.

**Key words:** Th7; Regulatory T cells; T cell plasticity; Inflammatory bowel disease

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**Core tip:** Recently, two innovative clinical failures in inflammatory bowel disease which sought to manipulate T helper (Th) subsets *via* either transplantation of regulatory T cells or interleukin-17 blockade using secukinumab, suggest that altering the balance between inflammatory and regulatory subsets in inflammatory bowel diseases (IBD) may be more complex than

previously thought. One reason may be the flexible nature of T helper subset commitment, otherwise referred to as plasticity. Here we discuss plasticity between regulatory and inflammatory subsets in T helper CD4<sup>+</sup> cells, especially Th17 cell subset, and the potential to therapeutically target this process in human IBD.

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## INTRODUCTION

The spectrum of immune-mediated disease encompasses a wide variety of chronic inflammatory conditions such as inflammatory bowel disease (IBD) comprised of Crohn's disease (CD), and ulcerative colitis (UC) as well as rheumatoid arthritis (RA), multiple sclerosis, and psoriasis. Although the underlying triggers remain poorly understood, it is now clear that T cells are essential to the development and perpetuation of these diseases<sup>[1-3]</sup>. Since the landmark description of functionally distinct T helper 1 (Th1) and Th2 CD4<sup>+</sup> effector subsets, each with unique cytokine profiles<sup>[4]</sup>, much work has focussed on dissecting their roles in both health and disease. The spotlight has recently been drawn to a novel subset, the Th17 cell, so named due to its ability to secrete interleukin (IL)-17A, which has emerged as a major player in tissue-specific immune pathology. The initial emphasis on the detrimental effects of Th17 is reflected by the plethora of early literature supporting such a role in both human and murine studies<sup>[5-10]</sup>. However, a growing body of evidence now suggests essential protective roles, particularly in the context of mucosal integrity and defence against extracellular pathogens<sup>[5,11-16]</sup>. Th17 cells and their associated cytokines have been found to interact more closely with other adaptive immune cells than previously thought, raising interesting questions about how to select and design therapeutic strategies targeting this cell population<sup>[2,17]</sup>. New technologies such as transcriptome profiling, global epigenetic mapping and computerized simulation analysis<sup>[18,19]</sup> have captured a more accurate picture of this T cell subset revealing it to be more transient, complex and perhaps more reversible than previously imagined. In addition to a well-established role in extracellular pathogen clearance, Th17 cells can also participate in intracellular pathogen clearance *via* unconventional interferon (IFN)- $\gamma$  secretion<sup>[20,21]</sup>. Human forkhead box p3 (Foxp3) + regulatory T cells (Treg) can differentiate into IL-17 promoting cells *in vitro*<sup>[22]</sup>. Flexibility within this subset may allow Th17 cells to embrace pro-

inflammatory and protective roles in mucosal immunity by secreting a spectrum of cytokines without requiring *de novo* differentiation of naïve T cells. Likewise, Th17 cells may be generated quickly from Treg in order to defend from acute invasion of pathogens. This ability to transition between functional states is defined as T cell plasticity.

This review mainly focuses on human studies and outlines the major features of Th17 plasticity including the Treg/Th17 paradigm shift in the context of IBD and in the maintenance of intestinal homeostasis.

## CHARACTERISATION OF TH17 AND TREG SUBSETS IN IBD

In the last 15 years or so, the focus of attention regarding T cell subsets has shifted from the classical Th1/Th2 paradigm to that of Th17/Treg. This has indeed been the case in IBD.

The discovery of extrathymic Treg development in the intestine has attracted enormous attention and highlights the importance of Treg cells in intestinal homeostasis. Hori *et al.*<sup>[23]</sup>, demonstrated that co-transfer of peripherally generated Foxp3 positive Treg cells could attenuate disease in the adoptive transfer model of mouse colitis. Shortly after this study, Makita *et al.*<sup>[24]</sup>, showed the intestinal prevalence of Treg in patients with IBD. Mucida *et al.*<sup>[25]</sup>, have since identified retinoic acid, derived from vitamin A and metabolized by dendritic cells, as a key signal regulating Foxp3 expression by naïve T cells in response to TGF- $\beta$ . Overall, the digestive tract requires high levels of inducible Treg cells in order to preserve tolerance to the enormous antigenic burden comprised by commensal flora and dietary antigens<sup>[26]</sup>.

At around the same time, Fujino *et al.*<sup>[27]</sup>, first reported on the prevalence of Th17 cells in patients with IBD. Patients with UC and CD show increased IL-17A levels in serum and mucosa<sup>[17]</sup> and an IL-17A gene polymorphism has been linked to UC susceptibility<sup>[28]</sup>. This cytokine, in addition to promoting barrier function, is a potent promoter of granulopoiesis and neutrophil chemotaxis and plays an important role in the clearance of extracellular bacterial and fungal infections<sup>[29]</sup>. Recently, Ciofani *et al.*<sup>[30]</sup> have described an intracellular network regulating Th17 specification. Interestingly, genome-wide association studies linked at least 24 loci within this network to single nucleotide polymorphisms (SNPs) associated with ulcerative colitis and Crohn's disease, highlighting the importance of this T cell subset towards the pathogenesis of IBD<sup>[30,31]</sup>.

### IL-17 secreting Th17 subset

Intestinal effector T cells arise from naïve lymphocytes derived from the thymus, which then undergo functional differentiation in the intestinal mucosa upon encountering their cognate antigen displayed by activated antigen-presenting cells (APCs). APCs and

potentially other cells release cytokines, which act in combination with environmental cues, including bacterial and dietary products as well as salt concentration<sup>[32,33]</sup>, thereby activating the Jak-STAT and other signalling pathways to exert their biological functions.

Differentiation of Th17 cells is exclusively dependent on signal transducer and activator of transcription 3 (STAT3)<sup>[34]</sup> and crucially requires the expression of the transcription factor retinoic acid receptor-related orphan receptor  $\gamma$  thymus in mouse (ROR $\gamma$ t)<sup>[35]</sup>. Studies in the mouse and *in vitro* human cell cultures have revealed the critical roles of transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) alongside IL-6<sup>[36-38]</sup>, IL-1 $\beta$ <sup>[39]</sup> and IL-21<sup>[40]</sup> in Th17 polarization. IL-23, secreted mainly by innate myeloid cells including activated dendritic cells (DC), monocytes and macrophages, is critical for Th17 proliferation and maintenance, though dispensable for the initiation of Th17 development. Importantly, mutations within the *il23r* locus, which encodes a receptor subunit unique to IL-23, are associated with psoriasis<sup>[41]</sup>, ankylosing spondylitis<sup>[42]</sup> and IBD<sup>[43,44]</sup>.

Whilst Th17 cells are distinguished by IL-17A production, they are also capable of producing other cytokines, including but not limited to IL-17F, IL-21 and IL-22. IL-17F, a member of the IL-17 family, may also have dual roles in the context of mucosal disease. In the DSS model of IBD, IL-17F<sup>-/-</sup> mice show less severe disease than wild-types<sup>[28]</sup>. IL-17F evidently appears to have a distinct set of roles, despite structural similarity to IL-17A, and further research will be necessary to establish its specific importance. Substantial evidence exists for pathogenic roles of IL-22, particularly in the context of psoriasis<sup>[45]</sup>. However, IL-22 may play a critical role in the maintenance of the intestinal epithelial barrier and in mucosal healing<sup>[45]</sup>. It is thus important to emphasize that although Th17 cells are defined by their expression of IL-17 and RORc, human counterpart of ROR $\gamma$ t, these cells likely express heterogeneous cytokine profiles, at times simultaneously expressing both protective (IL-22) and deleterious (IL-17A, IFN- $\gamma$ ) cytokines in a tissue-temporal specific manner<sup>[5]</sup>. In addition, the unexpected failure of secukinumab<sup>[46]</sup>, a human anti-IL-17 monoclonal antibody, in the treatment of Crohn's disease reflects the complex role of IL-17 and the heterogeneous causes of the disease<sup>[47]</sup>.

### **Foxp3<sup>+</sup> Treg subset**

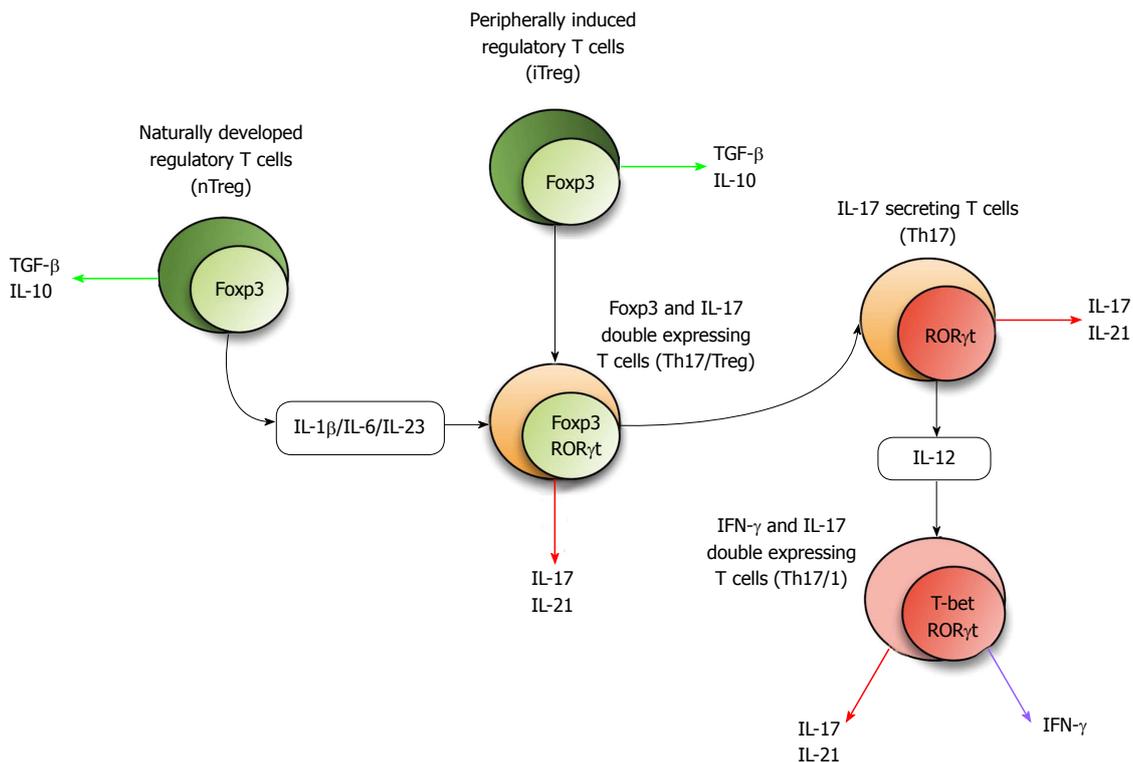
In contrast, anti-inflammatory Foxp3-expressing Treg cells play an important role in tissue homeostasis *via* controlling pro-inflammatory effector T cells. Treg cells were first described as "self"-recognising T cells which develop in the thymus. Nowadays this population of Treg cells has come to be referred to as naturally occurring Treg<sup>[48]</sup>. Initially, Treg cells were believed to differentiate along a distinct pathway to that of

conventional T cells which arise from naïve T cells in the periphery (extra-thymically). It is now apparent however that naïve progenitor T cells can give rise to a population of anti-inflammatory Foxp3 expressing T cells extra-thymically. This population is referred to as inducible Treg (iTreg)<sup>[48]</sup>. The major residential and developmental organs of iTreg cells are in fact the gut mucosa and mesenteric lymph nodes. Differentiation of iTreg cells is dependent on STAT5 and requires activation of the lineage-specifying transcription factor Foxp3. *In vitro* studies using human cells have revealed the critical roles for TGF- $\beta$ 1, together with the cofactor retinoic acid in iTreg development from naïve Th cells<sup>[49]</sup>.

### **Similarities and differences between Th17 and Treg development**

Interestingly, both Th17 and iTreg cells share essential developmental cues, and thus similar developmental pathways, as both subsets can be generated under the influence of TGF- $\beta$ 1. However additional signals specify development of each subset. Similar to Th1 and Th2 subsets, Th17 and Treg can negatively influence each other. In mice, increasing concentrations of TGF- $\beta$ 1 are associated with increased Foxp3 levels and decreased IL-23R expression, leading to decreased IL-23-dependent maintenance of Th17 cells and resulting in impaired Th17 development<sup>[50]</sup>. In addition, Foxp3 was found to directly inhibit IL-17 expression. As a result, Foxp3 and ROR $\gamma$ t double expressing T cells in the lamina propria produced lower levels of IL-17 compared to T cells expressing ROR $\gamma$ t alone<sup>[50]</sup>. Smad 2, 3, and 4, which transduce the extracellular TGF- $\beta$ 1 signal to the nucleus, are pivotal to iTreg generation whilst dispensable for Th17 development<sup>[51,52]</sup>.

Gut resident and pathogenic microbes contribute to gut homeostasis and disease in part by shaping Th subset polarization. Interestingly, Th17 cells are induced by components of the intestinal flora, as has been shown for segmented filamentous bacteria (SFB)<sup>[53]</sup>. This requires MHC class II-dependent presentation of SFB antigens by DCs. On the other hand, commensal bacteria are known to influence gut tolerance by generating Treg cells specific to themselves. Transplantation of specific *Clostridia* clusters into germ free mice induces increased colonic Treg cells<sup>[54,55]</sup>. *Lactobacillus reuteri* colonization is also associated with an increase in gut residential Treg cells<sup>[56]</sup>. Interestingly, bacterial fermentation products may also play an important role in Treg generation. The short-chain fatty acids can promote DC tolerance along with generation of colonic Treg cells<sup>[57,58]</sup>. Another bacterial product, polysaccharide A from *Bacteroides fragilis* can induce anti-inflammatory Foxp3<sup>+</sup>, IL-10 secreting Treg cells *via* TLR2 signalling<sup>[59]</sup>. Thus, intestinal dietary and commensal products can



**Figure 1 Concept of 17 secreting helper T plasticity.** The Foxp3 expressing Treg subset either develops naturally (nTreg) or is peripherally induced from naive T cells (iTreg). Th17 generating factors including cytokines, transcription factors, and other molecular cues can induce these cells to differentiate into transitional cells with co-expression of Foxp3 and RORc. Th17 cells may be converted into Th17/1-transitional cells with co-expression of RORc and TBX21. Th17: 17 secreting helper T; Foxp3: Forkhead box p3; RORγt: Related orphan receptor γ thymus in mouse; IL: Interleukin; TGF: Transforming growth factor; IFN: Interferon.

influence Treg and Th17 development.

## MECHANISMS OF PLASTICITY AND RECIPROCAL REGULATION BETWEEN TREG AND TH17 SUBSET

There are at least four major pathways and/or factors which contribute to Th17 plasticity. The cytokine milieu directs T cell subset development and also induces plasticity *via* the activation of different and specific STAT molecules and multiple transcription factors. Furthermore, it has emerged that immune-regulatory microRNA (miR) plays a fundamental role in controlling gene expression, thus influencing T cell fate and plasticity. There is also the unique role of aryl hydrocarbon receptor (AhR) and its environmental and physiological ligands alongside histone methylation and epigenetic modifications which may fundamentally influence T cell plasticity. Figure 1 summarizes the concept of Th17 plasticity.

### Cytokine pathways (main contributor to plasticity)

As described above, TGF-β signalling with the additional influence of IL-1β, IL-6 and IL-21 are critical to Th17 lineage development as well as the role of IL-23 signalling for the maintenance and function of this subset. High concentrations of

exogenous Th17-generating cytokines are able to convert Foxp3<sup>+</sup> Treg cells into IL-17 secreting Th cells *in vitro*. Since cytokine secretion is a final step in lineage differentiation, this population is considered to possess two signature features for two different subsets; Foxp3 for Treg, and IL-17 for Th17. We found increased levels of circulating IL-17 and Foxp3 double expressing T cells in IBD patients compared to healthy controls. Furthermore, we demonstrated the conversion of CD25<sup>+</sup> CD45RO<sup>-</sup> Treg cells from peripheral blood of IBD patients into IL-17 secreting Foxp3 expressing cells as well as RORc and Foxp3 expressing cells in the presence of combinations of the above mentioned cytokines<sup>[60]</sup>. Comparing the *in vitro* generation of double expressing cells in two types of IBD patients, CD patients have a higher prevalence of double expressing cells generated in the presence of IL-1β/TGF-β/IL-6 than UC while UC patients have an increased frequency of this population in response to IL-21/IL-23 than CD samples, suggesting disease-associated plasticity of Th cells in IBD<sup>[60]</sup>. A recent elegant study by Basu *et al*<sup>[61]</sup>, revealed that IL-1 signalling represses SOCS3, an inhibitory molecule of STAT3 altering the STAT3/STAT5 balance resulting in Th17 generation. This model offers an explanation for why exogenous IL-1β converts Foxp3<sup>+</sup> Treg cells into IL-17<sup>+</sup> Foxp3<sup>+</sup> double expressing Th cells<sup>[61]</sup>.

Cytokines which induce Th17 development and

**Table 1 Cytokines related to 17 secreting helper T development and plasticity in human**

Cytokine	Effect	Ref.
IL-1 $\beta$	Accelerate IL-17A secretion from IL-17 secreting Innate Lymphoid cells and Th17	[69]
IL-6	Induce autocrine IL-21 and generation of Th17	[20]
IL-10	Suppress IL-17A and Th17 generation	[62]
IL-12	Induce IFN- $\gamma$ secretion from Th17 cells (Th1/Th17 plasticity)	[20]
IL-21	Potentiates pathogenic effects of Th17 cells in the gut	[64,65]
IL-22	Attenuate the development of intestinal pathology <i>via</i> Stat3-mediated effects on epithelial cells	[66,67]
IL-23	Induce IL-22 and IL-17A secretions and maintain Th17 expansion	[68]
TGF- $\beta$ 1	Initiate generation of Treg and Th17 populations dependent on the concentration	[63]

Th17: 17 secreting helper T; IL: Interleukin; TGF: Transforming growth factor; IFN: Interferon.

plasticity are summarised in Table 1<sup>[62-69]</sup>.

### Transcription factors

There is now vast literature detailing multiple transcription factors and their relationship to T cell plasticity. These transcription factors directly regulate and/or promote gene expression by binding to their promoter regions in order to contribute to the multifaceted nature of T cell subsets.

Ciofani *et al.*<sup>[30]</sup> recently identified FOS-like antigen 2 (Fosl2) as a key determinant of Th17 plasticity in their remarkable study of Th17 cell specification<sup>[30]</sup>. *in vitro* differentiation of mouse CD4 T cells deficient in Fosl2 under Th17 polarizing conditions yielded IL-17 producing cells which co-expressed Foxp3. Interestingly, Fosl2 deficiency also enabled IFN- $\gamma$  production in Th17 and Th2 cultures, particularly when Th17 cells were subsequently exposed to Th1-skewing conditions.

Interferon regulatory factor 4 (IRF4) is a transcription factor expressed in hematopoietic cells and plays pivotal roles in the immune response. IRF4 levels were augmented in patients with active inflammatory bowel disease and correlated with enhanced production of IL-17 and IL-22 mRNA<sup>[70]</sup>. On the other hand, lack of IRF4 seems to cause resistance to Th17-mediated autoimmune diseases<sup>[71]</sup>. Basic leucine zipper transcription factor, BATF, along with IRF4, was recently proposed as a "pioneer factor" in T cells<sup>[30]</sup>. After T cell receptor ligation, BATF expression is rapidly induced in naive T cells. The BATF-JUN heterodimer and IRF4 bind to the same regulatory regions to mediate chromatin remodelling and facilitate accessibility to regulatory elements by other Th cell subset-specific transcription factors including STAT3, MAF and ROR $\gamma$ t in Th17. Interestingly, BATF and IRF4 are also necessary for Treg differentiation in visceral adipose tissue through

**Table 2 Transcription factors related to 17 secreting helper T development and plasticity**

Transcription factor	Effect	Ref.
Fosl2	A key determinant of cellular plasticity	[30]
IRF4	Th17 differentiation <i>via</i> ROR $\gamma$ t dependent and independent pathways	[115]
	Augmented in patients with IBD and correlated with enhanced production of IL-17 and IL-22 mRNA	[70]
BATF	Required for differentiation of Th17 <i>via</i> induction of ROR $\gamma$ t, and bound to IL-17, IL-21 and IL-22 promoters	[116]
	BATF+ RORC- Th17 cells are found in gut tissues from UC but not CD patients.	[73]
HIF-1	A key transregulator of Th17 polarization and suppressor of Foxp3 in Treg	[33,81]
	Reciprocal regulation between HIF-1 and miR210	[81]
Jmjd3	H3K27 demethylase, important for Th1/Th17 plasticity	[101]
RORc (human)	Essential for Th17 differentiation induced by ROR $\gamma$ t (mouse)	[35]
	TGF- $\beta$ 1 and IL-6 or IL-21	
IKZF3 (Aiolos)	Promotes Th17 differentiation <i>via</i> silencing of the IL-2 locus	[74]
	Aiolos <sup>+</sup> iTreg respond to IL-1 $\beta$ and downregulate their suppressor functions	[75]

ROR $\gamma$ t: Related orphan receptor  $\gamma$  thymus in mouse; IL: Interleukin; TGF: Transforming growth factor; CD: Crohn's disease; UC: Ulcerative colitis; HIF: Hypoxia-inducible factor; IRF4: Interferon regulatory factor 4; IBD: Inflammatory bowel diseases.

direct regulation of IL-33 receptor, ST2 and PPAR- $\gamma$  expression<sup>[72]</sup>. BATF<sup>+</sup> RORC<sup>-</sup> Th17 cells are found in gut tissues from UC but not CD patients<sup>[73]</sup>. Taken together BATF/IRF4 axis may direct Treg/Th17 balance and plasticity in the gut.

A member of the Ikaros family, IKZF3 (or Aiolos) is known to promote Th17 differentiation by suppressing IL-2 production<sup>[74]</sup>. Interestingly, IKZF3 is also expressed in iTreg lacking the expression IKZF2, (or Helios). These IKZF2<sup>-</sup> IKZF3<sup>+</sup> Foxp3<sup>+</sup> Th cells express IL-17 and exert reduced regulatory functions in healthy human blood samples<sup>[75]</sup>. Furthermore, polymorphism in *Ikzf3* locus shows an association with CD and UC<sup>[31]</sup>. Thus, IKZF3 may turn out to be an important regulator of Th17-Treg plasticity in IBD.

An environmental sensor, Hypoxia-inducible factor 1 (HIF-1), which is induced by Th17 cells to promote signalling in a Stat3-dependent manner, cooperates with ROR $\gamma$ t to control expression of Th17 genes, such as IL-17A, IL-17F, and IL-23R. Furthermore, HIF-1 negatively regulates Treg development by mediating Foxp3 protein degradation<sup>[33]</sup>.

On the other hand, Liu *et al.*<sup>[76]</sup> recently reported that TGF- $\beta$  and IL-6 regulate Th1 cell conversion into the Th17 subset *via* expression of Runx1. This is supported by the finding that siRNA mediated silencing of Runx1 inhibits this conversion. Furthermore, TGF- $\beta$  enhanced histone H3K9 acetylation but inhibited H3K9

**Table 3** MicroRNAs influencing 17 secreting helper T development and plasticity

MicroRNA	Inducer	Target	Effect	Ref.
miR10	TGF- $\beta$	Bcl-6	Limit Th17, convert Th cells into Treg	[78,83]
miR17-92 cluster		Creb1, TGF- $\beta$ RII, KZF4 (miR17), PTEN (miR19)	Accumulation of antigen-specific iTreg development, IL-10 production, and possibly Treg cell migration	[78,83]
miR29	NOD2	IL-12p40, IL-23p19	Inhibit IL-23R signalling	[80]
miR126		PIK3R2	Treg-mediated Immunosuppression	[83]
miR132/212 cluster	TCDD, FICZ	Bcl-6	Enhance Th17 development <i>via</i> AhR pathway	[82,83]
miR146a	TLR2-5	STAT1	Block Th1 development	[78,79]
miR155	TLR2-4, TLR9	SOCS1	Unleash STAT1, 4, and 5 signals, and promote Th1, Th2, and Treg	[78,79]
miR210		HIF-1 (counter regulator)	Control Foxp3 expression	[81,83]
miR301		PIAS3	Unleash STAT3 signal, and generate Th17	[78]
miR326		EST-1	Critical for Th17 development	[78]

TGF: Transforming growth factor; Th17: 17 secreting helper T; FICZ: 6-formylindolo [3,2-b] carbazole; TLR: Toll-like receptor; TCDD: Tetrachlorodibenzo-*p*-dioxin; FICZ: Formylindolo [3,2-b] carbazole.

trimethylation of Runx1- and ROR- $\gamma$ t-binding sites on the *IL-17* or *RORc* gene in Th1 cells in this disease model<sup>[76]</sup>.

Transcription factors which are critical for Th17 development and plasticity are summarised in Table 2.

#### Micro-RNA (a cause of plasticity)

miR are small fragments of non-coding RNA (mostly 17-22 nucleotides) that act as regulators of RNA expression through binding to the 3'-UTR of complementary mRNA resulting in repression/silencing of target RNAs. Several miRs have been reported to influence the differentiation of Th cell subsets<sup>[77]</sup> as well as plasticity and reciprocal regulation among Th cell subsets<sup>[78]</sup>.

Targeting STAT1, which is required for optimal Th1 development, miR146a plays an essential role in Treg function and development<sup>[78]</sup>. Targeting suppressor of cytokine signalling 1 (SOCS1), an inhibitor of STAT1, 4, and 5, miR155 plays a unique role in the development of Th1, Th2, and Treg cells and conversely in the suppression of Th17 differentiation. Targeting of PIAS3, an antagonist of STAT3, miR301 influences Th17 expansion<sup>[78]</sup>. Interestingly, the miR146a and miR155 are induced by toll-like receptors, well-known bacterial sensors, suggesting a critical involvement of micro-organisms<sup>[79]</sup>. Moreover, NOD2, a bacterial sensor closely linked to the pathogenesis of Crohn's disease, induces miR29 resulting in downregulation of IL-23 secretion by dendritic cells through targeting of IL-12p40 and IL-23p19. This, in turn, was shown to suppress ROR $\gamma$ t expression in the DSS mouse model of colitis<sup>[80]</sup>.

In activated T cells, miR-210, which targets HIF-1, is upregulated 100 fold. This is especially notable in Th17 cells, resulting in decreased HIF-1 $\alpha$  expression. Deletion of *Mir210* promotes Th17 differentiation under hypoxic conditions. In experimental colitis, miR210 reduced the abundance of *Hif1a* transcripts and the proportion of cells that produced inflammatory cytokines resulting in decreased disease severity<sup>[81]</sup>. Induced by natural and environmental ligands of the

aryl hydrocarbon receptor, the miR132/212 cluster promotes Th17 development<sup>[82]</sup>. The mechanisms of Th plasticity in aryl hydrocarbon receptor signalling will be described in the next section of this review.

Targeting EST1 which is a negative regulator of Th17 cells, miR326 is critical for Th17 differentiation. Furthermore, miR10, which is selectively expressed in Treg and induced by TGF- $\beta$  signalling together with retinoic acid, can limit Th17 differentiation and furthermore can convert conventional Th cells into iTreg. The contribution of this miRNA to Treg stability is highly dependent on Foxp3 expression yet not responsible for Foxp3 induction<sup>[78]</sup>. A regulator of the suppressive activity of Treg cells, miR-126 leads to enhanced Foxp3 expression by targeting PIK3R2, a regulatory component of PI3K which downregulates Foxp3 induction<sup>[83]</sup>. The cluster of miR17-92, a complex of 6 miRNAs, influences Treg function *in vitro* resulting in the generation of IL-10 secreting Foxp3<sup>+</sup> T cells. Although miR17 specifically targets TGF- $\beta$  receptor II and Creb1, the targets of other parts of this cluster are still unknown<sup>[78]</sup>.

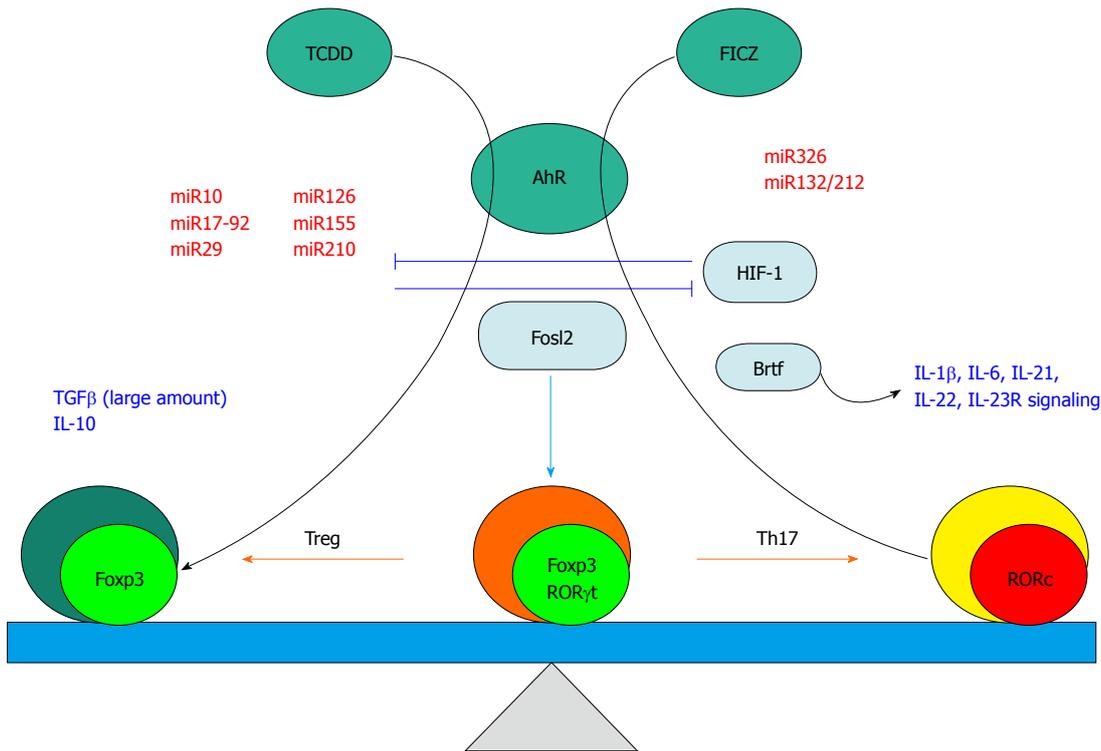
Interestingly, deletion of critical compounds for miR signalling, such as DICER or DROSHA which are found in the micro RNA biogenesis pathways, showed that Treg-specific micro RNA expression is required to suppress T effector cells and maintain tolerance, suggesting that lack of Treg-specific miR results in immune-dysregulation<sup>[78]</sup>.

Since miRs directly regulate the expression of many genes essential to Treg and Th17 subsets, it is highly likely they contribute to Th17-Treg plasticity. However, this exciting field is still in its infancy and further studies are undeniably required.

MicroRNA which influence Th17 development and plasticity are summarised in Table 3.

#### Aryl hydrocarbon receptor (unique mechanistic role of a receptor with dual functions)

The AhR first came to attention 1970-80s<sup>[84,85]</sup> as a receptor for a recognized carcinogen, 2,3,7,8-tetra-chlorodibenzo-*p*-dioxin (TCDD). This receptor is



**Figure 2 Factors influencing the plasticity between Treg and 17 secreting helper T subsets.** Cytokines and growth factors (shown in blue letters) may trigger transdifferentiation of the pre-committed FoXP3 expressing Treg population to RORc expressing cells. Micro RNAs (miR, shown in red letters) play a pivotal role in differentially regulating Treg/Th17 plasticity. Transcription factors (aqua ovals) direct the plasticity by positively or negatively controlling FoXP3 and/or RORc expression. The aryl hydrocarbon receptor (AhR, green circle) can promote distinct differentiation pathways in response to two pathway-specific ligands (TCDD and FICZ, Green circles) resulting in either augmentation of FoXP3 or RORc, respectively. Th17: 17 secreting helper T; FICZ: 6-formylindolo [3,2-b] carbazole; TCDD: Tetrachlorodibenzo-*p*-dioxin; FICZ: Formylindolo [3,2-b] carbazole; AhR: Aryl hydrocarbon receptor; Treg: Regulatory T cells.

a ligand-activated transcription factor, which is responsible for the regulation of several xenobiotic response genes, such as the cytochrome P450 family<sup>[86]</sup>. Soon, attention shifted to the contribution of this receptor to oncogenesis *via* the suppression of immune-surveillance in response to TCDD, suggesting a TCDD-induced immune regulatory function of AhR pathways<sup>[87]</sup>. Later, 6-formylindolo [3,2-b] carbazole (FICZ) was recognised as an endogenous ligand of AhR; however the function of the receptor bound to FICZ was not the same as that bound to TCDD, suggesting that this receptor has ligand specific functions<sup>[88]</sup>. In regard to T cell polarization, Quintana *et al*<sup>[89]</sup>, discovered that activation of the AhR with TCDD leads to the generation of Tregs, and in the same issue of Nature, Veldhoen *et al*<sup>[90]</sup>, reported alternative activation with FICZ leading to Th17 cell differentiation. The effect on Th17 generation has been confirmed by subsequent studies *in vitro* and *in vivo*<sup>[91,92]</sup>, while the influence on Treg generation has been more controversial<sup>[93]</sup>. Recently, Mezrich *et al*<sup>[94]</sup>, showed evidence for a missing link in AhR-derived Treg generation in that kynurenine, a metabolite in the indoleamine 2,3-dioxygenase (IDO) dependent tryptophan degradation pathway, is a key ligand of AhR<sup>[94,95]</sup>. IDO is an enzyme known to suppress effector T cells and is expressed in regulatory plasmacytoid

dendritic cells in response to IFN- $\gamma$ . This kynurenine bound AhR generates Treg *via* influencing the TGF- $\beta$  signalling pathway<sup>[94]</sup>. Furthermore, Moura-Alves *et al*<sup>[96]</sup>, has reported that AhR binds pathogen-associated molecular patterns (PAMPs), regulating immunity in response to bacteria. Although this observation was limited to myeloid and epithelial cells from lung in a murine infectious model, there is a possibility that bacterial activation of AhR may modulate development of Th subsets in a complex bacterial environment, such as the digestive tract.

Taken together one can speculate that a unique function of AhR may be to contribute to plasticity between the Treg and Th17 subsets *via* differential binding to environmental or physiological ligands including bacteria-derived metabolites and PAMPs.

Figure 2 illustrates the contributing factors to the plasticity between Treg and Th17.

### Histone methylation (monitoring the characteristics of plasticity)

Histone modifications including acetylation, methylation, and phosphorylation, are associated with gene expression or repression *via* alternations in chromatin structure<sup>[77]</sup>. In regard to Th1, Th2 and Th17 subset development, trimethylation of lysine 4 (H3K4me3) and lysine 27 (H3K27me3) play important roles in activation

and repression, respectively, of gene expression downstream of transcription factors specific to Th subsets. Thus, monitoring H3K4me3 and H3K27me3 status can visualize the potential for plasticity in T cell subsets.

H3K4me3 marks the signature cytokine genes (*Ifng* for Th1, *Il4* for Th2, *Il17a*) within the Th17 subset while repressive H3K27me3 is found on Th17 signature cytokine genes in Th1 (*Il4*, *Il17a*), Th2 (*Ifng*, *Il17a*) and Th17 (*Il4*, *Ifng*), suggesting lineage commitment to these particular subsets within these cells. Interestingly however, trimethylation on some transcription factor genes is bivalent (both H3K4 and H3K27) suggesting an element of reversibility in epigenetic status, particularly in Th17 cells. In these cells it is possible to find bivalent methylation in the Th1 transcription factor *Tbx21* and Th2 transcription factor *Gata3*, in addition, *Foxp3* may remain unmethylated suggesting a “neutral” state. Thus, histone methylation states may help explain why Th17 cells can swing to other subsets more easily than other T cell subsets<sup>[97-99]</sup>. Cytokines regulate the trimethylation status of Th17, resulting in subset conversion and plasticity. Also, the universal bivalent status of *Tbx21* in all Th subsets except Th1, where you have only permissive H3K4me3, explains why plasticity towards the Th1 subset is dominant<sup>[99]</sup>. Thus, monitoring trimethylation status of H3K4 and H3K27 is useful in predicting the potential for, and direction of Th cell plasticity.

A histone modifying enzyme, JMJD3 is a histone H3K27 demethylase<sup>[100]</sup>. Li *et al.*<sup>[101]</sup>, reported that JMJD3 ablation promoted Th cell differentiation into Th2 and Th17 cells in the small and large intestines, and inhibited T-cell differentiation into Th1 cells *in vitro* and in a Th1-dependent colitis model. JMJD3 deficiency also restrains plasticity of Th2, Th17 and Treg cells towards Th1 cells. The skewing of T-cell differentiation is concomitant with changes in the expression of key transcription factors and cytokines *via* changes in H3K27me3 and H3K4me3 levels<sup>[101]</sup>.

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## TH17 PLASTICITY IN CHRONIC INFLAMMATORY DISEASES INCLUDING IBD

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IFN- $\gamma$ <sup>+</sup> IL-17<sup>+</sup> double expressing cells are considered a cross-over transition of Th17 into Th1 lymphocytes<sup>[102]</sup>. This cell population represents an efficient local host defense system which shifts host defense from extracellular pathogens to intracellular microbial infections<sup>[103]</sup> and may contribute to autoimmune pathogenesis in both mouse models and in human diseases<sup>[104,105]</sup>. Globig *et al.*<sup>[106]</sup>, suggested that this population is indeed a subpopulation of Th17 cells and may be involved in IBD pathogenesis of both CD and UC. Interestingly, Weaver and colleagues recently have provided evidence that Th17 cells can act as

precursors for IFN- $\gamma$  secreting Th1 cells in a mouse of colitis, showing the indispensability of Th17/Th1 plasticity in the pathogenesis of colitis<sup>[21]</sup>.

Likewise, IL-17<sup>+</sup> *Foxp3*<sup>+</sup> double expressing CD4<sup>+</sup> T cells may differentiate into Th17 cells under pro-inflammatory conditions such as IL-1 $\beta$ , IL-6, IL-21, IL-23 and TGF- $\beta$ <sup>+</sup>, having as yet largely unknown consequences for human disease initiation or progression<sup>[107]</sup>. On the other hand, plasticity from Th17 to Treg has not been frequently reported. However, a recent study from Yale University, suggests that this can in fact occur in the context of intestinal immune responses. According to their findings, Th17 cells generated during bacterial infection can be converted into IL-10<sup>high</sup>, *Foxp3*<sup>lo</sup> Tr1-like regulatory T cells. This was dependent on TGF- $\beta$ 1 and could be enhanced *in vitro* using an AhR ligand, FICZ<sup>[108]</sup>. This suggests that Th17 cells may alter their inflammatory status during infection, thus quenching inflammation and suggests possible avenues *via* which this mechanism could be harnessed therapeutically<sup>[108]</sup>.

The Th17-promoting cytokine, IL-23 is known to play an essential role in driving intestinal inflammation. This cytokine also plays an inhibitor role in augmentation of intestinal iTreg generation<sup>[109]</sup>. Furthermore, IL-23 together with IL-12 signalling promotes IFN- $\gamma$  secretion from Th17 in intestine, leading Th17/Th1 plasticity<sup>[110]</sup>. IL-23 signalling pathway is considered as a plasticity initiator in regard of Th17 subset *via* decreasing *Foxp3* expression and assisting increased IFN- $\gamma$  secretion.

In 2011, a hallmark study of Hovhannisyan *et al.*<sup>[111]</sup> showed evidence for Treg/Th17 plasticity in IBD by showing the presence of IL-17 producing, *Foxp3* expressing Th cells in inflamed intestinal mucosa from Crohn's disease patients. Importantly, this population showed suppressor activity *in vitro*. We have gone on to demonstrate the presence of this unique T cell subset in peripheral blood from IBD patients<sup>[60]</sup> and have found evidence for several types of plasticity including Treg/Th17, Th1/Th17 and Th22/Th17 within the lamina propria of lesions from IBD patients<sup>[112]</sup>.

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## CONCLUSION

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Plasticity between Treg and Th17 likely occurs in the context of dynamic changes in the inflammatory milieu. Thus, pro-inflammatory stimuli may promote conversion of immune-suppressive regulatory T cells into pro-inflammatory Th17 cells, while resolution of inflammation may trigger or even require the alternate shift from Th17 to Treg. This concept is just becoming appreciated and requires further study to correlate both causes and outcomes. Targeting plasticity may offer avenues to pharmacologically restore the Th17/Treg balance in the intestine for therapeutic benefit<sup>[113]</sup>. In addition, targeting plasticity may help improve upon future therapies. Clinical trials of Treg therapy of Crohn's disease failed<sup>[114]</sup> perhaps in part due to Treg

instability. Further understanding of Treg plasticity may help to augment Treg therapy in the future.

Many studies have implicitly suggested the possibility of plasticity during their experiments and observation of inflammatory processes. It is clear however that several pathways give rise to the heterogeneous populations referred to as Th17 and Treg in the intestine. The field is in part limited due to constraints inherent to the techniques used to analyse these cells. Most investigators rely upon multicolor flow cytometry, requiring the precise selection of surface and intracellular markers and setting of conditions and controls in order to provide limited functional and expression data. New technologies look to overcome these technical issues as well as to enhance the depth of analysis. Examples include deep immune-phenotyping using CYTOF 2 mass spectrometry which allows the analysis of over 100 parameters at the single cell level without dealing with spectral overlap, alone or in combination with single cell transcriptomics.

To conclude, unravelling the complexity that underlies plasticity between Th17 and Treg cells may be key to understanding the intricate pathogenesis of T cell-mediated immune disorders, such as IBD. However, novel approaches and their application to human IBD will be required to reach this objective.

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