Seminars in Immunopathology (2019) 41:379–399
https://doi.org/10.1007/s00281-019-00732-9

REVIEW

Epigenetic regulation of T helper cells and intestinal pathogenicity

Yuya Hagihara[1] · Yusuke Yoshimatsu[1] · Yohei Mikami[1] · Yoshiaki Takada[1] · Shinta Mizuno[1] · Takanori Kanai[1,2]

Received: 25 January 2019 / Accepted: 5 March 2019 / Published online: 19 March 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Inflammatory bowel diseases (IBDs) are characterized by relapsing and remitting chronic intestinal inflammation. Previous studies have demonstrated the contributions of genetic background, environmental factors (food, microbiota, use of antibiotics), and host immunity in the development of IBDs. More than 200 genes have been shown to influence IBD susceptibility, most of which are involved in immunity. The vertebrate immune system comprises a complex network of innate and adaptive immune cells that protect the host from infection and cancer. Dysregulation of the mutualistic relationship between the immune system and the gut environment results in IBD. Considering the fundamental role of epigenetic regulation in immune cells, epigenetic mechanisms, particularly in T helper (Th) cells, may play a major role in the complex regulation of mucosal immunity. Epigenetic regulation and dysregulation of Th cells are involved in the maintenance of intestinal homeostasis and its breakdown in IBD.

Keywords CD4 T cell · Colitis · Mucosal immunology · Inflammatory bowel disease · Epigenetic regulation

Abbreviations

AhR	Aryl hydrocarbon receptor
Areg	Amphiregulin
AP-1	Activator protein 1
Ar5	Accessible region 5
CD	Crohn's disease
CBFβ	Core-binding factor, beta subunit
CNS	Conserved non-coding sequence
CREB	Cyclic adenosine monophosphate response element-binding protein
DC	Dendritic cell
DNMT	DNA-methyltransferase
DR3	Death receptor 3
DSS	Dextran sodium sulfate
EAE	Experimental autoimmune encephalomyelitis
FOXO	Forkhead box 0
GVHD	Graft-versus-host disease
H3K4me3	Histone 3 lysine 4 tri-methylation
H3K27Ac	H3 lysine 27 acetylation
HAT	Histone acethyltransferase
HDAC	Histone deacetylase
HS	Hypersensitive site
IBD	Inflammatory bowel disease
IFN	Interferon
IL	Interleukin
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome
IRF4	Interferon regulatory factor 4
LDTF	Lineage-defining transcription factor
lncRNA	Long non-coding RNA
LTβR	Lymphotoxin β receptor
miRNA	Micro RNA
miR-183C	miR-183-96-182 cluster
mLN	Mesenteric lymph node
MS	Multiple sclerosis
NFAT	Nuclear factor of activated T cells
NK	Natural killer
OVA	Ovalbumin
PCAF	p300/CREB-binding protein-associated factor
PcGs	Polycomb-group proteins
PRC	Polycomb repressive complex
RA	Retinoic acid

Yuya Hagihara, Yusuke Yoshimatsu and Yohei Mikami contributed equally to this work.

This article is a contribution to the special issue on The Pathogenicity of Acquired Immunity in Human Diseases - Guest Editor: Kiyoshi Hirahara

✉ Yohei Mikami
yoheimikami@keio.jp

[1] Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

[2] AMED-CREST, Japan Agency for Medical Research and Development, Tokyo 100-0004, Japan

ROR	Retinoic acid-related orphan receptor
SOCS	Suppressor of cytokine signaling
T-bet	T-box expressed in T
TCR	T cell receptor
TET	Ten-eleven translocation
TGF	Transforming growth factor
Th	Helper T
TNBS	Trinitrobenzene sulfonic acid
TNF	Tumor necrosis factor
Treg	Regulatory T
TRUC	T-bet$^{-/-}$ × *RAG2*$^{-/-}$
UC	Ulcerative colitis
TSDR	Treg cell-specific demethylated region;

Introduction

Inflammatory bowel diseases (IBDs) are relapsing and remitting conditions characterized by chronic intestinal inflammation. Several factors, including genetic background, environmental factors, and microbiome composition, have been shown to induce aberrant autoimmune responses in patients with IBD. These excessive inflammatory responses are mediated by multiple immune cell types, including CD4$^+$ T cells, which play a major role in the pathogenesis of IBD. In particular, effector T cell subsets (T helper type 1 (Th1), Th2, and Th17 cells) and an immunoregulatory subset (regulatory T (Treg) cells) are finely balanced to maintain immune homeostasis in the gut (Fig.1). Th1 cells express T-box expressed in T cells (T-bet) transcription factor and produce interleukin (IL)-2 and interferon (IFN)-γ. Th2 cells express GATA3 and produce IL-4, IL-5, and IL-13. Th1 cells are involved in immune responses against intracellular microbes and Th2 cells play a major role in defense against parasitic infection. Th17 cells produce a unique set of cytokines including IL-17, IL-21, and IL-22, and thus represent a distinct subset from Th1 and Th2 cells. The development and differentiation of Th17 cells require two key transcriptional factors: retinoic acid-related orphan receptor (ROR)γt and RORα [1, 2]. Th17 cells are important contributors to adaptive immune responses against certain microbes, including extracellular bacteria and fungi. By contrast, Treg cells express the master transcriptional regulator Foxp3 and suppress host immune responses to induce self-tolerance [3, 4]. Multiple lines of evidence support the idea that all of these T helper (Th) cell subsets are important for the ability of the host to combat infectious diseases. Moreover, the balance between effector and regulatory Th cell subsets is essential to support immune homeostasis and prevent autoimmunity [5, 6].

Th cell subset differentiation and proliferation are tightly regulated by the T cell receptor (TCR), co-stimulatory molecules, and cytokines. These stimuli are transmitted through a series of signaling molecules to transcription factors that binds to specific DNA sequences [7, 8]. In addition to transcription factors, recent advances using next-generation sequencing technologies have increased our understanding of the epigenetic factors that are important in controlling the specificity and plasticity of T cell subsets [9–11]. Epigenetic regulation occurs through DNA methylation and covalent chromatin modifications, such as acetylation, methylation, phosphorylation, ubiquitination, and sumoylation. In addition, non-coding RNAs, including miRNAs, play important roles in T cell development, maturation, activation, differentiation, and senescence [12]. Here, we review the impact of epigenetic regulation on each Th cell lineage and discuss the phenotypes of colitis that result from dysregulated epigenetic control and subsequent imbalance of regulatory and effector Th cells.

Treg cells

Foxp3$^+$ Treg cells are critical for maintaining intestinal homeostasis by preventing T cell proliferation and excessive inflammatory cytokine responses [13–15]. The frequency of CD4$^+$CD25$^+$FOXP3$^+$ Treg cells is increased in the intestinal mucosa of the patients with IBD [16–18]. Mutation of human FOXP3 results in spontaneous multiorgan inflammation, including at intestinal sites; this condition is called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) [19]. Among Th cell subsets, the epigenetic regulation of gene expression and lineage stability of Treg cells have been most extensively studied. Foxp3 expression in Treg cells has been shown to be under epigenetic control [20, 21]. A distinct DNA methylation pattern combined with characteristic histone modifications establishes as open chromatin structure, thereby imprinting Foxp3 expression in Treg cells [22].

The *Foxp3* locus contains several conserved non-coding sequences (CNSs) that are critical for the initiation and maintenance of *Foxp3* transcription [23]. CNSs exist nearby the promoter; they are the primary targets of epigenetic regulation and are necessary to modulate Foxp3 expression depending on the environmental signals received by T cells [24]. Among three *Foxp3* CNSs, CNS2 has been demonstrated to prevent autoimmunity, emphasizing the importance of CNS2 in the stability and function of Treg cells [25, 26]. CNS2 lies within the first intron, approximately 4 kb downstream of the promoter. Selective demethylation of CNS2 CpG motifs is critical for stabilization of Foxp3 expression in Treg cells. CNS2 deletion in mice consistently leads to spontaneous systemic inflammatory disease involving liver, lung, and small intestine starting from 6 months of age, and apparently fosters a relatively lymphoproliferative environment [25, 26]. Three main histone modifications of the Foxp3 protein have been described: acetylation, phosphorylation, and ubiquitination [27]. These modifications affect the stability and DNA-

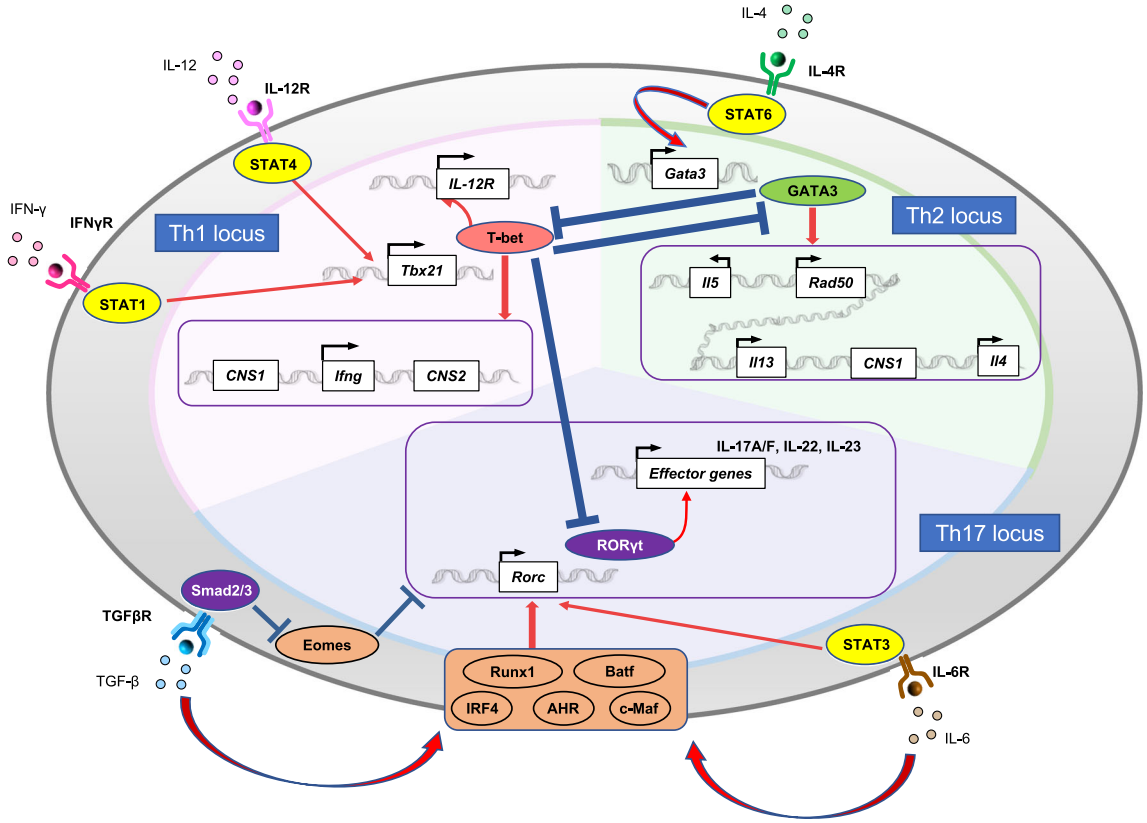

Fig. 1 Differentiation of effector Th subsets. 1. Loci closely associated with Th1 cells are shown in the upper left region (red background). First, expression of *Ifng* and *Tbx21* are induced by TCR signaling. Signaling from IL-12R further enhances *Ifng* expression via the STAT4 pathway. Subsequently, IFN-γ promotes expression of *Tbx21* which lead to Th1 differentiation. Production of IFN-γ is promoted by T-bet. 2. The upper right area (green background) represents the Th2 locus. Stimulation by IL-4R induces expression of *GATA3* via the STAT6 pathway. Subsequently, GATA3 recognizes and binds Th2 cytokine loci and promotes the production of IL-4, IL-5, and IL-13. GATA3 and T-bet interact with each other and suppress differentiation into other subsets. 3. The lower region (blue background) contains Th17 cell-related genes. IL-6R signals via the STAT3 pathway and TGF-β signals via the SMAD2/3 pathway to induce expression of *Rorc*. Transcription factors such as Runx1, Batf, IRF4, AhR, and c-Maf cooperate and enhance the production of Th17 cytokines. Eomes inhibits the *Rorc* and Th17 cytokine loci by directly binding their promoters, while TGF-β induces Th17 differentiation by blocking its action

binding capacity of Foxp3 and thus modulate Treg cell function and the development of autoimmunity. Acetylation of specific lysine residues by lysine acetyltransferases globally stabilizes Foxp3 expression and promotes T cell function by favoring the binding of Foxp3 to its transcriptional targets and allowing it to avoid proteasomal degradation. To achieve stable expression of Foxp3, the CNS2 region is hypomethylated and bound by key transcription factors [22, 28].

Previous studies showed that demethylation of a CpG-rich element in CNS2 known as Treg cell-specific demethylated region (TSDR) occurs during thymic Treg cell development [22]. The demethylated state of CNS2 accounts for the stability of *Foxp3* expression in thymic Treg cells. By contrast with thymic Tregs, Treg cells induced in the periphery or in vitro do not show hypomethylation of CNS2 [29, 30] and can lose *Foxp3* expression under certain circumstances. The methylation state of CNS2 is highly influenced by demethylating enzymes, such as the ten-eleven translocation (TET) demethylases, and methylating enzymes, such as the DNA methyltransferases (DNMTs). Treg cells lacking TET2 and TET3 show loss of Foxp3 expression and compromised Treg suppressive function in vitro and in vivo [31]. Conversely, retroviral induction of the TET catalytic domain (TET-CD) in iTreg cells leads to demethylation of CNS2. In the context of colitis, iTreg cells expressing TET-CD show enhanced suppressive capacity compared with control iTregs when co-transferred alongside naïve T cells into lymphopenic mice [32]. Similarly, TET activators such as vitamin C demethylate the CNS2 locus and reinforce the stability of Foxp3 expression in human and mouse iTreg cells [31]. Although an important role of vitamin C in colitis has been suggested in several studies [33], few clinical trials have been conducted and the efficacy of vitamin C for treating IBD patients remains unknown. By contrast with thymic Treg cells, the CNS2 region of conventional T cells is highly bound by DNMTs. Genetic deletion of DNMTs and inhibition of DNA methylation with azacytidine demethylates the CNS2 region and induces Foxp3 expression [29, 34]. Conversely, TET family inhibition by metabolites or dysregulated mitochondrial electron transport chain in Treg cells increases DNA methylation. Treg cells lacking an essential subunit of mitochondrial complex III exhibits reduced

suppressive function, resulting in failure to suppress colitis in adoptive transfer colitis model [35]. Additionally, it has been shown that Foxp3 expression is induced by TGF-β in combination with multiple other factors such as retinoic acid (RA) and rapamycin [36–39]. However, the CNS2 region is less methylated in thymic Treg cells compared with Foxp3$^+$ cells induced from naïve T cells or differentiated Th1 cells in vitro [22, 39, 40]. It still remains unclear which factors are critical to achieve full and stable demethylation of the CNS2 region during induction of FoxP3 expression.

The methylation status of the CNS2 region is also directly affected or otherwise influenced by a wide range of transcription factors. Suppressor of cytokine signaling 1 (SOCS1), a negative regulator of the JAK-STAT pathways, plays a critical role in cytokine signal transduction and differentiation of T cell subsets, including Treg cells [41, 42]. In mice whose T cells are deficient in SOCS1, Treg cells show rapid methylation of the CNS2 region, lose Foxp3 expression, and fail to suppress colitis after co-transfer with naïve T cells into lymphopenic mice [43]. Rapid downregulation of Foxp3 in two different genotypes of SOCS1-deficient Treg cells (*Foxp3*^{cre}*SOCS1*$^{fl/fl}$ and *Lck*^{cre}*SOCS1*$^{fl/fl}$ mice) was attributed to unrestrained activation of the IFN-γ-STAT1 [44] and IL-12-STAT4 pathways [45]. In inflamed tissue, IFN-γ also induces expression of T-bet, a lineage-defining transcription factor for Th1 cells, in Treg cells, and T-bet$^+$ Treg cells were preferentially recruited to suppress Th1 responses via CXCR3 [46–48]. In addition to T-bet, lineage-determining transcription factors (LDTFs) for other T cell lineages are co-expressed in Treg cells. GATA3, a LDTF for Th2 cells, binds to the demethylated CNS2 region and stabilizes the expression of Foxp3 in Treg cells. Moreover, GATA3-deficient (*Tnfrsf4* (OX40)^{cre}*Gata3*$^{fl/fl}$) Treg cells failed to suppress colitis in the T cell transfer colitis model [49]. This is consistent with recent attempts at global mapping of DNA methylation, which showed that tissue-resident Treg cells achieve a Th2 cell-like methylation pattern and express Th2 cell-associated signature genes such as *Il1rl1* (ST2), *Klrg1* (KLRG1), *Tigit* (TIGIT), and *Gata3* (GATA3) [50]. ST2 is preferentially expressed on colonic Treg cells in comparison with mesenteric lymph node (mLN) Treg cells, where its ligand IL-33 stimulates Treg cells to stabilize Foxp3 expression and ensure full Treg function in the colon [51]. In ST2$^+$ Treg cells, the alarmin IL-33 phosphorylates GATA3 and leads to the expression of a set of genes co-regulated by Foxp3 and GATA3 [51]. ST2$^+$ Treg cells, which are found in adipose tissue, muscle, brain, and intestine during inflammation, proliferate, and repair tissue damage by producing amphiregulin (Areg) in response to IL-33 and IL-2 [52–56]. In addition, IL-33/ST2 signaling promoted proliferation of intestinal Treg cells in a p38/MAPK-dependent manner in a mouse model of acute graft-versus-host disease (GVHD) [57]. Since IL-33 and ST2 are upregulated in the epithelium and CD4$^+$ T cells of patients with active ulcerative colitis and are normalized after anti-TNF treatment [58], the IL-33/ST2 system may represent an important negative feedback loop for intestinal inflammation. Although the protective role of IL-33 during intestinal inflammation remains less clear than in lung and adipose tissues [49, 51, 59], it is highly suggestive that a positive feedback loop involving IL-33, ST2, and GATA3 promotes Foxp3 expression and boosts Treg signatures [60]. In addition, both inflammatory and regulatory roles of IL-33 have been shown in colitis models [61], and the immunoregulatory or wound repair function of IL-33 during colitis appears to be phase-dependent. IL-33 is a member of the IL-1-family cytokines, inducing Areg production by Treg cells and fueling the tissue-repair program in lung and adipose tissues. Among the IL-1 family and related cytokines, IL-18, but not IL-1α, IL-1β, or IL-36, increased Areg production by in vitro-cultured Treg cells [54] (Fig.2). IL-18 is produced by intestinal epithelial cells like IL-33 and is upregulated in patients with Crohn's disease (CD) [62, 63]. In experimental colitis models, conflicting roles of IL-18 have been described [64–68]. The discordant data were presumably influenced by different genetic models and related confounding environmental factors, including the gut microbiome. In the context of Treg cells, IL-18/IL-18R signaling is critical for preventing colitis following T cell transfer in animal models [69]. Similarly, IL-18 contributes to Areg production by Treg cells and causes lung damage [54]. However, unlike IL-33, the role of IL-18 in formation of Treg cell-specific methylome patterns remains largely unclear. Moreover, it is highly likely that multiple subpopulations of Treg cells differentiate in the presence of IL-18, IL-33, and other cytokines. Describing the heterogeneity of Treg cells would be an interesting goal for future studies.

Beyond methylation states, CNS2 serves as an enhancer of Foxp3 expression and contains increased levels of H3K4 methylation as well as H3/H4 acetylation in Treg cells [28]. The polycomb repressor complex is replaced by p300/CREB-binding protein-associated factor (PCAF), a histone acetyltransferase recruited via KLF10 to the *Foxp3* promoter, which then results in opening of the *Foxp3* promoter by permissive histone modifications. The acetyltransferase TIP60 promotes acetylation-dependent dimerization of Foxp3; in the absence of TIP60, lethal autoimmunity develops [70]. Other post-translational Foxp3 regulatory processes include phosphorylation at serine and threonine residues by several kinases, including PIM-1, PIM-2 and CDK2, and ubiquitination at lysine residues, which targets Foxp3 for proteasomal degradation [27]. Under inflammatory conditions, proteasome-dependent degradation of Foxp3 is mediated by the ubiquitinase STIP1 homology and U box-containing protein 1 (Stub1) [71]. By contrast, the deubiquitinating enzyme ubiquitin-specific protease 7 (USP7) regulates the turnover of Foxp3 is highly expressed in Treg cells and is associated with Foxp3 in the nucleus [72]. Conditional deletion of USP7 in Treg cells leads to lethal autoimmunity, decreased numbers of Treg cells in the periphery, and development of autoantibodies against gastric parietal cells, pancreatic islet cells, endomysium, and smooth muscle.

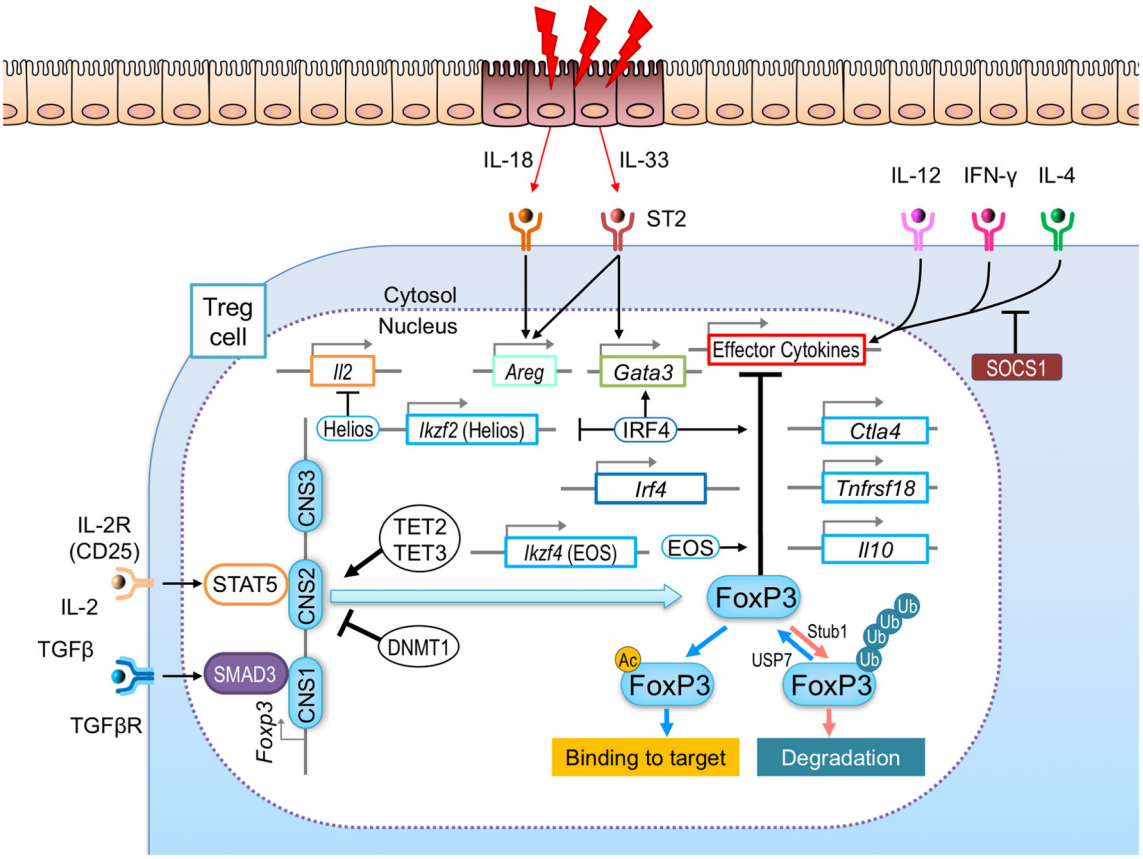

Fig. 2 Epigenetic regulation of Treg function. In the steady state, *Foxp3* transcription is positively regulated by cytokines such as TGF-β and IL-2. After transcription and translation, Foxp3 protein promotes transcription of anti-inflammatory cytokines such as *Ctla4*, *Tnfrsf18*, and *Il10*, while inhibiting transcription of signature cytokines of effector T cells. Suppressor of cytokine signaling 1 (SOCS-1) also inhibits the JAK-STAT pathways that induce these effector cytokines. Acetylation of specific residues stabilizes Foxp3 expression and promotes binding of Foxp3 to its transcriptional targets. The deubiquitinating enzyme USP7 regulates the turnover of Foxp3 and is highly expressed in the steady state. In inflammatory environments, *Foxp3* transcription can be negatively influenced by DNMT1, which is induced by pro-inflammatory cytokines. Proteasome-dependent degradation of Foxp3 is mediated by the ubiquitinase Stub1. IL-18 and IL-33, which are produced from intestinal epithelial cells, induce *Gata3* and *Areg* transcription from Treg cells that contribute to tissue repair. IRF4 promotes the functions of Foxp3 and Eos and also promotes *Gata3* transcription. By contrast, IRF4 represses transcription of *Ikzf2*, which encodes Helios. Helios, which is highly expressed in thymic Treg cells, directly binds to the *Il2* locus and represses its transcription

The CNS2 region is bound by a set of transcription factors (Fig.3). Several pathways downstream of the TCR are known to be involved in this process. Long-range chromatin interactions are known to play important roles in transcriptional regulation, and Foxp3 dimers can preferentially bind sites separated from one another because of its structure [73]. Physical interaction between CNS2 and the Foxp3 promoter region occurs in an NFAT-dependent manner in response to TCR stimulation [26]. Upon TCR activation, runt-related transcription factor (Runx) 1 and core-binding factor, beta subunit (CBFβ) form a trimeric complex with Foxp3, which then binds to CNS2, establishing a loop that stabilizes Foxp3 expression upon TCR activation [24]. The NF-κB pathway is another important regulator of Treg cell development. Genetic deletion of c-Rel or other NF-κB pathway components leads to impairment in Treg cell development [74]. In addition to signals from the TCR, IL-2 is a critical cytokine for the development and maintenance of Treg cells. Treg cells are obligate IL-2 consumers and rely on activated T cells as a source of IL-2. Helios, encoded by *Ikzf2*, is one of the transcription factors that suppresses IL-2 expression through epigenetic silencing of the *Il2* locus [75]. Perturbation of IL-2 signaling in mice lacking IL-2, IL-2Rα, IL-2Rβ, or its downstream signal transducer, STAT5, results in spontaneous systemic inflammation due to impaired Treg development [76–79]. IL-2-induced STAT5 is phosphorylated and recruited to the CNS2 region, where it maintains transcription of *Foxp3* under normal physiological conditions [79]. Despite the importance of and dependency on IL-2 for Treg cells, basiliximab, and daclizumab, humanized monoclonal antibodies that block the engagement of IL-2 with its receptor (IL-2Rα), have been shown to be effective in treating multiple sclerosis (MS) and GVHD. By contrast, results from clinical trials with basiliximab and daclizumab were negative in patients with moderate to severe ulcerative colitis (UC) [80, 81].

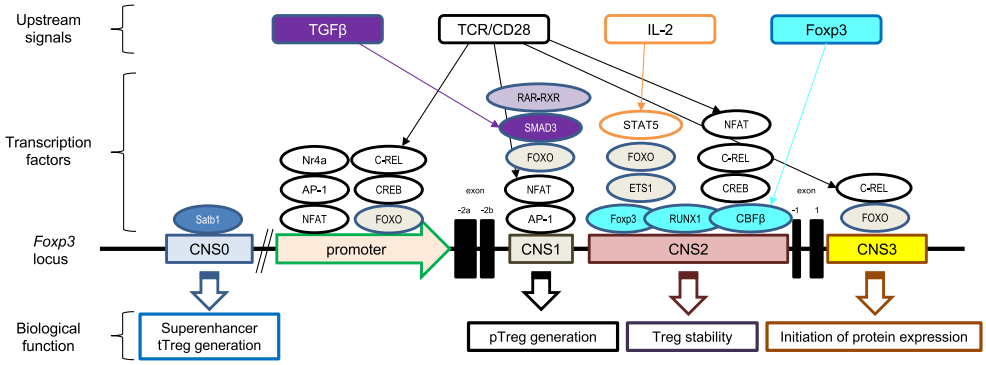

Fig. 3 Transcriptional regulation of the *Foxp3* locus. TCR and CD28 co-stimulatory signals, TGF-β, paracrine IL-2, and an autocrine Foxp3-dependent feedback loop are important in transcription of Foxp3. Foxp3 expression is regulated by binding of several transcription factors to the promoter region and CNSs of the Foxp3 locus. Transcription factors and corresponding pairs of upstream signals are shown using the same color scheme. TGF-β signaling (purple): SMAD3. TCR/CD28 signaling (white with purple frame): AP-1(activator protein 1), c-Rel (member of NF-κB transcription factor family), CREB (cyclic AMP-responsive element-binding protein), and NFAT (nuclear factor of activated T cells). IL-2 signaling (white with orange frame): STAT5 (signal transducer and activator of transcription 5). Foxp3 signaling (light blue): CBFβ (core-binding factor, beta subunit), Foxp3, and RUNX1 (runt-related transcription factor 1). The other molecules, FOXO (forkhead box 0) (inhibitory factors) and Ets-1 (E26 avian leukemia oncogene 1), are constitutive and inhibitory factors, respectively

Since TGF-β, IL-2, and RA are abundant, Nrp1(−) peripherally induced Treg cells are differentiated in the gut [15]. Among IL-2 receptors, IL-2Rα is essential for high-affinity binding of IL-2, Treg cell survival, and T cell differentiation and function. Neutralization of IL-2Rα significantly reduces the number of Treg cells in patients treated with basiliximab and daclizumab though lower affinity signaling, despite IL-2Rβ and γc remaining unperturbed [82]. Consistently, the strength of downstream signaling from IL-2R influences the induction of Treg cells and the expression of the STAT5 paralogs, STAT5A and 5B, which critically drive Foxp3 expression in a dose-dependent manner. The binding sites of STAT5A and 5B largely overlap, while the absence of a single copy of STAT5A or STAT5B reduced binding of STAT5 to genes involved in Treg differentiation and maintenance such as *Il2ra* [83–85]. In addition to STAT5, Bach2 is a critical transcription factor required for inducing peripheral Treg cells and repressing effector programs of non-Treg cells [86]. In the absence of Bach2, mice spontaneously develop lethal lymphoproliferative disease with gut manifestations. Patients with heterozygous mutations in the *BACH2* gene locus consistently exhibit IBD-like intestinal inflammation [87]. Therefore, the paradoxical efficacies of anti-IL-2Rα interventions in UC, MS, and GVHD patients highlight the importance of gut Treg cells in patients with IBD and the high dependency of these cells on IL-2 for differentiation and survival [16–18, 88].

RA is another important factor regulating intestinal Treg cells. RA has a pervasive effect on Th cell subsets, but the impact of RA is greater in TGF-β-dependent cells such as iTreg, Th17, and Th9 cells compared with Th0, Th1, and Th2 cells [89]. Among TGF-β-dependent cells, RA has been shown to suppress trans-differentiation to other Th cell lineages by inhibiting expression of key transcription factors or cytokine receptors of these lineages. RA downregulates IL-6R, IL-23R, and Interferon regulatory factor 4 (IRF4) expression and induces Foxp3 expression in Th cells stimulated under conditions favorable for Th17 cell differentiation in the presence of TGF-β and IL-6 or IL-21 [37]. In addition, RA represses IL-9 expression but increases Foxp3 expression in a dose-dependent manner. RARα, the receptor for RA, directly binds to the *Il9* promoter region and directly represses IL-9 expression, while RARα antagonists significantly increase IL-9 production [89]. Consistent with its role in enforcing Foxp3 expression and inhibiting differentiation of other Th cell lineages, beneficial effects of RA have been reported in multiple IBD models, such as trinitrobenzene sulfonic acid (TNBS)-induced colitis and dextran sodium sulfate (DSS)-induced colitis [90, 91]. Moreover, RA has been shown to induce differentiation of a specific subset of intestinal $CD161^+$ Treg cells that control the wound healing program in patients with Crohn's disease [92]. Although clinical applications exploiting the beneficial effects of RA and/or TGF-β are currently limited due to potentially increased risks of colitis or other adverse events [93, 94], adjusting the dose or innovative drug delivery systems might enable future exploitation of the immune regulatory function of RA for treating IBD patients.

miRNAs/long non-coding RNAs in Treg cells

Treg cells exhibit a distinct miRNA profile compared with conventional T cells, and individual miRNA or miRNA clusters contribute to Treg cell biology through targeting a distinct set of genes. Treg cells have a degree of plasticity, and miRNAs integrate the external signals that drive this phenomenon [95].

The miRNA, miR-10a, is induced by TGF-β and RA and contributes to Treg stability by targeting the transcriptional repressor Bcl-6, resulting in high and sustained Foxp3 expression [96]. In addition, miR-95 is also highly expressed in human Treg cells ($CD4^+CD25^+CD127^{low}$ cells) purified from peripheral blood and enhances FOXP3 mRNA and protein expression [97]. By contrast, miRNAs can also function as negative regulators of Foxp3 expression. Overexpression of miR-15a-16 [98] in Treg cells resulted in decreased Foxp3 expression. Additionally, miR-24, miR-145, and miR-210 are markedly under-expressed in human Treg cells, and function to downregulate Foxp3 mRNA and protein expression.

With regard to Treg cell stability, miR-21 regulates Foxp3 expression and correlates with imbalances of Th17 and Treg cells by modulating STAT3 and STAT5 expression, respectively, in patients with rheumatoid arthritis [99]. Another miRNA, miR-146a, targets STAT1 expression and minimizes Th1 cell-mediated pathology including conjunctivitis, blepharitis, and dermatitis, by blocking the IFN-γ/SOCS1/STAT1 axis [44].

In addition, miR-7, miR-18a, miR-34a, and miR-155 have been shown to contribute to stabilization of Treg suppressor function [97, 100, 101]. The activities of these miRNAs are mediated by Treg expression of SATB1, a genome organizer that regulates chromatin structure and gene expression [102]. Treg cell-specific super-enhancers, which are defined as genomic regions with dense clustering of highly active enhancers, begin to be established prior to expression of Foxp3 during thymic Treg cell development in a SATB-1 dependent manner. SATB1 deficiency impairs Treg super-enhancer activation, expression of Treg cell signature genes, and causes severe autoimmunity [103]. These miRNAs bind to the *Satb1* 3′ untranslated region and indirectly suppress SATB1. Thus, increased expression of these miRNAs may be particularly helpful in inflammatory diseases since they promote Foxp3 expression and function. In terms of gut phenotypes, excessive expression of miR-17 [104] and miR-27 [105] exacerbates colitis induced by effector T cell transfer and results in lower Treg cell accumulation in the colonic lamina propria.

In terms of long non-coding RNAs (lncRNAs), *Flicr* is a negative regulator that tunes Foxp3 expression, resulting in a subset of Tregs expressing lower levels of Foxp3. *Flicr* does not affect DNA methylation, but modifies chromatin accessibility in the CNS3/Accessible region 5(AR5) region of *Foxp3*. *Flicr* markedly promotes autoimmune diabetes and restrains antiviral responses [106]. Another lncRNA called *Flatr* is produced prior to Foxp3 expression and is highly conserved and enriched in activated Tregs. *Flatr*-deficient naïve T cells in spleen and lymph nodes showed lower Treg induction in a T cell transfer model, although *Flatr*-deficient Tregs maintained their suppressive function [107].

Th1 cells

Th1 cells, defined by the expression of signature Th1 genes including the cytokine *Ifng* and the cell-surface receptor *Cxcr3*, require T-bet for differentiation [108–110]. Th1 cells and the cytokines they produce are crucial for driving IBD, and their potential to induce potent inflammation has been demonstrated by adoptive transfer in murine models [111]. One of the major cytokines produced by Th1 cells is IFN-γ. When wild-type mice are treated with DSS, IFN-γ is abundantly produced, coincident with prominent weight loss and high mortality; these responses are suppressed in $Ifng^{-/-}$ mice [112]. CD, a prototypical IBD, was originally thought to be primarily associated with Th1 immune responses [113], while UC, another IBD, was thought to represent a Th2-driven disease. However, later studies revealed considerably greater complexity. The findings that T-$bet^{-/-}$ mice developed severe DSS-induced colitis and that T-$bet^{-/-}$ × $RAG2^{-/-}$ (TRUC) mice developed a highly penetrant and severe colitis [114, 115] both contradicted the original hypothesis. These findings were explained through the bilateral nature of T-bet: that is, T-bet regulates both the mucosal immune system and barrier functions [115]. Another contradictory finding was that both IL-13 and IFN-γ, but not IL-4, were detected at elevated levels in the mucosa of patients with UC [116]. Based on the potential association of Th1 cells and/or their signature cytokine, IFN-γ, with the pathogenesis of IBD, several clinical trials targeting IFN-γ have been performed. For instance, fontolizumab, an antibody blocking the Th1 signature cytokine IFN-γ, was administered to CD patients, but further research was abandoned due to the lack of a clear dose-dependent clinical benefit [117, 118]. However, IFN-γ blockade with fontolizumab significantly decreased C-reactive protein levels, suggesting that functional blockade of IFN-γ might be biologically beneficial in IBD, especially for patients with CD. This might explain the positive results of clinical trials of ustekinumab, one of whose targets is IL-12, a critical cytokine for Th1 differentiation [119].

T-bet, encoded by *Tbx21* [120], is defined by a central 180-residue DNA-binding domain called the T-box [121]. T-bet functions with Runx3 and Ets family members to promote IFN-γ production. Therefore, the role of T-bet as an activator has long focused onTh1 cells. However, similar numbers of genes are activated and repressed by T-bet in Th cells upon TCR stimulation [122]. Indeed, T-bet inhibits the functions of GATA3 and RORγt and antagonizes Th2 and Th17 cell differentiation [123]. Beyond its inhibitory roles in restricting differentiation toward other Th cell lineages, T-bet also represses aberrant type I IFN circuitry in IFN-γ-rich environments. In the absence of T-bet, Th cells sense IFN-γ as type I IFN and express IFN-inducible genes [122]. It remains to be elucidated how the dual roles of T-bet as an activator or a repressor are governed. Presumably, this occurs via

collaborative transcriptional partners, chromatin and histone modifications, and 3D-chromatin conformational changes.

The classical epigenetic modification associated with gene expression is DNA methylation. The mammalian DNA methylation process is comprised of two components. The first components are the DNMTs, which are concerned with DNA methylation patterns, and the second are the methyl-CpG binding proteins, which are involved in reading methylation signatures. DNA methylation of CpG dinucleotides is a major epigenetic mechanism to achieve transcriptional silencing of specific genes during developmental processes. Usually, DNA methylation leads chromatin to become condensed and inaccessible. By contrast, demethylation of CpG motifs leads to a relaxation of chromatin and increased accessibility of target sequences for binding by specific transcription factors.

DNMTs are composed of several subsets. DNMT1 is thought to be required to maintain DNA methylation at the *IFNG* locus in undifferentiated $CD4^+$ T cells [124]. By contrast, DNMT3a catalyzes DNA methylation of the *IFNG* promoter in response to Th2 and Th17 differentiation signals to sustain *IFNG* silencing. This silencing effect continues during subsequent Th1 differentiation signals and might control the balance among lineages [125]. Gonsky et al. reported that IBD patients requiring surgery had reduced *IFNG* methylation compared with non-surgical patients, and that decreased *IFNG* methylation correlated with enhanced IFN-γ secretion in UC [126].

Histone modification also regulates gene expression. Both active euchromatin and silenced heterochromatin are modulated by specific histone modifications. For example, histone 3 lysine 4 tri-methylation (H3K4me3) is associated with accessible promoters whereas H3K36me3 is associated with actively transcribed coding regions. Enhancers are marked by H3K4me1 and H3K4me2. Among these enhancer markers, H3 lysine 27 acetylation (H3K27Ac) indicates the existence of active enhancers. By contrast, inactive genes are characterized by the presence of H3K27me3 or H3K9me3. These enhancer marks in Th cells are formed in a lineage-specific manner, and lineage-specific global enhancer structure contributes to unique patterns of gene expression [127]. Like Th cells, each subpopulation of innate lymphoid cells, classified into subpopulations similarly to Th cell subsets, has unique enhancer patterns [127–129]. The uniqueness of enhancer signatures provides important information for better understanding of the underlying mechanisms contributing to each Th cell lineage.

H3K27 trimethylation is mainly mediated by Polycomb-group proteins (PcGs), which consist of two major repressive complexes: Polycomb repressive complex 1 (PRC1) and PRC2 [130, 131]. There are two types of PRC2 complexes. Both contain an invariant core of five proteins (E(z), Esc, Su(z)12, Caf1 and Jing) but differ in the presence of alternative subunits (Jarid2 or Pcl) [132]. Ezh2, a component of the PRC2, is responsible for the methylation activity of PRC2. In Th1 cells, Ezh2 works in this manner by directly binding to *Tbx21* and is an essential suppressor of Th1 responses through roles in differentiation and stabilization of phenotype. EZH2 deletion was associated with upregulation of IFN-γ and IL-10 under Th0 conditions, and with enhanced induction of IFN-γ under Th1 conditions [133]. Another study showed that EZH2-deficient Th0 cells produced more IFN-γ during stimulation in the presence of IL-12, inducing Th1 polarization [134]. Moreover, EZH2 depletion caused a substantial reduction in H3K27me3 levels in a murine model of DSS-induced colitis [134, 135]. Apart from IBD, it was reported that GSK126, a highly selective inhibitor of EZH2 methyltransferase activity, effectively inhibited the proliferation of EZH2-mutant DLBCL cell lines [136]. In primary colon cancer cells, GSK126 led to higher levels of IFN-γ-induced *CXCL10* expression [137], which was consistent with the results of mouse experiments. Currently, treatment with an Ezh2 inhibitor is being attempted in CD patients, though these results are not yet published.

Recently, the H3K27 demethylase Jmjd3 (also known as KDM6B) was found to catalyze demethylation of H3K27me2/3 in vitro [138, 139]. Jmjd3 is induced by vitamin D and pro-inflammatory stimuli in macrophages. Although Jmjd3 has been shown to interact with the Th1 master regulator, T-bet [140, 141], its in vivo function in T cell differentiation remains unknown. Recently, a study of T cell-specific Jmjd3-deficient mice suggested that Jmjd3 deletion inhibited Th1 and Treg differentiation and promoted Th2 and Th17 differentiation [142, 143]. It has been suggested that Jmjd3 deficiency suppresses the plastic conversion of Th2, Th17, or Treg cells into Th1 cells and that adoptive transfer of *Jmjd3*-deficient T cells limits colitis in a mouse model of disease [142]. In another study, however, Jmjd3 deletion did not alter the ability of Th0 cells to differentiate into Th1 cells. [143]

miRNAs/long non-coding RNAs in Th1 cells

Only 1–2% of the genome has protein-coding potential, whereas 85% of the genome is transcribed [144]. Transcribed RNAs are divided into two groups: lncRNAs and small RNAs. LncRNAs, which are mainly expressed from CNSs, are major regulators of chromatin remodeling, transcription, and posttranscriptional regulation of gene expression in diverse biological contexts [145], including the immune system [146]. Of small RNAs, miRNAs are implicated in the differentiation and functions of many cell types. The first discovery of miRNAs was in 1993 [147, 148]. In 2008, changes in miRNAs associated with human IBD were described [149] and their function in IBD through regulation of the immune system was examined.

Nest, also known as *Tmvpeg1* or *IFNG-As1*, is a lncRNA gene located nearby both *Ifng* and *IFNG* that seems to be involved in inflammation. *Nest* is expressed in immune cells such as CD8 and CD4 T cells [150, 151]. Nest RNA was found to bind WDR5, a component of the histone H3 lysine 4 methytransferase complex, and to regulate H3 methylation at the *Ifng* locus. In this manner, Nest alters expression of IFN-γ [152]. Moreover, expression of Nest was suggested to be associated with severity of UC [153]. Since treatments targeting lncRNAs are already under investigation in other fields, including cancer [154], it is also expected that lncRNAs could be new targets for treating IBD.

Many miRNAs also have additional effects on gene expression. MiR-155 promotes Th1 differentiation by targeting IFN-γ receptor α chain [155]. Expression of miR-155 is induced by inflammatory cytokines and Toll-like receptor ligands, and recent studies have demonstrated that miR-155 is upregulated in both UC and CD patients [156, 157]. The miR-17-92 cluster promotes Th1 differentiation. The function of miR-19b is mediated through phosphatase and tensin homolog, while miR-17 targets transforming growth factor (TGF)-β receptor II and cAMP-responsive element-binding protein 1 [158]. Through direct targeting of T-box transcription factor, miR-29 regulates Th cell differentiation by T-bet and eomesodermin to suppress IFN-γ production [159]. Finally, miR-146a may inhibit Th1 differentiation by targeting protein kinase Cε [160].

Th2 cells

Th2 cells can produce various cytokines such as IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. GATA3, a LDTF of Th2 cells, is stimulated by IL-4. Stimulated GATA3 promotes differentiation of Th2 cells in two ways: by suppressing expression of the IL-12R β2 chain, which is necessary for differentiation of Th1 cells, and by applying positive feedback to its own expression [161, 162]. Cytokines secreted by Th2 are thought to be closely involved in allergic reactions including inflammatory reactions.

IL-13, one of the main Th2 cytokines, is produced by various cells including basophils, eosinophils, mast cells, NKT cells, and Th2 cells [163]. NKT cells induce Th2 cells, and these cells are thought to be coordinated to produce pathogenicity against epithelial barriers which may relate to the development of UC [164]. A study of IL-13 deficient mice showed impaired Th2 differentiation and a protective effect against oxazolone-induced colitis [165]. In addition, expression of *IL-13* was elevated in biopsy specimens from patients with UC compared with healthy subjects [166]. Thus, IL-13 is thought to play a key role as an effector cytokine in UC. The efficacy of the humanized anti-IL-13 monoclonal antibodies, tralokinumab, and anrukinzumab, was assessed against UC; both failed to demonstrate significant therapeutic effects [167, 168]. Therefore, a direct relation between IBD and Th2 cells or their signature cytokines is still controversial, and their role as therapeutic targets is especially uncertain.

IL-10 is another Th2 cytokine that is considered to maintain gut homeostasis through its anti-inflammatory properties [169]. IL-10 knockout mice develop spontaneous colitis, and the characteristics of this model resemble those of IBD patients in terms of histology and pathophysiology [170]. In the DSS-induced colitis model, IL-10 suppresses secretion of the inflammatory cytokines, IL-1β and TNFα [171]. Administration of IL-10 significantly and consistently improves DSS- [171] and TNBS-induced colitis [172]. Most importantly, IL-10 signaling is associated with the development of early onset IBD [173]. These studies strongly suggest that supplementation with IL-10 may represent a reasonable therapeutic strategy to treat IBD. After the safety and tolerability of IL-10 therapy was confirmed [174], some studies have reported improvements in clinical disease activity index and endoscopic findings following IL-10 therapy [175], while other reports showed no significant improvement [176]. Despite the negative results of clinical trials, enforcement of IL-10 expression is still a promising strategy to treat IBD. Recent advances in microbiology revealed that certain *Bacteroides*, *Clostridium*, *Lactobacillus*, and *Faecalibacterium* species induced production IL-10 from intestinal immune cells [177–181] [182, 183] (Fig. 4). Since an early clinical trial showed the safety of genetically engineered bacteria encoding mature human IL-10 [184], this is a promising therapeutic approach to alter the microbiome and deliver IL-10 to the mucosal immune system through the intestinal lumen.

Genes encoding the Th2 cytokine IL-4, IL-5, and IL-13 are closely interspersed in a Th2 cytokine locus, a 125-kb region on human chromosome 5 and mouse chromosome 11 [185] (Fig.5). Th2 cytokine genes are regulated by a locus control region (LCR) termed the RAD50 gene. The *RAD50* locus is present between IL-5 and IL-13 and consists of four hypersensitive sites (HSs): RHS 4, RHS 5, RHS 6, and RHS 7 [186]. Between the IL-4 and IL-13 genes lies CNS1 containing HSS1 and HSS2, both of which are unique to Th2 cells. CATA-1 is induced by GATA3, resulting in chromatin remodeling and increased activity as an enhancer [187]. CNS-1 is thought to be a regulator of Th2 cytokine genes, since deletion of CNS1 led to reduction of IL-4, IL-5, and IL-13 [188]. By contrast, deletion of CNS2 leads to reduction of IL-4 expression in T follicular helper cells but not in Th2 cells, suggesting the specificity of enhancer usage in each Th cell subset [184, 189]. Like other T cell subsets, histone modification supports the control of Th2 cytokine activation. GATA3, the LDTF of Th2 cells, binds directly to HS II/IE and HSVa in the IL-4 gene locus, inducing acetylation of H3K4 and methylation of H3K27 and promoting the translation of IL-4 [190].

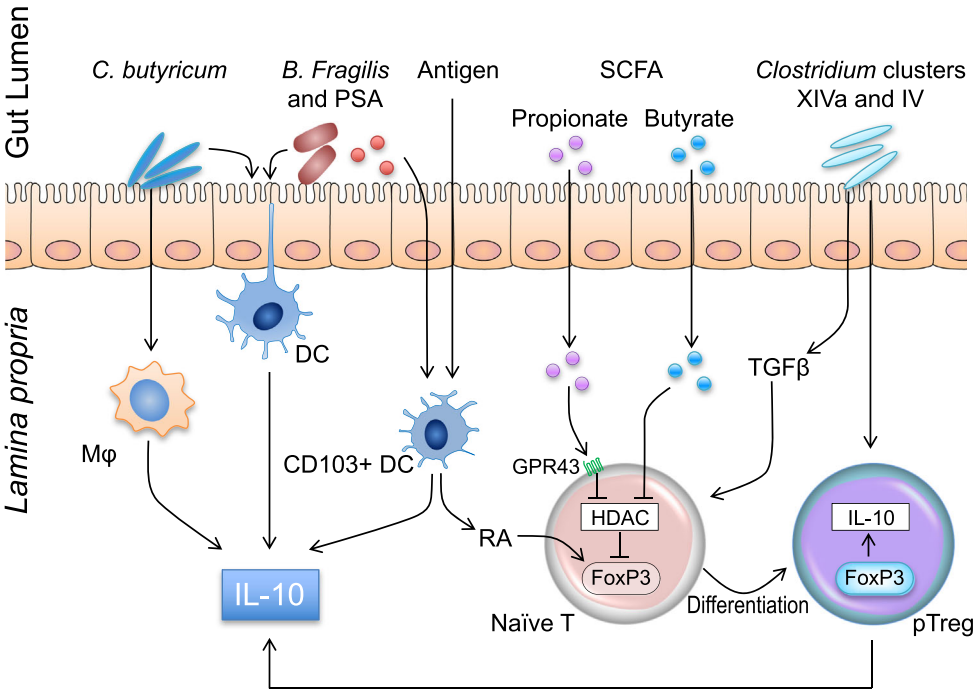

Fig. 4 Impact of the gut microbiota on Treg cells and IL-10 regulation. Luminal *Bacteroides fragilis* or *Clostridium* spp. in mice have been shown to induce intestinal Foxp3+ Treg cells and to enhance the expression of IL-10 in Treg cells, dendritic cells (DCs) and macrophages (Mφs)

Similarly, GATA3 and STAT6 cooperate to methylate and acetylate the conserved GATA3 response element in the IL-13 gene locus and induce IL-13 production [191]. In a mouse model of asthma involving histone deacetylase (HDAC) -1 deficient T cells, exacerbated disease activity was confirmed along with increased levels of IL-4 [192]. Chromatin remodeling and histone modification are clearly involved with Th2 culture and augmentation, but little is known about their association with IBD.

Th17 cells

Th17 cells have recently been classified as a new Th cell subset [1, 193] and are critically involved in host defense, inflammation, and autoimmunity [194]. Since the identification of Th17 cells, a growing number of studies have reported the importance of Th17 cells in experimental models of colitis [195]. Moreover, the inflamed gastrointestinal mucosa of patients with IBD shows massive infiltration of Th17 cells, and

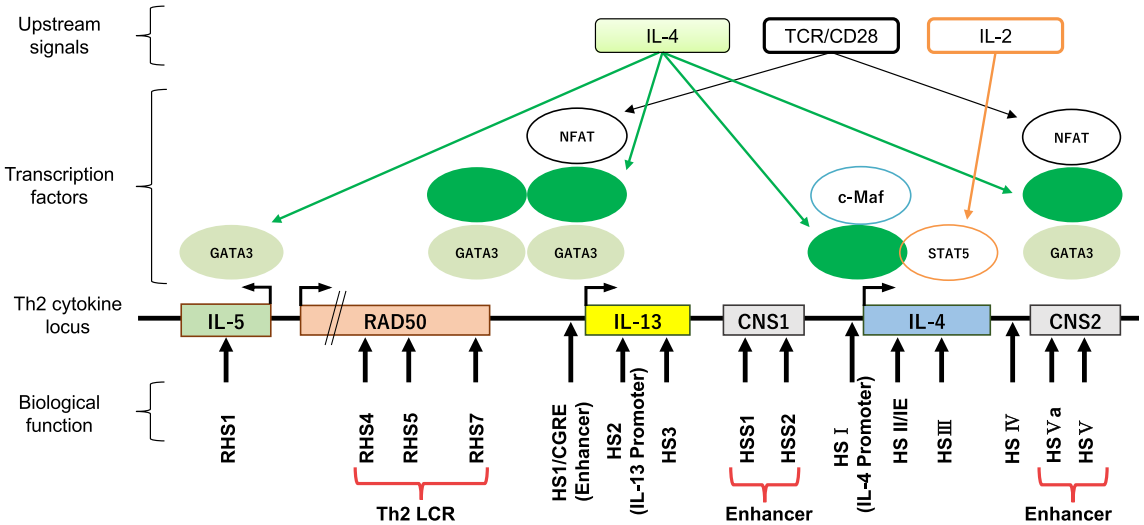

Fig. 5 Transcriptional regulation of the Th2 cytokine locus. The Th2 locus mainly consists of genes encoding IL-5, RAD50, IL-13, and IL-4. GATA3 binds to the promoter and/or enhancer regions of this locus, increasing the accessibility of each locus and inducing H3K4 trimethylation and H3K9 acetylation. GATA3 works in cooperation with various transcription factors. Corresponding pairs of upstream signals and transcription factors are shown in the same color. IL-4 signaling (green): GATA3 and STAT6; TCR/CD28 signaling (white with black frame): NFAT (nuclear factor of activated T cells); c-Maf (white with blue frame); IL-2 signaling (white with orange frame): STAT5

Th17-related cytokines are produced in excess in both CD and UC tissues [196–198]. However, it has been suggested that blocking IL-17, a major Th17 cytokine, in CD patients does more harm than good. Treatment with secukinumab, a human anti-IL17A monoclonal antibody, is ineffective and confers higher rates of adverse effects compared with placebo [199]. Thus, it is necessary explore the relation between Th17 cells and IBD more deeply.

Th17 cells produce the effector cytokines IL-17 and IL-22. Th17 cells are generated from naïve T cells by the combined action of IL-6 and TGF-β, with or without IL-1β [200], and differentiated Th17 cells are maintained by IL-23 [201]. Cytokines like IL-6 and IL-23 induce *Rorc*/RORγt, the master regulators of Th17 cells, via the STAT3 pathway. c-Maf has been recently reported as a key regulator of RORγt [202–205] and the action of c-Maf that induces RORγt is independent of STAT3 [206]. Other factors such as aryl hydrocarbon receptor (Ahr), Batf, Iκβζ, IRF-4, and Runx1 are reported to be involved in Th17 cell differentiation. Foxp3, Gfi-1, and Ets-1 are reported to inhibit Th17 cell differentiation. Tcf-1, another repressor of Th17 cells, directly binds and represses the *Il17* gene and negatively regulates IL-7R on Th17 cells [123].

Th17 cells have been considered pathogenic in autoimmune diseases [207]. However, the pathogenic or protective roles of Th17 cells or their signature cytokines, IL-17A and IL-17F, appear to be complex and context-dependent in intestinal immunity. When *Rag1*$^{-/-}$ mice were reconstituted with T cells lacking IL-17A, IL-17F, or IL-23, they developed colitis. However, colitis was not induced when RORγt$^{-/-}$ T cells were transferred to *RAG1*$^{-/-}$ mice, supporting the pathogenic role of Th17 cells in colitis [208]. Transferring CD45RB^{hi} CD25^{-}CD4^{+} T cells is known to induce colitis, and when purified CD45RB^{hi} CD25^{-}CD4^{+} T cells from *Il17a*$^{-/-}$ mice were transferred into *Rag1*$^{-/-}$ recipients, more severe colitis was observed compared with adoptive transfer of cells from wild-type mice [209]. This finding might be attributed to the fact that IL-17A regulates gut integrity [210] or competes with IFN-γ-producing Th1 cells [211, 212]. Inflammation is induced in the small intestine by administering an antibody specific for CD3, which is a T cell-specific surface marker. In this model, the concentrations of TGF-β and IL-6 increased in the small intestine, and massive infiltration of Th17 cells was observed. Importantly, these Th17 cells possessed more immunoregulatory features than Th17 cells observed during the development of experimental autoimmune encephalomyelitis (EAE) [213]. Intestinal Th17 cells and Treg cells both express CCR6, and since Th17 cells produce CCL20 (a ligand of CCR6), Th17 cells can promote their own migration [214]. CD4^{+}Foxp3^{-} IL-10 producing (Tr1) cells and Treg cells, which function to suppress enteritis, control Th17 cells in an IL-10 dependent manner [215]. IL-17A induces CCL20 production from Th17 cells in the small intestine [213, 216]. Following treatment with anti-CD3 antibody, CCL20 was increased in the small intestine, while no increase in Th17 cells was observed in *Ccr6*$^{-/-}$ or *Il6*$^{-/-}$ mice [213]. This indicates that the CCR6/CCL20 axis is important for migration of Th17 cells [213]. It has become clear that Th17 cells are a heterogeneous population that includes pathogenic and non-pathogenic signatures [217–219]. One of the key cytokines used to decipher pathogenic and non-pathogenic Th17 cells is IL-23. Exposure to IL-23 decreased the production of IL-10, an anti-inflammatory cytokine, and led to development of pathogenic Th17 cells [217, 218, 220]. Th17 cells are controlled by various cytokines, chemokines, and surrounding cells, and can have both pathogenic and protective effects against enteritis. Therefore, further studies are required to identify the colitogenic Th17 cell population that must be targeted in IBD as well as to understand such additional factors as dissecting Th17 cells into pathogenic and non-pathogenic populations, upstream stimulations, signal transduction mechanisms, and epigenetic modifications.

Histone modification impacts the expression of LDTF and effector cytokines in Th17 cells. TGF-β inhibited H3K9 trimethylation of the Runx1- and RORγt-binding sites on *Il17* as well as *Rorc* in Th1 cells, and induced conversion of Th1 cells into Th17 cells [221]. The mechanisms through which the H3K27 demethylase *Jmjd3* affects differentiation are controversial. Deletion of *Jmjd3* promotes differentiation into Th17 cells [142]. Conversely, another study showed that deletion of *Jmjd3* in Th0 cells impaired Th17 cell differentiation [143].

Since HDAC inhibitors repress polarization of Th17 cells, histone acetylation is required for the differentiation or maintenance of Th17 cells [222]. MOF is one of the histone acethyltransferases (HATs) that specifically acetylates H4K16, and leads to active target gene transcription [223]. H4ac has already been reported to be responsible for driving inflammation in experimental colitis [224]. Yang et al. found that deficiency of MOF causes downregulation of Th17-associated genes, including *Il17a, Il22, RORγt, RORα, Stat3, TGF-β1*, and *Il6*, in colon tissues in a DSS-induced colitis model [225].

By contrast, HDAC inhibits IL-6 production and thus suppress Th17 cell differentiation. It has been recently revealed that SKI interacts with HDAC and SMAD4 and induces deacetylation of the *Rorc* locus. In the presence of SKI, HDAC inhibits H3K9 acetylation of the *Rorc* locus, resulting in impaired *Rorc* expression and Th17 cell differentiation [226]. HDACs have been categorized into several subsets based on structure. Inhibitors targeting HDACs have already been produced: pan-HDAC inhibitors as the first-generation drugs and selective HDAC inhibitors as the second generation [227]. Salkowska et al. showed that RORγt expression was downregulated in naïve Th cells cultured with two HDAC inhibitors, butyrate and apicidin [228]. Another study showed that treatment with an HDAC inhibitor resulted in a 90% decrease in IL-6 in lamina propria mononuclear cells stimulated with concanavalin A, and profoundly suppressed Th17

cell differentiation from naïve $CD4^+$ T cells [229]. Additionally, HDAC inhibitors have protective effect in both murine models of DSS- and TNBS-induced colitis [230]. HDAC inhibitors are expected to be effective, especially in the field of cancer, and many studies have been conducted using HDAC inhibitors alone or in combination with other drugs [231]. However, few clinical studies are currently ongoing in the IBD field and there is much still to be learned regarding the clinical effects and safety of HDAC inhibitors.

miRNAs/long non-coding RNAs in Th17 cells

As in other $CD4^+$ T cell lineages, non-coding RNA also serve as important factors in regulation of Th17 cells. Although little is known regarding the role of lncRNAs in Th17 cell development, many miRNAs have been studied. MiR-22 promotesTh17 cell differentiation via HDAC4, and its levels were increased in the peripheral blood and intestinal mucosa of IBD patients [232]. The miR-17-92 cluster (miR-17, miR-18a, miR-19a, miR-20a, miR-19b, and miR-92a) also coordinate to drive Th17 cell differentiation [98, 233]. Increased expression of miR-155 in IBD patients has been reported previously [234, 235]. MiR-155 induces inflammation by inhibiting Ets-1, a negative regulator of Th17 cells [236]. DSS-induced-colitis in miR-155-deficient mice showed decreased numbers of Th1 cells, Th17 cells, and dendritic cells compared with WT mice; these frequencies correlated with clinical scores and severity of colitis [237]. Therefore, miR-155 might have a pathogenic role in UC patients. The miR-183-96-182 cluster (miR-183C) was highly expressed in Th17 cells. MiR326 also inhibited Ets-1 and promoted Th17 cell differentiation [238]. MiR-183C directly repressed expression of the transcription factor Forkhead box 0 (Foxo) 1, negatively regulating the pathogenicity of Th17 cells by inhibiting expression of the cytokine receptor, IL-1R1 [239].

In contrast with the above, miR29 induced by NOD2 downregulated secretion of IL-23, and thus DSS-induced colitis was worse in miR29-deficient mice [240]. MiR-124 is thought to regulate expression of STAT3 and to have protective functions against inflammation and UC pathogenesis. MiR-210 also appears to be protective because it is induced by HIF-1α, and negatively regulates *HIF-1α* expression [241]. As noted above, miRNAs have both protective and pathogenic roles. Although their role is not fully understood, they represent novel therapeutic targets.

Conclusion

The intestine is continuously exposed to food and the microbiome. These external stimulations shape proper development and maintenance of the mucosal immune system to maintain gut homeostasis. Recent advances in next-generation sequencing techniques have significantly increased our understanding of regulation of intestinal immunity, as well as the relative frequencies of immune cells in the gut compared with other organs. Indeed, global chromatin accessibility represents cellular lineages or states more stably than mRNA expression profiles [242]. It is necessary to probe how chromatin accessibility and transcription factor-binding impact cellular lineages and their gene transcription during steady state and during inflammatory conditions in the gut. Th cells are critical contributors to the development of IBD and have been well-studied in terms of epigenetic regulation, especially for Treg cells. Although considerable progress has been made to elucidate the epigenetic mechanisms that regulate proliferation, differentiation, and maintenance of Treg cells and other effector T cells, it still remains unclear how the tissue-specific properties of Th cell lineages are formed through stimulation in the intestinal microenvironment. Which bacteria or metabolites epigenetically specify gut uniqueness in Th cells? How do these signals alter epigenetic modifications of Th cells? Do these signals target Th cells directly or indirectly? What factors determine the global or site-specific alteration of epigenetic marks? What is the degree of heterogeneity of tissue-specific Th cells? A key to tackling these challenging questions is multidisciplinary analyses comprising studies of computational strategies, chromatin accessibility, transcription factor-binding sites, DNA methylation, metabolome, microbiome, and single cell omics. It will also likely be necessary to consider upstream signal transduction pathways and downstream gene expression. The combination of these techniques will allow clarification of the critical pathways that should be targeted to treat chronic intestinal inflammation.

Funding This study was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (A) 15H02534 and Grant-in-Aid for Young Scientists (B) 17K15966; Advanced Research and Development Programs for Medical Innovation (AMED-CREST; 16gm1010003h0001 and 18gm1210001h0001); the Takeda Science Foundation; the Kanae Foundation for The Promotion of Medical Science; and Keio University Medical Fund.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ivanov II, McKenzie BS, Zhou L, Tadokoro CE, Lepelley A, Lafaille JJ, Cua DJ, Littman DR (2006) The orphan nuclear receptor RORgammat directs the differentiation program of

proinflammatory IL-17+ T helper cells. Cell 126:1121–1133. https://doi.org/10.1016/j.cell.2006.07.035
2. Yang XO, Pappu BP, Nurieva R, Akimzhanov A, Kang HS, Chung Y, Ma L, Shah B, Panopoulos AD, Schluns KS, Watowich SS, Tian Q, Jetten AM, Dong C (2008) T helper 17 lineage differentiation is programmed by orphan nuclear receptors ROR alpha and ROR gamma. Immunity 28:29–39. https://doi.org/10.1016/j.immuni.2007.11.016
3. Zheng Y, Rudensky AY (2007) Foxp3 in control of the regulatory T cell lineage. Nat Immunol 8:457–462. https://doi.org/10.1038/ni1455
4. Josefowicz SZ, Lu LF, Rudensky AY (2012) Regulatory T cells: mechanisms of differentiation and function. Annu Rev Immunol 30:531–564. https://doi.org/10.1146/annurev.immunol.25.022106.141623
5. Sakaguchi S, Miyara M, Costantino CM, Hafler DA (2010) FOXP3+ regulatory T cells in the human immune system. Nat Rev Immunol 10:490–500. https://doi.org/10.1038/nri2785
6. Zou W, Restifo NP (2010) T(H)17 cells in tumour immunity and immunotherapy. Nat Rev Immunol 10:248–256. https://doi.org/10.1038/nri2742
7. Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol 28:445–489. https://doi.org/10.1146/annurev-immunol-030409-101212
8. O'Shea JJ, Lahesmaa R, Vahedi G, Laurence A, Kanno Y (2011) Genomic views of STAT function in CD4+ T helper cell differentiation. Nat Rev Immunol 11:239–250. https://doi.org/10.1038/nri2958
9. Bonelli M, Shih HY, Hirahara K, Singelton K, Laurence A, Poholek A, Hand T, Mikami Y, Vahedi G, Kanno Y, O'Shea JJ (2014) Helper T cell plasticity: impact of extrinsic and intrinsic signals on transcriptomes and epigenomes. Curr Top Microbiol Immunol 381:279–326. https://doi.org/10.1007/82_2014_371
10. Allan RS, Zueva E, Cammas F, Schreiber HA, Masson V, Belz GT, Roche D, Maison C, Quivy JP, Almouzni G, Amigorena S (2012) An epigenetic silencing pathway controlling T helper 2 cell lineage commitment. Nature 487:249–253. https://doi.org/10.1038/nature11173
11. Rodriguez RM, Lopez-Larrea C, Suarez-Alvarez B (2015) Epigenetic dynamics during CD4(+) T cells lineage commitment. Int J Biochem Cell Biol 67:75–85. https://doi.org/10.1016/j.biocel.2015.04.020
12. Kroesen BJ, Teteloshvili N, Smigielska-Czepiel K, Brouwer E, Boots AM, van den Berg A, Kluiver J (2015) Immuno-miRs: critical regulators of T-cell development, function and ageing. Immunology 144:1–10. https://doi.org/10.1111/imm.12367
13. Kaser A, Zeissig S, Blumberg RS (2010) Inflammatory bowel disease. Annu Rev Immunol 28:573–621. https://doi.org/10.1146/annurev-immunol-030409-101225
14. Littman DR, Rudensky AY (2010) Th17 and regulatory T cells in mediating and restraining inflammation. Cell 140:845–858. https://doi.org/10.1016/j.cell.2010.02.021
15. Honda K, Littman DR (2016) The microbiota in adaptive immune homeostasis and disease. Nature 535:75–84. https://doi.org/10.1038/nature18848
16. Maul J, Loddenkemper C, Mundt P, Berg E, Giese T, Stallmach A, Zeitz M, Duchmann R (2005) Peripheral and intestinal regulatory CD4+ CD25(high) T cells in inflammatory bowel disease. Gastroenterology 128:1868–1878
17. Saruta M, Yu QT, Fleshner PR, Mantel PY, Schmidt-Weber CB, Banham AH, Papadakis KA (2007) Characterization of FOXP3+ CD4+ regulatory T cells in Crohn's disease. Clin Immunol 125:281–290. https://doi.org/10.1016/j.clim.2007.08.003
18. Makita S, Kanai T, Oshima S, Uraushihara K, Totsuka T, Sawada T, Nakamura T, Koganei K, Fukushima T, Watanabe M (2004) CD4+CD25bright T cells in human intestinal lamina propria as regulatory cells. J Immunol 173:3119–3130
19. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 27:20–21. https://doi.org/10.1038/83713
20. Kitagawa Y, Ohkura N, Sakaguchi S (2015) Epigenetic control of thymic Treg-cell development. Eur J Immunol 45:11–16. https://doi.org/10.1002/eji.201444577
21. Ohkura N, Kitagawa Y, Sakaguchi S (2013) Development and maintenance of regulatory T cells. Immunity 38:414–423. https://doi.org/10.1016/j.immuni.2013.03.002
22. Ohkura N, Hamaguchi M, Morikawa H, Sugimura K, Tanaka A, Ito Y, Osaki M, Tanaka Y, Yamashita R, Nakano N, Huehn J, Fehling HJ, Sparwasser T, Nakai K, Sakaguchi S (2012) T cell receptor stimulation-induced epigenetic changes and Foxp3 expression are independent and complementary events required for Treg cell development. Immunity 37:785–799. https://doi.org/10.1016/j.immuni.2012.09.010
23. Zheng Y, Josefowicz S, Chaudhry A, Peng XP, Forbush K, Rudensky AY (2010) Role of conserved non-coding DNA elements in the Foxp3 gene in regulatory T-cell fate. Nature 463:808–812. https://doi.org/10.1038/nature08750
24. Huehn J, Beyer M (2015) Epigenetic and transcriptional control of Foxp3+ regulatory T cells. Semin Immunol 27:10–18. https://doi.org/10.1016/j.smim.2015.02.002
25. Feng Y, Arvey A, Chinen T, van der Veeken J, Gasteiger G, Rudensky AY (2014) Control of the inheritance of regulatory T cell identity by a cis element in the Foxp3 locus. Cell 158:749–763. https://doi.org/10.1016/j.cell.2014.07.031
26. Li X, Liang Y, LeBlanc M, Benner C, Zheng Y (2014) Function of a Foxp3 cis-element in protecting regulatory T cell identity. Cell 158:734–748. https://doi.org/10.1016/j.cell.2014.07.030
27. Dominguez-Villar M, Hafler DA (2018) Regulatory T cells in autoimmune disease. Nat Immunol. https://doi.org/10.1038/s41590-018-0120-4
28. Lu L, Barbi J, Pan F (2017) The regulation of immune tolerance by FOXP3. Nat Rev Immunol 17:703–717. https://doi.org/10.1038/nri.2017.75
29. Polansky JK, Kretschmer K, Freyer J, Floess S, Garbe A, Baron U, Olek S, Hamann A, von Boehmer H, Huehn J (2008) DNA methylation controls Foxp3 gene expression. Eur J Immunol 38:1654–1663. https://doi.org/10.1002/eji.200838105
30. Janson PC, Winerdal ME, Marits P, Thorn M, Ohlsson R, Winqvist O (2008) FOXP3 promoter demethylation reveals the committed Treg population in humans. PLoS One 3:e1612. https://doi.org/10.1371/journal.pone.0001612
31. Yue X, Trifari S, Aijo T, Tsagaratou A, Pastor WA, Zepeda-Martinez JA, Lio CW, Li X, Huang Y, Vijayanand P, Lahdesmaki H, Rao A (2016) Control of Foxp3 stability through modulation of TET activity. J Exp Med 213:377–397. https://doi.org/10.1084/jem.20151438
32. Someya K, Nakatsukasa H, Ito M, Kondo T, Tateda KI, Akanuma T, Koya I, Sanosaka T, Kohyama J, Tsukada YI, Takamura-Enya T, Yoshimura A (2017) Improvement of Foxp3 stability through CNS2 demethylation by TET enzyme induction and activation. Int Immunol 29:365–375. https://doi.org/10.1093/intimm/dxx049
33. Reif S, Klein I, Lubin F, Farbstein M, Hallak A, Gilat T (1997) Pre-illness dietary factors in inflammatory bowel disease. Gut 40:754–760
34. Wang L, Liu Y, Beier UH, Han R, Bhatti TR, Akimova T, Hancock WW (2013) Foxp3+ T-regulatory cells require DNA methyltransferase 1 expression to prevent development of lethal autoimmunity. Blood 121:3631–3639. https://doi.org/10.1182/blood-2012-08-451765

35. Weinberg SE, Singer BD, Steinert EM, Martinez CA, Mehta MM, Martinez-Reyes I, Gao P, Helmin KA, Abdala-Valencia H, Sena LA, Schumacker PT, Turka LA, Chandel NS (2019) Mitochondrial complex III is essential for suppressive function of regulatory T cells. Nature 565:495–499. https://doi.org/10.1038/s41586-018-0846-z
36. Battaglia M, Stabilini A, Migliavacca B, Horejs-Hoeck J, Kaupper T, Roncarolo MG (2006) Rapamycin promotes expansion of functional CD4+CD25+FOXP3+ regulatory T cells of both healthy subjects and type 1 diabetic patients. J Immunol 177:8338–8347
37. Xiao S, Jin H, Korn T, Liu SM, Oukka M, Lim B, Kuchroo VK (2008) Retinoic acid increases Foxp3+ regulatory T cells and inhibits development of Th17 cells by enhancing TGF-beta-driven Smad3 signaling and inhibiting IL-6 and IL-23 receptor expression. J Immunol 181:2277–2284
38. Mucida D, Park Y, Kim G, Turovskaya O, Scott I, Kronenberg M, Cheroutre H (2007) Reciprocal TH17 and regulatory T cell differentiation mediated by retinoic acid. Science 317:256–260. https://doi.org/10.1126/science.1145697
39. Hill JA, Hall JA, Sun CM, Cai Q, Ghyselinck N, Chambon P, Belkaid Y, Mathis D, Benoist C (2008) Retinoic acid enhances Foxp3 induction indirectly by relieving inhibition from CD4+ CD44hi Cells. Immunity 29:758–770. https://doi.org/10.1016/j.immuni.2008.09.018
40. Kanamori M, Nakatsukasa H, Ito M, Chikuma S, Yoshimura A (2018) Reprogramming of Th1 cells into regulatory T cells through rewiring of the metabolic status. Int Immunol 30:357–373. https://doi.org/10.1093/intimm/dxy043
41. Yoshimura A, Naka T, Kubo M (2007) SOCS proteins, cytokine signalling and immune regulation. Nat Rev Immunol 7:454–465. https://doi.org/10.1038/nri2093
42. Yoshimura A, Ito M, Chikuma S, Akanuma T, Nakatsukasa H (2018) Negative regulation of cytokine signaling in immunity. Cold Spring Harb Perspect Biol 10. https://doi.org/10.1101/cshperspect.a028571
43. Takahashi R, Nishimoto S, Muto G, Sekiya T, Tamiya T, Kimura A, Morita R, Asakawa M, Chinen T, Yoshimura A (2011) SOCS1 is essential for regulatory T cell functions by preventing loss of Foxp3 expression as well as IFN-{gamma} and IL-17A production. J Exp Med 208:2055–2067. https://doi.org/10.1084/jem.20110428
44. Lu LF, Boldin MP, Chaudhry A, Lin LL, Taganov KD, Hanada T, Yoshimura A, Baltimore D, Rudensky AY (2010) Function of miR-146a in controlling Treg cell-mediated regulation of Th1 responses. Cell 142:914–929. https://doi.org/10.1016/j.cell.2010.08.012
45. Takahashi R, Nakatsukasa H, Shiozawa S, Yoshimura A (2017) SOCS1 is a key molecule that prevents regulatory T cell plasticity under inflammatory conditions. J Immunol 199:149–158. https://doi.org/10.4049/jimmunol.1600441
46. Koch MA, Tucker-Heard G, Perdue NR, Killebrew JR, Urdahl KB, Campbell DJ (2009) The transcription factor T-bet controls regulatory T cell homeostasis and function during type 1 inflammation. Nat Immunol 10:595–602. https://doi.org/10.1038/ni.1731
47. Hall AO, Beiting DP, Tato C, John B, Oldenhove G, Lombana CG, Pritchard GH, Silver JS, Bouladoux N, Stumhofer JS, Harris TH, Grainger J, Wojno ED, Wagage S, Roos DS, Scott P, Turka LA, Cherry S, Reiner SL, Cua D, Belkaid Y, Elloso MM, Hunter CA (2012) The cytokines interleukin 27 and interferon-gamma promote distinct Treg cell populations required to limit infection-induced pathology. Immunity 37:511–523. https://doi.org/10.1016/j.immuni.2012.06.014
48. Levine AG, Mendoza A, Hemmers S, Moltedo B, Niec RE, Schizas M, Hoyos BE, Putintseva EV, Chaudhry A, Dikiy S, Fujisawa S, Chudakov DM, Treuting PM, Rudensky AY (2017) Stability and function of regulatory T cells expressing the transcription factor T-bet. Nature 546:421–425. https://doi.org/10.1038/nature22360
49. Wohlfert EA, Grainger JR, Bouladoux N, Konkel JE, Oldenhove G, Ribeiro CH, Hall JA, Yagi R, Naik S, Bhairavabhotla R, Paul WE, Bosselut R, Wei G, Zhao K, Oukka M, Zhu J, Belkaid Y (2011) GATA3 controls Foxp3(+) regulatory T cell fate during inflammation in mice. J Clin Invest 121:4503–4515. https://doi.org/10.1172/jci57456
50. Delacher M, Imbusch CD, Weichenhan D, Breiling A, Hotz-Wagenblatt A, Trager U, Hofer AC, Kagebein D, Wang Q, Frauhammer F, Mallm JP, Bauer K, Herrmann C, Lang PA, Brors B, Plass C, Feuerer M (2017) Corrigendum: genome-wide DNA-methylation landscape defines specialization of regulatory T cells in tissues. Nat Immunol 18:1361. https://doi.org/10.1038/ni1217-1361b
51. Schiering C, Krausgruber T, Chomka A, Frohlich A, Adelmann K, Wohlfert EA, Pott J, Griseri T, Bollrath J, Hegazy AN, Harrison OJ, Owens BMJ, Lohning M, Belkaid Y, Fallon PG, Powrie F (2014) The alarmin IL-33 promotes regulatory T-cell function in the intestine. Nature 513:564–568. https://doi.org/10.1038/nature13577
52. Cipolletta D, Feuerer M, Li A, Kamei N, Lee J, Shoelson SE, Benoist C, Mathis D (2012) PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature 486:549–553. https://doi.org/10.1038/nature11132
53. Burzyn D, Kuswanto W, Kolodin D, Shadrach JL, Cerletti M, Jang Y, Sefik E, Tan TG, Wagers AJ, Benoist C, Mathis D (2013) A special population of regulatory T cells potentiates muscle repair. Cell 155:1282–1295. https://doi.org/10.1016/j.cell.2013.10.054
54. Arpaia N, Green JA, Moltedo B, Arvey A, Hemmers S, Yuan S, Treuting PM, Rudensky AY (2015) A distinct function of regulatory T cells in tissue protection. Cell 162:1078–1089. https://doi.org/10.1016/j.cell.2015.08.021
55. Panduro M, Benoist C, Mathis D (2016) Tissue Tregs. Annu Rev Immunol 34:609–633. https://doi.org/10.1146/annurev-immunol-032712-095948
56. Ito M, Komai K, Mise-Omata S, Iizuka-Koga M, Noguchi Y, Kondo T, Sakai R, Matsuo K, Nakayama T, Yoshie O, Nakatsukasa H, Chikuma S, Shichita T, Yoshimura A (2019) Brain regulatory T cells suppress astrogliosis and potentiate neurological recovery. Nature. https://doi.org/10.1038/s41586-018-0824-5
57. Matta BM, Reichenbach DK, Zhang X, Mathews L, Koehn BH, Dwyer GK, Lott JM, Uhl FM, Pfeifer D, Feser CJ, Smith MJ, Liu Q, Zeiser R, Blazar BR, Turnquist HR (2016) Peri-alloHCT IL-33 administration expands recipient T-regulatory cells that protect mice against acute GVHD. Blood 128:427–439. https://doi.org/10.1182/blood-2015-12-684142
58. Pastorelli L, Garg RR, Hoang SB, Spina L, Mattioli B, Scarpa M, Fiocchi C, Vecchi M, Pizarro TT (2010) Epithelial-derived IL-33 and its receptor ST2 are dysregulated in ulcerative colitis and in experimental Th1/Th2 driven enteritis. Proc Natl Acad Sci U S A 107:8017–8022. https://doi.org/10.1073/pnas.0912678107
59. Verheijden KA, Akbari P, Willemsen LE, Kraneveld AD, Folkerts G, Garssen J, Fink-Gremmels J, Braber S (2015) Inflammation-induced expression of the alarmin interleukin 33 can be suppressed by galacto-oligosaccharides. Int Arch Allergy Immunol 167:127–136. https://doi.org/10.1159/000437327
60. Peine M, Marek RM, Lohning M (2016) IL-33 in T cell differentiation, function, and immune homeostasis. Trends Immunol 37:321–333. https://doi.org/10.1016/j.it.2016.03.007
61. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zurawski G, Moshrefi M, Qin J, Li X, Gorman DM, Bazan JF, Kastelein RA (2005) IL-33, an

interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 23:479–490. https://doi.org/10.1016/j.immuni.2005.09.015

62. Monteleone G, Trapasso F, Parrello T, Biancone L, Stella A, Iuliano R, Luzza F, Fusco A, Pallone F (1999) Bioactive IL-18 expression is up-regulated in Crohn's disease. J Immunol 163:143–147
63. Pizarro TT, Michie MH, Bentz M, Woraratanadharm J, Smith MF Jr, Foley E, Moskaluk CA, Bickston SJ, Cominelli F (1999) IL-18, a novel immunoregulatory cytokine, is up-regulated in Crohn's disease: expression and localization in intestinal mucosal cells. J Immunol 162:6829–6835
64. Kanai T, Watanabe M, Okazawa A, Sato T, Yamazaki M, Okamoto S, Ishii H, Totsuka T, Iiyama R, Okamoto R, Ikeda M, Kurimoto M, Takeda K, Akira S, Hibi T (2001) Macrophage-derived IL-18-mediated intestinal inflammation in the murine model of Crohn's disease. Gastroenterology 121:875–888
65. Ten Hove T, Corbaz A, Amitai H, Aloni S, Belzer I, Graber P, Drillenburg P, van Deventer SJ, Chvatchko Y, Te Velde AA (2001) Blockade of endogenous IL-18 ameliorates TNBS-induced colitis by decreasing local TNF-alpha production in mice. Gastroenterology 121:1372–1379
66. Nowarski R, Jackson R, Gagliani N, de Zoete MR, Palm NW, Bailis W, Low JS, Harman CC, Graham M, Elinav E, Flavell RA (2015) Epithelial IL-18 equilibrium controls barrier function in colitis. Cell 163:1444–1456. https://doi.org/10.1016/j.cell.2015.10.072
67. Dupaul-Chicoine J, Yeretssian G, Doiron K, Bergstrom KS, McIntire CR, LeBlanc PM, Meunier C, Turbide C, Gros P, Beauchemin N, Vallance BA, Saleh M (2010) Control of intestinal homeostasis, colitis, and colitis-associated colorectal cancer by the inflammatory caspases. Immunity 32:367–378. https://doi.org/10.1016/j.immuni.2010.02.012
68. Zaki MH, Boyd KL, Vogel P, Kastan MB, Lamkanfi M, Kanneganti TD (2010) The NLRP3 inflammasome protects against loss of epithelial integrity and mortality during experimental colitis. Immunity 32:379–391. https://doi.org/10.1016/j.immuni.2010.03.003
69. Harrison OJ, Srinivasan N, Pott J, Schiering C, Krausgruber T, Ilott NE, Maloy KJ (2015) Epithelial-derived IL-18 regulates Th17 cell differentiation and Foxp3(+) Treg cell function in the intestine. Mucosal Immunol 8:1226–1236. https://doi.org/10.1038/mi.2015.13
70. Xiao Y, Nagai Y, Deng G, Ohtani T, Zhu Z, Zhou Z, Zhang H, Ji MQ, Lough JW, Samanta A, Hancock WW, Greene MI (2014) Dynamic interactions between TIP60 and p300 regulate FOXP3 function through a structural switch defined by a single lysine on TIP60. Cell Rep 7:1471–1480. https://doi.org/10.1016/j.celrep.2014.04.021
71. Chen Z, Barbi J, Bu S, Yang HY, Li Z, Gao Y, Jinasena D, Fu J, Lin F, Chen C, Zhang J, Yu N, Li X, Shan Z, Nie J, Gao Z, Tian H, Li Y, Yao Z, Zheng Y, Park BV, Pan Z, Zhang J, Dang E, Li Z, Wang H, Luo W, Li L, Semenza GL, Zheng SG, Loser K, Tsun A, Greene MI, Pardoll DM, Pan F, Li B (2013) The ubiquitin ligase Stub1 negatively modulates regulatory T cell suppressive activity by promoting degradation of the transcription factor Foxp3. Immunity 39:272–285. https://doi.org/10.1016/j.immuni.2013.08.006
72. van Loosdregt J, Vercoulen Y, Guichelaar T, Gent YY, Beekman JM, van Beekum O, Brenkman AB, Hijnen DJ, Mutis T, Kalkhoven E, Prakken BJ, Coffer PJ (2010) Regulation of Treg functionality by acetylation-mediated Foxp3 protein stabilization. Blood 115:965–974. https://doi.org/10.1182/blood-2009-02-207118
73. Chen Y, Chen C, Zhang Z, Liu CC, Johnson ME, Espinoza CA, Edsall LE, Ren B, Zhou XJ, Grant SF, Wells AD, Chen L (2015) DNA binding by FOXP3 domain-swapped dimer suggests mechanisms of long-range chromosomal interactions. Nucleic Acids Res 43:1268–1282. https://doi.org/10.1093/nar/gku1373
74. Ruan Q, Kameswaran V, Tone Y, Li L, Liou HC, Greene MI, Tone M, Chen YH (2009) Development of Foxp3(+) regulatory t cells is driven by the c-Rel enhanceosome. Immunity 31:932–940. https://doi.org/10.1016/j.immuni.2009.10.006
75. Baine I, Basu S, Ames R, Sellers RS, Macian F (2013) Helios induces epigenetic silencing of IL2 gene expression in regulatory T cells. J Immunol 190:1008–1016. https://doi.org/10.4049/jimmunol.1200792
76. Malek TR, Yu A, Vincek V, Scibelli P, Kong L (2002) CD4 regulatory T cells prevent lethal autoimmunity in IL-2Rbeta-deficient mice. Implications for the nonredundant function of IL-2. Immunity 17:167–178
77. Papiernik M, de Moraes ML, Pontoux C, Vasseur F, Penit C (1998) Regulatory CD4 T cells: expression of IL-2R alpha chain, resistance to clonal deletion and IL-2 dependency. Int Immunol 10:371–378
78. Almeida AR, Legrand N, Papiernik M, Freitas AA (2002) Homeostasis of peripheral CD4+ T cells: IL-2R alpha and IL-2 shape a population of regulatory cells that controls CD4+ T cell numbers. J Immunol 169:4850–4860
79. Burchill MA, Yang J, Vogtenhuber C, Blazar BR, Farrar MA (2007) IL-2 receptor beta-dependent STAT5 activation is required for the development of Foxp3+ regulatory T cells. J Immunol 178:280–290
80. Van Assche G, Sandborn WJ, Feagan BG, Salzberg BA, Silvers D, Monroe PS, Pandak WM, Anderson FH, Valentine JF, Wild GE, Geenen DJ, Sprague R, Targan SR, Rutgeerts P, Vexler V, Young D, Shames RS (2006) Daclizumab, a humanised monoclonal antibody to the interleukin 2 receptor (CD25), for the treatment of moderately to severely active ulcerative colitis: a randomised, double blind, placebo controlled, dose ranging trial. Gut 55:1568–1574. https://doi.org/10.1136/gut.2005.089854
81. Sands BE, Sandborn WJ, Creed TJ, Dayan CM, Dhanda AD, Van Assche GA, Gregus M, Sood A, Choudhuri G, Stempien MJ, Levitt D, Probert CS (2012) Basiliximab does not increase efficacy of corticosteroids in patients with steroid-refractory ulcerative colitis. Gastroenterology 143:356-364.e351. https://doi.org/10.1053/j.gastro.2012.04.043
82. Huss DJ, Mehta DS, Sharma A, You X, Riester KA, Sheridan JP, Amaravadi LS, Elkins JS, Fontenot JD (2015) In vivo maintenance of human regulatory T cells during CD25 blockade. J Immunol 194:84–92. https://doi.org/10.4049/jimmunol.1402140
83. Villarino A, Laurence A, Robinson GW, Bonelli M, Dema B, Afzali B, Shih HY, Sun HW, Brooks SR, Hennighausen L, Kanno Y, O'Shea JJ (2016) Signal transducer and activator of transcription 5 (STAT5) paralog dose governs T cell effector and regulatory functions. Elife 5. https://doi.org/10.7554/eLife.08384
84. Sari NK, Setiati S, Taher A, Wiwie M, Djauzi S, Pandelaki J, Purba JS, Sadikin M (2017) The role of autosuggestion in geriatric patients' quality of life: a study on psycho-neuro-endocrine-immunology pathway. Soc Neurosci 12:551–559. https://doi.org/10.1080/17470919.2016.1196243
85. Liao W, Schones DE, Oh J, Cui Y, Cui K, Roh TY, Zhao K, Leonard WJ (2008) Priming for T helper type 2 differentiation by interleukin 2-mediated induction of interleukin 4 receptor alpha-chain expression. Nat Immunol 9:1288–1296. https://doi.org/10.1038/ni.1656
86. Roychoudhuri R, Hirahara K, Mousavi K, Clever D, Klebanoff CA, Bonelli M, Sciume G, Zare H, Vahedi G, Dema B, Yu Z, Liu H, Takahashi H, Rao M, Muranski P, Crompton JG, Punkosdy G, Bedognetti D, Wang E, Hoffmann V, Rivera J, Marincola FM, Nakamura A, Sartorelli V, Kanno Y, Gattinoni L, Muto A, Igarashi K, O'Shea JJ, Restifo NP (2013) BACH2 represses

effector programs to stabilize T(reg)-mediated immune homeostasis. Nature 498:506–510. https://doi.org/10.1038/nature12199

87. Afzali B, Gronholm J, Vandrovcova J, O'Brien C, Sun HW, Vanderleyden I, Davis FP, Khoder A, Zhang Y, Hegazy AN, Villarino AV, Palmer IW, Kaufman J, Watts NR, Kazemian M, Kamenyeva O, Keith J, Sayed A, Kasperaviciute D, Mueller M, Hughes JD, Fuss IJ, Sadiyah MF, Montgomery-Recht K, McElwee J, Restifo NP, Strober W, Linterman MA, Wingfield PT, Uhlig HH, Roychoudhuri R, Aitman TJ, Kelleher P, Lenardo MJ, O'Shea JJ, Cooper N, Laurence ADJ (2017) BACH2 immunodeficiency illustrates an association between super-enhancers and haploinsufficiency. Nat Immunol 18:813–823. https://doi.org/10.1038/ni.3753
88. Chinen T, Kannan AK, Levine AG, Fan X, Klein U, Zheng Y, Gasteiger G, Feng Y, Fontenot JD, Rudensky AY (2016) An essential role for the IL-2 receptor in Treg cell function. Nat Immunol 17:1322–1333. https://doi.org/10.1038/ni.3540
89. Schwartz DM, O'Shea JJ (2019) Retinoic acid receptor alpha represses a Th9 transcriptional and epigenomic program to reduce allergic pathology. Immunity 50(1):106–120.e10. https://doi.org/10.1016/j.immuni.2018.12.014
90. Bai A, Lu N, Zeng H, Li Z, Zhou X, Chen J, Liu P, Peng Z, Guo Y (2010) All-trans retinoic acid ameliorates trinitrobenzene sulfonic acid-induced colitis by shifting Th1 to Th2 profile. J Interf Cytokine Res 30:399–406. https://doi.org/10.1089/jir.2009.0028
91. Hong K, Zhang Y, Guo Y, Xie J, Wang J, He X, Lu N, Bai A (2014) All-trans retinoic acid attenuates experimental colitis through inhibition of NF-kappaB signaling. Immunol Lett 162:34–40. https://doi.org/10.1016/j.imlet.2014.06.011
92. Povoleri GAM, Nova-Lamperti E, Scotta C, Fanelli G, Chen YC, Becker PD, Boardman D, Costantini B, Romano M, Pavlidis P, McGregor R, Pantazi E, Chauss D, Sun HW, Shih HY, Cousins DJ, Cooper N, Powell N, Kemper C, Pirooznia M, Laurence A, Kordasti S, Kazemian M, Lombardi G, Afzali B (2018) Human retinoic acid-regulated CD161(+) regulatory T cells support wound repair in intestinal mucosa. Nat Immunol 19:1403–1414. https://doi.org/10.1038/s41590-018-0230-z
93. Prevost N, English JC (2013) Isotretinoin: update on controversial issues. J Pediatr Adolesc Gynecol 26:290–293
94. Reddy D, Siegel CA, Sands BE, Kane S (2006) Possible association between isotretinoin and inflammatory bowel disease. Am J Gastroenterol 101:1569–1573. https://doi.org/10.1111/j.1572-0241.2006.00632.x
95. Hippen KL, Loschi M, Nicholls J, MacDonald KPA, Blazar BR (2018) Effects of MicroRNA on regulatory T cells and implications for adoptive cellular therapy to ameliorate graft-versus-host disease. Front Immunol 9:57. https://doi.org/10.3389/fimmu.2018.00057
96. Baumjohann D, Ansel KM (2013) MicroRNA-mediated regulation of T helper cell differentiation and plasticity. Nat Rev Immunol 13:666–678. https://doi.org/10.1038/nri3494
97. Fayyad-Kazan H, Rouas R, Fayyad-Kazan M, Badran R, El Zein N, Lewalle P, Najar M, Hamade E, Jebbawi F, Merimi M, Romero P, Burny A, Badran B, Martiat P (2012) MicroRNA profile of circulating CD4-positive regulatory T cells in human adults and impact of differentially expressed microRNAs on expression of two genes essential to their function. J Biol Chem 287:9910–9922. https://doi.org/10.1074/jbc.M111.337154
98. Liu SQ, Jiang S, Li C, Zhang B, Li QJ (2014) miR-17-92 cluster targets phosphatase and tensin homology and Ikaros family zinc finger 4 to promote TH17-mediated inflammation. J Biol Chem 289:12446–12456. https://doi.org/10.1074/jbc.M114.550723
99. Dong L, Wang X, Tan J, Li H, Qian W, Chen J, Chen Q, Wang J, Xu W, Tao C, Wang S (2014) Decreased expression of microRNA-21 correlates with the imbalance of Th17 and Treg cells in patients with rheumatoid arthritis. J Cell Mol Med 18:2213–2224. https://doi.org/10.1111/jcmm.12353
100. Dooley J, Linterman MA, Liston A (2013) MicroRNA regulation of T-cell development. Immunol Rev 253:53–64. https://doi.org/10.1111/imr.12049
101. Lu LF, Gasteiger G, Yu IS, Chaudhry A, Hsin JP, Lu Y, Bos PD, Lin LL, Zawislak CL, Cho S, Sun JC, Leslie CS, Lin SW, Rudensky AY (2015) A single miRNA-mRNA interaction affects the immune response in a context- and cell-type-specific manner. Immunity 43:52–64. https://doi.org/10.1016/j.immuni.2015.04.022
102. Beyer M, Thabet Y, Muller RU, Sadlon T, Classen S, Lahl K, Basu S, Zhou X, Bailey-Bucktrout SL, Krebs W, Schonfeld EA, Bottcher J, Golovina T, Mayer CT, Hofmann A, Sommer D, Debey-Pascher S, Endl E, Limmer A, Hippen KL, Blazar BR, Balderas R, Quast T, Waha A, Mayer G, Famulok M, Knolle PA, Wickenhauser C, Kolanus W, Schermer B, Bluestone JA, Barry SC, Sparwasser T, Riley JL, Schultze JL (2011) Repression of the genome organizer SATB1 in regulatory T cells is required for suppressive function and inhibition of effector differentiation. Nat Immunol 12:898–907. https://doi.org/10.1038/ni.2084
103. Kitagawa Y, Ohkura N, Kidani Y, Vandenbon A, Hirota K, Kawakami R, Yasuda K, Motooka D, Nakamura S, Kondo M, Taniuchi I, Kohwi-Shigematsu T, Sakaguchi S (2017) Addendum: guidance of regulatory T cell development by Satb1-dependent super-enhancer establishment. Nat Immunol 18:1270. https://doi.org/10.1038/ni1117-1270a
104. Yang HY, Barbi J, Wu CY, Zheng Y, Vignali PD, Wu X, Tao JH, Park BV, Bandara S, Novack L, Ni X, Yang X, Chang KY, Wu RC, Zhang J, Yang CW, Pardoll DM, Li H, Pan F (2016) MicroRNA-17 modulates regulatory T cell function by targeting co-regulators of the Foxp3 transcription factor. Immunity 45:83–93. https://doi.org/10.1016/j.immuni.2016.06.022
105. Cruz LO, Hashemifar SS, Wu CJ, Cho S, Nguyen DT, Lin LL, Khan AA, Lu LF (2017) Excessive expression of miR-27 impairs Treg-mediated immunological tolerance. J Clin Invest 127:530–542. https://doi.org/10.1172/jci88415
106. Zemmour D, Pratama A, Loughhead SM, Mathis D, Benoist C (2017) Flicr, a long noncoding RNA, modulates Foxp3 expression and autoimmunity. Proc Natl Acad Sci U S A 114:E3472–e3480. https://doi.org/10.1073/pnas.1700946114
107. Brajic A, Franckaert D, Burton O, Bornschein S, Calvanese AL, Demeyer S, Cools J, Dooley J, Schlenner S, Liston A (2018) The long non-coding RNA Flatr anticipates Foxp3 expression in regulatory T cells. Front Immunol 9:1989. https://doi.org/10.3389/fimmu.2018.01989
108. Szabo SJ, Sullivan BM, Stemmann C, Satoskar AR, Sleckman BP, Glimcher LH (2002) Distinct effects of T-bet in TH1 lineage commitment and IFN-gamma production in CD4 and CD8 T cells. Science 295:338–342. https://doi.org/10.1126/science.1065543
109. Peng SL (2006) The T-box transcription factor T-bet in immunity and autoimmunity. Cell Mol Immunol 3:87–95
110. Lugo-Villarino G, Maldonado-Lopez R, Possemato R, Penaranda C, Glimcher LH (2003) T-bet is required for optimal production of IFN-gamma and antigen-specific T cell activation by dendritic cells. Proc Natl Acad Sci U S A 100:7749–7754. https://doi.org/10.1073/pnas.1332767100
111. Iqbal N, Oliver JR, Wagner FH, Lazenby AS, Elson CO, Weaver CT (2002) T helper 1 and T helper 2 cells are pathogenic in an antigen-specific model of colitis. J Exp Med 195:71–84
112. Ito R, Shin-Ya M, Kishida T, Urano A, Takada R, Sakagami J, Imanishi J, Kita M, Ueda Y, Iwakura Y, Kataoka K, Okanoue T, Mazda O (2006) Interferon-gamma is causatively involved in experimental inflammatory bowel disease in mice. Clin Exp

Immunol 146:330–338. https://doi.org/10.1111/j.1365-2249.2006.03214.x
113. Muzes G, Molnar B, Tulassay Z, Sipos F (2012) Changes of the cytokine profile in inflammatory bowel diseases. World J Gastroenterol 18:5848–5861. https://doi.org/10.3748/wjg.v18.i41.5848
114. Garrett WS, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, Glickman JN, Glimcher LH (2007) Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. Cell 131:33–45. https://doi.org/10.1016/j.cell.2007.08.017
115. Zimmermann J, Durek P, Kuhl AA, Schattenberg F, Maschmeyer P, Siracusa F, Lehmann K, Westendorf K, Weber M, Riedel R, Muller S, Radbruch A, Chang HD (2018) The intestinal microbiota determines the colitis-inducing potential of T-bet-deficient Th cells in mice. Eur J Immunol 48:161–167. https://doi.org/10.1002/eji.201747100
116. Bouma G, Strober W (2003) The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol 3:521–533. https://doi.org/10.1038/nri1132
117. Hommes DW, Mikhajlova TL, Stoinov S, Stimac D, Vucelic B, Lonovics J, Zakuciova M, D'Haens G, Van Assche G, Ba S, Lee S, Pearce T (2006) Fontolizumab, a humanised anti-interferon gamma antibody, demonstrates safety and clinical activity in patients with moderate to severe Crohn's disease. Gut 55:1131–1137. https://doi.org/10.1136/gut.2005.079392
118. Reinisch W, de Villiers W, Bene L, Simon L, Racz I, Katz S, Altorjay I, Feagan B, Riff D, Bernstein CN, Hommes D, Rutgeerts P, Cortot A, Gaspari M, Cheng M, Pearce T, Sands BE (2010) Fontolizumab in moderate to severe Crohn's disease: a phase 2, randomized, double-blind, placebo-controlled, multiple-dose study. Inflamm Bowel Dis 16:233–242. https://doi.org/10.1002/ibd.21038
119. Sandborn WJ, Gasink C, Gao LL, Blank MA, Johanns J, Guzzo C, Sands BE, Hanauer SB, Targan S, Rutgeerts P, Ghosh S, de Villiers WJ, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan BG (2012) Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med 367:1519–1528. https://doi.org/10.1056/NEJMoa1203572
120. Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH (2000) A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell 100:655–669
121. Naiche LA, Harrelson Z, Kelly RG, Papaioannou VE (2005) T-box genes in vertebrate development. Annu Rev Genet 39:219–239. https://doi.org/10.1146/annurev.genet.39.073003.105925
122. Iwata S, Mikami Y, Sun HW, Brooks SR, Jankovic D, Hirahara K, Onodera A, Shih HY, Kawabe T, Jiang K, Nakayama T, Sher A, O'Shea JJ, Davis FP, Kanno Y (2017) The transcription factor T-bet limits amplification of type I IFN transcriptome and circuitry in T helper 1 cells. Immunity 46:983-991.e984. https://doi.org/10.1016/j.immuni.2017.05.005
123. Kanno Y, Vahedi G, Hirahara K, Singleton K, O'Shea JJ (2012) Transcriptional and epigenetic control of T helper cell specification: molecular mechanisms underlying commitment and plasticity. Annu Rev Immunol 30:707–731. https://doi.org/10.1146/annurev-immunol-020711-075058
124. Wilson CB, Makar KW, Perez-Melgosa M (2002) Epigenetic regulation of T cell fate and function. J Infect Dis 185(Suppl 1):S37–S45. https://doi.org/10.1086/338001
125. Thomas RM, Gamper CJ, Ladle BH, Powell JD, Wells AD (2012) De novo DNA methylation is required to restrict T helper lineage plasticity. J Biol Chem 287:22900–22909. https://doi.org/10.1074/jbc.M111.312785
126. Gonsky R, Deem RL, Landers CJ, Derkowski CA, Berel D, McGovern DP, Targan SR (2011) Distinct IFNG methylation in a subset of ulcerative colitis patients based on reactivity to microbial antigens. Inflamm Bowel Dis 17:171–178. https://doi.org/10.1002/ibd.21352
127. Vahedi G, Takahashi H, Nakayamada S, Sun HW, Sartorelli V, Kanno Y, O'Shea JJ (2012) STATs shape the active enhancer landscape of T cell populations. Cell 151:981–993. https://doi.org/10.1016/j.cell.2012.09.044
128. Koues OI, Collins PL, Cella M, Robinette ML, Porter SI, Pyfrom SC, Payton JE, Colonna M, Oltz EM (2016) Distinct gene regulatory pathways for human innate versus adaptive lymphoid cells. Cell 165:1134–1146. https://doi.org/10.1016/j.cell.2016.04.014
129. Gury-BenAri M, Thaiss CA, Serafini N, Winter DR, Giladi A, Lara-Astiaso D, Levy M, Salame TM, Weiner A, David E, Shapiro H, Dori-Bachash M, Pevsner-Fischer M, Lorenzo-Vivas E, Keren-Shaul H, Paul F, Harmelin A, Eberl G, Itzkovitz S, Tanay A, Di Santo JP, Elinav E, Amit I (2016) The spectrum and regulatory landscape of intestinal innate lymphoid cells are shaped by the microbiome. Cell 166:1231-1246.e1213. https://doi.org/10.1016/j.cell.2016.07.043
130. Cao R, Wang L, Wang H, Xia L, Erdjument-Bromage H, Tempst P, Jones RS, Zhang Y (2002) Role of histone H3 lysine 27 methylation in Polycomb-group silencing. Science 298:1039–1043. https://doi.org/10.1126/science.1076997
131. Kuzmichev A, Nishioka K, Erdjument-Bromage H, Tempst P, Reinberg D (2002) Histone methyltransferase activity associated with a human multiprotein complex containing the enhancer of Zeste protein. Genes Dev 16:2893–2905. https://doi.org/10.1101/gad.1035902
132. Schwartz YB, Pirrotta V (2013) A new world of Polycombs: unexpected partnerships and emerging functions. Nat Rev Genet 14:853–864. https://doi.org/10.1038/nrg3603
133. Zhang Y, Kinkel S, Maksimovic J, Bandala-Sanchez E, Tanzer MC, Naselli G, Zhang JG, Zhan Y, Lew AM, Silke J, Oshlack A, Blewitt ME, Harrison LC (2014) The polycomb repressive complex 2 governs life and death of peripheral T cells. Blood 124:737–749. https://doi.org/10.1182/blood-2013-12-544106
134. Tumes DJ, Onodera A, Suzuki A, Shinoda K, Endo Y, Iwamura C, Hosokawa H, Koseki H, Tokoyoda K, Suzuki Y, Motohashi S, Nakayama T (2013) The polycomb protein Ezh2 regulates differentiation and plasticity of CD4(+) T helper type 1 and type 2 cells. Immunity 39:819–832. https://doi.org/10.1016/j.immuni.2013.09.012
135. Liu Y, Peng J, Sun T, Li N, Zhang L, Ren J, Yuan H, Kan S, Pan Q, Li X, Ding Y, Jiang M, Cong X, Tan M, Ma Y, Fu D, Cai S, Xiao Y, Wang X, Qin J (2017) Epithelial EZH2 serves as an epigenetic determinant in experimental colitis by inhibiting TNFalpha-mediated inflammation and apoptosis. Proc Natl Acad Sci U S A 114:E3796–e3805. https://doi.org/10.1073/pnas.1700909114
136. McCabe MT, Ott HM, Ganji G, Korenchuk S, Thompson C, Van Aller GS, Liu Y, Graves AP, Della Pietra A 3rd, Diaz E, LaFrance LV, Mellinger M, Duquenne C, Tian X, Kruger RG, McHugh CF, Brandt M, Miller WH, Dhanak D, Verma SK, Tummino PJ, Creasy CL (2012) EZH2 inhibition as a therapeutic strategy for lymphoma with EZH2-activating mutations. Nature 492:108–112. https://doi.org/10.1038/nature11606
137. Nagarsheth N, Peng D, Kryczek I, Wu K, Li W, Zhao E, Zhao L, Wei S, Frankel T, Vatan L, Szeliga W, Dou Y, Owens S, Marquez V, Tao K, Huang E, Wang G, Zou W (2016) PRC2 epigenetically silences Th1-type chemokines to suppress effector T-cell trafficking in colon cancer. Cancer Res 76:275–282. https://doi.org/10.1158/0008-5472.Can-15-1938
138. Agger K, Cloos PA, Christensen J, Pasini D, Rose S, Rappsilber J, Issaeva I, Canaani E, Salcini AE, Helin K (2007) UTX and JMJD3 are histone H3K27 demethylases involved in HOX gene regulation and development. Nature 449:731–734. https://doi.org/10.1038/nature06145

139. Swigut T, Wysocka J (2007) H3K27 demethylases, at long last. Cell 131:29–32. https://doi.org/10.1016/j.cell.2007.09.026
140. Miller SA, Mohn SE, Weinmann AS (2010) Jmjd3 and UTX play a demethylase-independent role in chromatin remodeling to regulate T-box family member-dependent gene expression. Mol Cell 40:594–605. https://doi.org/10.1016/j.molcel.2010.10.028
141. Zhao W, Li Q, Ayers S, Gu Y, Shi Z, Zhu Q, Chen Y, Wang HY, Wang RF (2013) Jmjd3 inhibits reprogramming by upregulating expression of INK4a/Arf and targeting PHF20 for ubiquitination. Cell 152:1037–1050. https://doi.org/10.1016/j.cell.2013.02.006
142. Li Q, Zou J, Wang M, Ding X, Chepelev I, Zhou X, Zhao W, Wei G, Cui J, Zhao K, Wang HY, Wang RF (2014) Critical role of histone demethylase Jmjd3 in the regulation of CD4+ T-cell differentiation. Nat Commun 5:5780. https://doi.org/10.1038/ncomms6780
143. Liu Z, Cao W, Xu L, Chen X, Zhan Y, Yang Q, Liu S, Chen P, Jiang Y, Sun X, Tao Y, Hu Y, Li C, Wang Q, Wang Y, Chen CD, Shi Y, Zhang X (2015) The histone H3 lysine-27 demethylase Jmjd3 plays a critical role in specific regulation of Th17 cell differentiation. J Mol Cell Biol 7:505–516. https://doi.org/10.1093/jmcb/mjv022
144. Hangauer MJ, Vaughn IW, McManus MT (2013) Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs. PLoS Genet 9: e1003569. https://doi.org/10.1371/journal.pgen.1003569
145. Rinn JL, Chang HY (2012) Genome regulation by long noncoding RNAs. Annu Rev Biochem 81:145–166. https://doi.org/10.1146/annurev-biochem-051410-092902
146. Chen YG, Satpathy AT, Chang HY (2017) Gene regulation in the immune system by long noncoding RNAs. Nat Immunol 18:962–972. https://doi.org/10.1038/ni.3771
147. Lee RC, Feinbaum RL, Ambros V (1993) The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 75:843–854
148. Wightman B, Ha I, Ruvkun G (1993) Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell 75:855–862
149. Wu F, Zikusoka M, Trindade A, Dassopoulos T, Harris ML, Bayless TM, Brant SR, Chakravarti S, Kwon JH (2008) MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2 alpha. Gastroenterology 135:1624-1635.e1624. https://doi.org/10.1053/j.gastro.2008.07.068
150. Vigneau S, Rohrlich PS, Brahic M, Bureau JF (2003) Tmevpg1, a candidate gene for the control of Theiler's virus persistence, could be implicated in the regulation of gamma interferon. J Virol 77: 5632–5638
151. Collier SP, Collins PL, Williams CL, Boothby MR, Aune TM (2012) Cutting edge: influence of Tmevpg1, a long intergenic noncoding RNA, on the expression of Ifng by Th1 cells. J Immunol 189:2084–2088. https://doi.org/10.4049/jimmunol.1200774
152. Gomez JA, Wapinski OL, Yang YW, Bureau JF, Gopinath S, Monack DM, Chang HY, Brahic M, Kirkegaard K (2013) The NeST long ncRNA controls microbial susceptibility and epigenetic activation of the interferon-gamma locus. Cell 152:743–754. https://doi.org/10.1016/j.cell.2013.01.015
153. Padua D, Mahurkar-Joshi S, Law IK, Polytarchou C, Vu JP, Pisegna JR, Shih D, Iliopoulos D, Pothoulakis C (2016) A long noncoding RNA signature for ulcerative colitis identifies IFNG-AS1 as an enhancer of inflammation. Am J Physiol Gastrointest Liver Physiol 311:G446–G457. https://doi.org/10.1152/ajpgi.00212.2016
154. Malik R, Patel L, Prensner JR, Shi Y, Iyer MK, Subramaniyan S, Carley A, Niknafs YS, Sahu A, Han S, Ma T, Liu M, Asangani IA, Jing X, Cao X, Dhanasekaran SM, Robinson DR, Feng FY, Chinnaiyan AM (2014) The lncRNA PCAT29 inhibits oncogenic phenotypes in prostate cancer. Mol Cancer Res 12:1081–1087. https://doi.org/10.1158/1541-7786.Mcr-14-0257
155. Banerjee A, Schambach F, DeJong CS, Hammond SM, Reiner SL (2010) Micro-RNA-155 inhibits IFN-gamma signaling in CD4+ T cells. Eur J Immunol 40:225–231. https://doi.org/10.1002/eji.200939381
156. Beres NJ, Szabo D, Kocsis D, Szucs D, Kiss Z, Muller KE, Lendvai G, Kiss A, Arato A, Sziksz E, Vannay A, Szabo AJ, Veres G (2016) Role of altered expression of miR-146a, miR-155, and miR-122 in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 22:327–335. https://doi.org/10.1097/mib.0000000000000687
157. Svrcek M, El-Murr N, Wanherdrick K, Dumont S, Beaugerie L, Cosnes J, Colombel JF, Tiret E, Flejou JF, Lesuffleur T, Duval A (2013) Overexpression of microRNAs-155 and 21 targeting mismatch repair proteins in inflammatory bowel diseases. Carcinogenesis 34:828–834. https://doi.org/10.1093/carcin/bgs408
158. Jiang S, Li C, Olive V, Lykken E, Feng F, Sevilla J, Wan Y, He L, Li QJ (2011) Molecular dissection of the miR-17-92 cluster's critical dual roles in promoting Th1 responses and preventing inducible Treg differentiation. Blood 118:5487–5497. https://doi.org/10.1182/blood-2011-05-355644
159. Steiner DF, Thomas MF, Hu JK, Yang Z, Babiarz JE, Allen CD, Matloubian M, Blelloch R, Ansel KM (2011) MicroRNA-29 regulates T-box transcription factors and interferon-gamma production in helper T cells. Immunity 35:169–181. https://doi.org/10.1016/j.immuni.2011.07.009
160. Mohnle P, Schutz SV, van der Heide V, Hubner M, Luchting B, Sedlbauer J, Limbeck E, Hinske LC, Briegel J, Kreth S (2015) MicroRNA-146a controls Th1-cell differentiation of human CD4+ T lymphocytes by targeting PRKCepsilon. Eur J Immunol 45:260–272. https://doi.org/10.1002/eji.201444667
161. Zhou M, Ouyang W (2003) The function role of GATA-3 in Th1 and Th2 differentiation. Immunol Res 28:25–37. https://doi.org/10.1385/ir:28:1:25
162. Kanhere A, Hertweck A, Bhatia U, Gokmen MR, Perucha E, Jackson I, Lord GM, Jenner RG (2012) T-bet and GATA3 orchestrate Th1 and Th2 differentiation through lineage-specific targeting of distal regulatory elements. Nat Commun 3:1268. https://doi.org/10.1038/ncomms2260
163. Mannon P, Reinisch W (2012) Interleukin 13 and its role in gut defence and inflammation. Gut 61:1765–1773. https://doi.org/10.1136/gutjnl-2012-303461
164. Fuss IJ, Heller F, Boirivant M, Leon F, Yoshida M, Fichtner-Feigl S, Yang Z, Exley M, Kitani A, Blumberg RS, Mannon P, Strober W (2004) Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. J Clin Invest 113:1490–1497. https://doi.org/10.1172/jci19836
165. McKenzie GJ, Emson CL, Bell SE, Anderson S, Fallon P, Zurawski G, Murray R, Grencis R, McKenzie AN (1998) Impaired development of Th2 cells in IL-13-deficient mice. Immunity 9:423–432
166. Inoue S, Matsumoto T, Iida M, Mizuno M, Kuroki F, Hoshika K, Shimizu M (1999) Characterization of cytokine expression in the rectal mucosa of ulcerative colitis: correlation with disease activity. Am J Gastroenterol 94:2441–2446. https://doi.org/10.1111/j.1572-0241.1999.01372.x
167. Reinisch W, Panes J, Khurana S, Toth G, Hua F, Comer GM, Hinz M, Page K, O'Toole M, Moorehead TM, Zhu H, Sun Y, Cataldi F (2015) Anrukinzumab, an anti-interleukin 13 monoclonal antibody, in active UC: efficacy and safety from a phase IIa randomised multicentre study. Gut 64:894–900. https://doi.org/10.1136/gutjnl-2014-308337

168. Danese S, Rudzinski J, Brandt W, Dupas JL, Peyrin-Biroulet L, Bouhnik Y, Kleczkowski D, Uebel P, Lukas M, Knutsson M, Erlandsson F, Hansen MB, Keshav S (2015) Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study. Gut 64:243–249. https://doi.org/10.1136/gutjnl-2014-308004
169. Kole A, Maloy KJ (2014) Control of intestinal inflammation by interleukin-10. Curr Top Microbiol Immunol 380:19–38. https://doi.org/10.1007/978-3-662-43492-5_2
170. Kuhn R, Lohler J, Rennick D, Rajewsky K, Muller W (1993) Interleukin-10-deficient mice develop chronic enterocolitis. Cell 75:263–274
171. Tomoyose M, Mitsuyama K, Ishida H, Toyonaga A, Tanikawa K (1998) Role of interleukin-10 in a murine model of dextran sulfate sodium-induced colitis. Scand J Gastroenterol 33:435–440
172. Duchmann R, Schmitt E, Knolle P, Meyer zum Buschenfelde KH, Neurath M (1996) Tolerance towards resident intestinal flora in mice is abrogated in experimental colitis and restored by treatment with interleukin-10 or antibodies to interleukin-12. Eur J Immunol 26:934–938. https://doi.org/10.1002/eji.1830260432
173. Glocker EO, Kotlarz D, Boztug K, Gertz EM, Schaffer AA, Noyan F, Perro M, Diestelhorst J, Allroth A, Murugan D, Hatscher N, Pfeifer D, Sykora KW, Sauer M, Kreipe H, Lacher M, Nustede R, Woellner C, Baumann U, Salzer U, Koletzko S, Shah N, Segal AW, Sauerbrey A, Buderus S, Snapper SB, Grimbacher B, Klein C (2009) Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. N Engl J Med 361:2033–2045. https://doi.org/10.1056/NEJMoa0907206
174. van Deventer SJ, Elson CO, Fedorak RN (1997) Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's Disease Study Group Gastroenterology 113:383–389
175. Fedorak RN, Gangl A, Elson CO, Rutgeerts P, Schreiber S, Wild G, Hanauer SB, Kilian A, Cohard M, LeBeaut A, Feagan B (2000) Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The interleukin 10 inflammatory bowel disease cooperative study group. Gastroenterology 119:1473–1482
176. Schreiber S, Fedorak RN, Nielsen OH, Wild G, Williams CN, Nikolaus S, Jacyna M, Lashner BA, Gangl A, Rutgeerts P, Isaacs K, van Deventer SJ, Koningsberger JC, Cohard M, LeBeaut A, Hanauer SB (2000) Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's disease IL-10 cooperative study group. Gastroenterology 119:1461–1472
177. Mazmanian SK, Round JL, Kasper DL (2008) A microbial symbiosis factor prevents intestinal inflammatory disease. Nature 453:620–625. https://doi.org/10.1038/nature07008
178. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermudez-Humaran LG, Gratadoux JJ, Blugeon S, Bridonneau C, Furet JP, Corthier G, Grangette C, Vasquez N, Pochart P, Trugnan G, Thomas G, Blottiere HM, Dore J, Marteau P, Seksik P, Langella P (2008) Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 105:16731–16736. https://doi.org/10.1073/pnas.0804812105
179. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, Cheng G, Yamasaki S, Saito T, Ohba Y, Taniguchi T, Takeda K, Hori S, Ivanov II, Umesaki Y, Itoh K, Honda K (2011) Induction of colonic regulatory T cells by indigenous Clostridium species. Science 331:337–341. https://doi.org/10.1126/science.1198469
180. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, Fukuda S, Saito T, Narushima S, Hase K, Kim S, Fritz JV, Wilmes P, Ueha S, Matsushima K, Ohno H, Olle B, Sakaguchi S, Taniguchi T, Morita H, Hattori M, Honda K (2013) Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature 500:232–236. https://doi.org/10.1038/nature12331
181. Hayashi A, Sato T, Kamada N, Mikami Y, Matsuoka K, Hisamatsu T, Hibi T, Roers A, Yagita H, Ohteki T, Yoshimura A, Kanai T (2013) A single strain of Clostridium butyricum induces intestinal IL-10-producing macrophages to suppress acute experimental colitis in mice. Cell Host Microbe 13:711–722. https://doi.org/10.1016/j.chom.2013.05.013
182. Kashiwagi I, Morita R, Schichita T, Komai K, Saeki K, Matsumoto M, Takeda K, Nomura M, Hayashi A, Kanai T, Yoshimura A (2015) Smad2 and Smad3 inversely regulate TGF-beta autoinduction in Clostridium butyricum-activated dendritic cells. Immunity 43:65–79. https://doi.org/10.1016/j.immuni.2015.06.010
183. Nakamoto N, Amiya T, Aoki R, Taniki N, Koda Y, Miyamoto K, Teratani T, Suzuki T, Chiba S, Chu PS, Hayashi A, Yamaguchi A, Shiba S, Miyake R, Katayama T, Suda W, Mikami Y, Kamada N, Ebinuma H, Saito H, Hattori M, Kanai T (2017) Commensal lactobacillus controls immune tolerance during acute liver injury in mice. Cell Rep 21:1215–1226. https://doi.org/10.1016/j.celrep.2017.10.022
184. Braat H, Rottiers P, Hommes DW, Huyghebaert N, Remaut E, Remon JP, van Deventer SJ, Neirynck S, Peppelenbosch MP, Steidler L (2006) A phase I trial with transgenic bacteria expressing interleukin-10 in Crohn's disease. Clin Gastroenterol Hepatol 4:754–759. https://doi.org/10.1016/j.cgh.2006.03.028
185. Mohrs M, Blankespoor CM, Wang ZE, Loots GG, Afzal V, Hadeiba H, Shinkai K, Rubin EM, Locksley RM (2001) Deletion of a coordinate regulator of type 2 cytokine expression in mice. Nat Immunol 2:842–847. https://doi.org/10.1038/ni0901-842
186. Fields PE, Lee GR, Kim ST, Bartsevich VV, Flavell RA (2004) Th2-specific chromatin remodeling and enhancer activity in the Th2 cytokine locus control region. Immunity 21:865–876. https://doi.org/10.1016/j.immuni.2004.10.015
187. Takemoto N, Kamogawa Y, Jun Lee H, Kurata H, Arai KI, O'Garra A, Arai N, Miyatake S (2000) Cutting edge: chromatin remodeling at the IL-4/IL-13 intergenic regulatory region for Th2-specific cytokine gene cluster. J Immunol 165:6687–6691
188. Loots GG, Locksley RM, Blankespoor CM, Wang ZE, Miller W, Rubin EM, Frazer KA (2000) Identification of a coordinate regulator of interleukins 4, 13, and 5 by cross-species sequence comparisons. Science 288:136–140
189. Amsen D, Blander JM, Lee GR, Tanigaki K, Honjo T, Flavell RA (2004) Instruction of distinct CD4 T helper cell fates by different notch ligands on antigen-presenting cells. Cell 117:515–526
190. Tanaka S, Motomura Y, Suzuki Y, Yagi R, Inoue H, Miyatake S, Kubo M (2011) The enhancer HS2 critically regulates GATA-3-mediated Il4 transcription in T(H)2 cells. Nat Immunol 12:77–85. https://doi.org/10.1038/ni.1966
191. Yamashita M, Ukai-Tadenuma M, Kimura M, Omori M, Inami M, Taniguchi M, Nakayama T (2002) Identification of a conserved GATA3 response element upstream proximal from the interleukin-13 gene locus. J Biol Chem 277:42399–42408. https://doi.org/10.1074/jbc.M205876200
192. Grausenburger R, Bilic I, Boucheron N, Zupkovitz G, El-Housseiny L, Tschismarov R, Zhang Y, Rembold M, Gaisberger M, Hartl A, Epstein MM, Matthias P, Seiser C, Ellmeier W (2010) Conditional deletion of histone deacetylase 1 in T cells leads to enhanced airway inflammation and increased Th2 cytokine production. J Immunol 185:3489–3497. https://doi.org/10.4049/jimmunol.0903610
193. Weaver CT, Hatton RD, Mangan PR, Harrington LE (2007) IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol 25:821–852. https://doi.org/10.1146/annurev.immunol.25.022106.141557

194. Iwakura Y, Ishigame H (2006) The IL-23/IL-17 axis in inflammation. J Clin Invest 116:1218–1222. https://doi.org/10.1172/jci28508
195. Lee SJ, McLachlan JB, Kurtz JR, Fan D, Winter SE, Baumler AJ, Jenkins MK, McSorley SJ (2012) Temporal expression of bacterial proteins instructs host CD4 T cell expansion and Th17 development. PLoS Pathog 8:e1002499. https://doi.org/10.1371/journal.ppat.1002499
196. Galvez J (2014) Role of Th17 cells in the pathogenesis of human IBD. ISRN Inflamm 2014:928461. https://doi.org/10.1155/2014/928461
197. Kobayashi T, Okamoto S, Hisamatsu T, Kamada N, Chinen H, Saito R, Kitazume MT, Nakazawa A, Sugita A, Koganei K, Isobe K, Hibi T (2008) IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. Gut 57:1682–1689. https://doi.org/10.1136/gut.2007.135053
198. Sakuraba A, Sato T, Kamada N, Kitazume M, Sugita A, Hibi T (2009) Th1/Th17 immune response is induced by mesenteric lymph node dendritic cells in Crohn's disease. Gastroenterology 137:1736–1745. https://doi.org/10.1053/j.gastro.2009.07.049
199. Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PD, Wehkamp J, Feagan BG, Yao MD, Karczewski M, Karczewski J, Pezous N, Bek S, Bruin G, Mellgard B, Berger C, Londei M, Bertolino AP, Tougas G, Travis SP (2012) Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut 61:1693–1700. https://doi.org/10.1136/gutjnl-2011-301668
200. Acosta-Rodriguez EV, Napolitani G, Lanzavecchia A, Sallusto F (2007) Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells. Nat Immunol 8:942–949. https://doi.org/10.1038/ni1496
201. Stritesky GL, Yeh N, Kaplan MH (2008) IL-23 promotes maintenance but not commitment to the Th17 lineage. J Immunol 181:5948–5955
202. Rutz S, Noubade R, Eidenschenk C, Ota N, Zeng W, Zheng Y, Hackney J, Ding J, Singh H, Ouyang W (2011) Transcription factor c-Maf mediates the TGF-beta-dependent suppression of IL-22 production in T(H)17 cells. Nat Immunol 12:1238–1245. https://doi.org/10.1038/ni.2134
203. Ciofani M, Madar A, Galan C, Sellars M, Mace K, Pauli F, Agarwal A, Huang W, Parkhurst CN, Muratet M, Newberry KM, Meadows S, Greenfield A, Yang Y, Jain P, Kirigin FK, Birchmeier C, Wagner EF, Murphy KM, Myers RM, Bonneau R, Littman DR (2012) A validated regulatory network for Th17 cell specification. Cell 151:289–303. https://doi.org/10.1016/j.cell.2012.09.016
204. Wheaton JD, Yeh CH, Ciofani M (2017) Cutting edge: c-Maf is required for regulatory T cells to adopt RORgammat(+) and follicular phenotypes. J Immunol 199:3931–3936. https://doi.org/10.4049/jimmunol.1701134
205. Xu M, Pokrovskii M, Ding Y, Yi R, Au C, Harrison OJ, Galan C, Belkaid Y, Bonneau R, Littman DR (2018) C-MAF-dependent regulatory T cells mediate immunological tolerance to a gut pathobiont. Nature 554:373–377. https://doi.org/10.1038/nature25500
206. Tanaka S, Suto A, Iwamoto T, Kashiwakuma D, Kagami S, Suzuki K, Takatori H, Tamachi T, Hirose K, Onodera A, Suzuki J, Ohara O, Yamashita M, Nakayama T, Nakajima H (2014) Sox5 and c-Maf cooperatively induce Th17 cell differentiation via RORgammat induction as downstream targets of Stat3. J Exp Med 211:1857–1874. https://doi.org/10.1084/jem.20130791
207. Bettelli E, Korn T, Oukka M, Kuchroo VK (2008) Induction and effector functions of T(H)17 cells. Nature 453:1051–1057. https://doi.org/10.1038/nature07036
208. Leppkes M, Becker C, Ivanov II, Hirth S, Wirtz S, Neufert C, Pouly S, Murphy AJ, Valenzuela DM, Yancopoulos GD, Becher B, Littman DR, Neurath MF (2009) RORgamma-expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F. Gastroenterology 136:257–267. https://doi.org/10.1053/j.gastro.2008.10.018
209. O'Connor W Jr, Kamanaka M, Booth CJ, Town T, Nakae S, Iwakura Y, Kolls JK, Flavell RA (2009) A protective function for interleukin 17A in T cell-mediated intestinal inflammation. Nat Immunol 10:603–609. https://doi.org/10.1038/ni.1736
210. Lee JS, Tato CM, Joyce-Shaikh B, Gulen MF, Cayatte C, Chen Y, Blumenschein WM, Judo M, Ayanoglu G, McClanahan TK, Li X, Cua DJ (2015) Interleukin-23-independent IL-17 production regulates intestinal epithelial permeability. Immunity 43:727–738. https://doi.org/10.1016/j.immuni.2015.09.003
211. Mikami Y, Kanai T, Sujino T, Ono Y, Hayashi A, Okazawa A, Kamada N, Matsuoka K, Hisamatsu T, Okamoto S, Takaishi H, Inoue N, Ogata H, Hibi T (2010) Competition between colitogenic Th1 and Th17 cells contributes to the amelioration of colitis. Eur J Immunol 40:2409–2422. https://doi.org/10.1002/eji.201040379
212. Griseri T, Asquith M, Thompson C, Powrie F (2010) OX40 is required for regulatory T cell-mediated control of colitis. J Exp Med 207:699–709. https://doi.org/10.1084/jem.20091618
213. Esplugues E, Huber S, Gagliani N, Hauser AE, Town T, Wan YY, O'Connor W Jr, Rongvaux A, Van Rooijen N, Haberman AM, Iwakura Y, Kuchroo VK, Kolls JK, Bluestone JA, Herold KC, Flavell RA (2011) Control of TH17 cells occurs in the small intestine. Nature 475:514–518. https://doi.org/10.1038/nature10228
214. Yamazaki T, Yang XO, Chung Y, Fukunaga A, Nurieva R, Pappu B, Martin-Orozco N, Kang HS, Ma L, Panopoulos AD, Craig S, Watowich SS, Jetten AM, Tian Q, Dong C (2008) CCR6 regulates the migration of inflammatory and regulatory T cells. J Immunol 181:8391–8401
215. Huber S, Gagliani N, Esplugues E, O'Connor W Jr, Huber FJ, Chaudhry A, Kamanaka M, Kobayashi Y, Booth CJ, Rudensky AY, Roncarolo MG, Battaglia M, Flavell RA (2011) Th17 cells express interleukin-10 receptor and are controlled by Foxp3(−) and Foxp3+ regulatory CD4+ T cells in an interleukin-10-dependent manner. Immunity 34:554–565. https://doi.org/10.1016/j.immuni.2011.01.020
216. Gagliani N, Amezcua Vesely MC, Iseppon A, Brockmann L, Xu H, Palm NW, de Zoete MR, Licona-Limon P, Paiva RS, Ching T, Weaver C, Zi X, Pan X, Fan R, Garmire LX, Cotton MJ, Drier Y, Bernstein B, Geginat J, Stockinger B, Esplugues E, Huber S, Flavell RA (2015) Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. Nature 523:221–225. https://doi.org/10.1038/nature14452
217. Lee Y, Awasthi A, Yosef N, Quintana FJ, Xiao S, Peters A, Wu C, Kleinewietfeld M, Kunder S, Hafler DA, Sobel RA, Regev A, Kuchroo VK (2012) Induction and molecular signature of pathogenic TH17 cells. Nat Immunol 13:991–999. https://doi.org/10.1038/ni.2416
218. Ghoreschi K, Laurence A, Yang XP, Tato CM, McGeachy MJ, Konkel JE, Ramos HL, Wei L, Davidson TS, Bouladoux N, Grainger JR, Chen Q, Kanno Y, Watford WT, Sun HW, Eberl G, Shevach EM, Belkaid Y, Cua DJ, Chen W, O'Shea JJ (2010) Generation of pathogenic T(H)17 cells in the absence of TGF-beta signalling. Nature 467:967–971. https://doi.org/10.1038/nature09447
219. Gaublomme JT, Yosef N, Lee Y, Gertner RS, Yang LV, Wu C, Pandolfi PP, Mak T, Satija R, Shalek AK, Kuchroo VK, Park H, Regev A (2015) Single-cell genomics unveils critical regulators of Th17 cell pathogenicity. Cell 163:1400–1412. https://doi.org/10.1016/j.cell.2015.11.009
220. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, Cua DJ (2007) TGF-beta and IL-6 drive the

production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. Nat Immunol 8:1390–1397. https://doi.org/10.1038/ni1539

221. Liu HP, Cao AT, Feng T, Li Q, Zhang W, Yao S, Dann SM, Elson CO, Cong Y (2015) TGF-beta converts Th1 cells into Th17 cells through stimulation of Runx1 expression. Eur J Immunol 45: 1010–1018. https://doi.org/10.1002/eji.201444726
222. Glauben R, Siegmund B (2011) Inhibition of histone deacetylases in inflammatory bowel diseases. Mol Med 17:426–433. https://doi.org/10.2119/molmed.2011.00069
223. Li X, Wu L, Corsa CA, Kunkel S, Dou Y (2009) Two mammalian MOF complexes regulate transcription activation by distinct mechanisms. Mol Cell 36:290–301. https://doi.org/10.1016/j.molcel.2009.07.031
224. Tsaprouni LG, Ito K, Powell JJ, Adcock IM, Punchard N (2011) Differential patterns of histone acetylation in inflammatory bowel diseases. J Inflamm (Lond) 8:1. https://doi.org/10.1186/1476-9255-8-1
225. Yang Y, Guan J, Shaikh AS, Liang Y, Sun L, Wang M, Li D, Qiu C, Li X (2018) Histone acetyltransferase Mof affects the progression of DSS-induced colitis. Cell Physiol Biochem 47:2159–2169. https://doi.org/10.1159/000491527
226. Zhang S, Takaku M, Zou L, Gu AD, Chou WC, Zhang G, Wu B, Kong Q, Thomas SY, Serody JS, Chen X, Xu X, Wade PA, Cook DN, Ting JPY, Wan YY (2017) Reversing SKI-SMAD4-mediated suppression is essential for TH17 cell differentiation. Nature 551: 105–109. https://doi.org/10.1038/nature24283
227. Dallavalle S, Pisano C, Zunino F (2012) Development and therapeutic impact of HDAC6-selective inhibitors. Biochem Pharmacol 84:756–765. https://doi.org/10.1016/j.bcp.2012.06.014
228. Salkowska A, Karas K, Walczak-Drzewiecka A, Dastych J, Ratajewski M (2017) Differentiation stage-specific effect of histone deacetylase inhibitors on the expression of RORgammaT in human lymphocytes. J Leukoc Biol 102:1487–1495. https://doi.org/10.1189/jlb.6A0617-217R
229. Glauben R, Sonnenberg E, Wetzel M, Mascagni P, Siegmund B (2014) Histone deacetylase inhibitors modulate interleukin 6-dependent CD4+ T cell polarization in vitro and in vivo. J Biol Chem 289:6142–6151. https://doi.org/10.1074/jbc.M113.517599
230. Glauben R, Batra A, Fedke I, Zeitz M, Lehr HA, Leoni F, Mascagni P, Fantuzzi G, Dinarello CA, Siegmund B (2006) Histone hyperacetylation is associated with amelioration of experimental colitis in mice. J Immunol 176:5015–5022
231. Cosenza M, Pozzi S (2018) The therapeutic strategy of HDAC6 inhibitors in lymphoproliferative disease. Int J Mol Sci 19. https://doi.org/10.3390/ijms19082337
232. Pei XF, Cao LL, Huang F, Qiao X, Yu J, Ye H, Xi CL, Zhou QC, Zhang GF, Gong ZL (2018) Role of miR-22 in intestinal mucosa tissues and peripheral blood CD4+ T cells of inflammatory bowel disease. Pathol Res Pract 214:1095–1104. https://doi.org/10.1016/j.prp.2018.04.009
233. Lykken EA, Li QJ (2011) microRNAs at the regulatory frontier: an investigation into how microRNAs impact the development and effector functions of CD4 T cells. Immunol Res 49:87–96. https://doi.org/10.1007/s12026-010-8196-4
234. Takagi T, Naito Y, Mizushima K, Hirata I, Yagi N, Tomatsuri N, Ando T, Oyamada Y, Isozaki Y, Hongo H, Uchiyama K, Handa O, Kokura S, Ichikawa H, Yoshikawa T (2010) Increased expression of microRNA in the inflamed colonic mucosa of patients with active ulcerative colitis. J Gastroenterol Hepatol 25(Suppl 1): S129–S133. https://doi.org/10.1111/j.1440-1746.2009.06216.x
235. Fasseu M, Treton X, Guichard C, Pedruzzi E, Cazals-Hatem D, Richard C, Aparicio T, Daniel F, Soule JC, Moreau R, Bouhnik Y, Laburthe M, Groyer A, Ogier-Denis E (2010) Identification of restricted subsets of mature microRNA abnormally expressed in inactive colonic mucosa of patients with inflammatory bowel disease. PLoS One 5. https://doi.org/10.1371/journal.pone.0013160
236. Hou J, Hu X, Chen B, Chen X, Zhao L, Chen Z, Liu F, Liu Z (2017) miR-155 targets Est-1 and induces ulcerative colitis via the IL-23/17/6-mediated Th17 pathway. Pathol Res Pract 213:1289–1295. https://doi.org/10.1016/j.prp.2017.08.001
237. Singh UP, Murphy AE, Enos RT, Shamran HA, Singh NP, Guan H, Hegde VL, Fan D, Price RL, Taub DD, Mishra MK, Nagarkatti M, Nagarkatti PS (2014) miR-155 deficiency protects mice from experimental colitis by reducing T helper type 1/type 17 responses. Immunology 143:478–489. https://doi.org/10.1111/imm.12328
238. Du C, Liu C, Kang J, Zhao G, Ye Z, Huang S, Li Z, Wu Z, Pei G (2009) MicroRNA miR-326 regulates TH-17 differentiation and is associated with the pathogenesis of multiple sclerosis. Nat Immunol 10:1252–1259. https://doi.org/10.1038/ni.1798
239. Ichiyama K, Gonzalez-Martin A, Kim BS, Jin HY, Jin W, Xu W, Sabouri-Ghomi M, Xu S, Zheng P, Xiao C, Dong C (2016) The MicroRNA-183-96-182 cluster promotes T helper 17 cell pathogenicity by negatively regulating transcription factor Foxo1 expression. Immunity 44:1284–1298. https://doi.org/10.1016/j.immuni.2016.05.015
240. Brain O, Owens BM, Pichulik T, Allan P, Khatamzas E, Leslie A, Steevels T, Sharma S, Mayer A, Catuneanu AM, Morton V, Sun MY, Jewell D, Coccia M, Harrison O, Maloy K, Schonefeldt S, Bornschein S, Liston A, Simmons A (2013) The intracellular sensor NOD2 induces microRNA-29 expression in human dendritic cells to limit IL-23 release. Immunity 39:521–536. https://doi.org/10.1016/j.immuni.2013.08.035
241. Wang H, Flach H, Onizawa M, Wei L, McManus MT, Weiss A (2014) Negative regulation of Hif1a expression and TH17 differentiation by the hypoxia-regulated microRNA miR-210. Nat Immunol 15:393–401. https://doi.org/10.1038/ni.2846
242. Shih HY, Sciume G, Mikami Y, Guo L, Sun HW, Brooks SR, Urban JF Jr, Davis FP, Kanno Y, O'Shea JJ (2016) Developmental acquisition of regulomes underlies innate lymphoid cell functionality. Cell 165:1120–1133. https://doi.org/10.1016/j.cell.2016.04.029

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.