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Balancing Pro- and Anti-Inflammatory CD4+ T Helper Cells in the Intestine

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1. Introduction

The intestinal mucosal surface represents a huge border where different pathogenic particles, such as bacteria, fungi, viruses or parasites can potentially invade and harm the body. One crucial task of the immune system in the intestine is to maintain this epithelial barrier, in order to prohibit or defeat a microbial invasion. Pro-inflammatory effector CD4+ T helper cells play a crucial role during this task. These effector T helper cells can be subdivided into different subsets (Figure 1), which are characterized by a master transcriptional regulator and a unique cytokine profile: Th17 cells express RORyt that in turn promotes the transcription of Il17a, Il17f, Il21 and Il22. Th1 cells express T-bet and produce IFN-γ, IL-2 and TNF-α. Th2 cells express GATA-3 and secrete IL-4, IL-5 and IL-13 [1-5]. The intestine also contains numerous non-pathogenic bacteria (commensal bacteria), which are beneficial to the host, as well as food antigens. This vast collection of non-self antigens can also promote the activation of T helper cells, and in turn cause immune-pathology. Therefore it is important for the immune system to control effector T helper cells. Indeed different types of regulatory T cells with anti-inflammatory properties team up in order to control effector T cells. The two most studied regulatory T cell subtypes are Foxp3+ regulatory T cells, which can be generated either in the thymus (nTreg) or induced in peripheral lymphoid organs (iTregs) and type 1 regulatory T cells (Tr1), which are induced in the periphery (Figure 1).

2. Differentiation of naïve CD4+ T cells into effector T helper cells

Naïve T cells, which are functionally immature, can be differentiated into different subsets of effector T cells upon activation. The fate of naïve T cell is directed by cytokines. These cytokines signal via different members of the STAT family, which induce master transcriptional regulators. Most of these transcriptional factors bind then to the effector...
cytokine gene thereby inducing gene activation, repression or epigenetic modification [6] (Figure 1). It should be noted that there is a certain amount of T helper cell heterogeneity and plasticity regarding cytokine production and expression of the master transcriptional factor of each T helper cell subset. This fact is currently also one of the most intriguing aspect of the ongoing research in Immunobiology. However, the model of different T helper cell lineages as first proposed by Mosmann and Coffman [7] is still the most useful one in order to understand the function and differentiation of T helper cells.

**Figure 1. Differentiation of naïve T cells into different effector and regulatory T cells.** A specific combination of cytokine signals leads to the differentiation of naïve T cells into different T helper cell subsets. Each T helper cell subset is characterized by the production of a combination of cytokines and exerts specific functions.

### 2.1. Differentiation and function of Th1 cells

Th1 cells produce IFN-γ as their signature cytokine. Th1 cells secrete also IL-2 and/ or TNF-α. Naive T cells upon TCR stimulation in the presence of IL-12 differentiate in Th1 cells [8].
IL-12 signals via STAT4 promoting the expression of T-bet, which transcribes the *Ifng* gene [9, 10]. T-bet is the master transcriptional regulator of Th1 cells, which is essential for the IFN-γ production [5]. Accordingly T-bet deficient mice have a defective Th1 differentiation [11]. One other important function of T-bet is the inhibition of GATA-3 expression, the master transcriptional regulator of Th2 cells [9].

Th1 cells are particularly important for the defense against intra-cellular bacteria. Some microorganisms such as mycobacteria, like *Mycobacterium tuberculosis* or *Mycobacterium lepramatosis*, are examples for these intracellular pathogens. These bacteria grow primarily in phagolysosomes of macrophages. Because of this feature these microorganisms are protected from the effects of antibodies and cytotoxic T cells. These bacteria can inhibit the fusion of lysosomes to the phagosomes, in which they grow and prevent the activation of the lysosomal proteases. The defense against these microorganisms is the important task of Th1 effector cells because they can activate macrophages, which are then able to kill ingested pathogens. Accordingly, deficiency in Th1 cells increases the susceptibility to infections with intracellular pathogens in humans [12]. These patients suffer from infections with mycobacteria, particularly *Mycobacterium tuberculosis*, but also with *Salmonella*. Of note both of these bacteria strains can typically infect the gastrointestinal system.

### 2.2 Differentiation and function of Th2 cells

The signature cytokines of Th2 cells are IL-4, IL-5, and IL-13. Some Th2 cells also produce TNF-α and/or IL-9. Additionally, some Th2 cells can secrete small amounts of IL-2. The cytokines leading to Th2 differentiation are IL-2 and IL-4. Therefore the signature cytokine of Th2 cells, IL-4 also promotes the differentiation of Th2 cells [13-15]. STAT6 is the major signaling pathway of IL-4 mediated Th2 differentiation, and induces GATA-3 expression [16-20]. GATA-3 is the master transcriptional regulator of Th2 cells [3, 21] and the differentiation of these cells is indeed dependent on the induction of this master transcriptional regulator [22]. GATA-3 binds to the promoters of *Il5* and *Il13*, and the enhancer of *Il4* thereby promoting their transcription [6]. Additionally STAT5, which can be activated by IL-2, is important for Th2 differentiation and for the maintenance of GATA-3 expression [23].

Th2 cells and their effector cytokines IL-4, IL-5, and IL-13 are essential to control helminth infections in the intestine. In line with this, mice deficient in IL-4 receptor α-chain (IL-4Rα), STAT6 or GATA-3 show highly compromised anti-helminth immunity [24]. One of the most unique tasks of Th2 cells is the induction of B-cell immunoglobulin class switching. Through CD40-CD40L interaction, Th2 cells promote B cells to secret IgG1, IgE and (in humans) IgG4 isotype antibodies. These antibodies are again important for mediating protection against helminth infections. The Th2-immune response involves also eosinophils, basophils and mast cells, which all together mount the immune response controlling helminth infection. The release of IL-4 and IL-13 is key for eliciting the alternative activation of macrophage, which is crucial in order to trap the intestinal parasite [25, 26]. Th2-cytokines, in particular
IL-4 and IL-13, promote the goblet cell differentiation, the enhancement of mucus secretion and the production of resistin-like molecule-β (RELMβ), an innate protein with direct anti-helminth activity [27-29]. Moreover IL-4 stimulates intestinal muscle hyper-contraction and accelerates epithelial turnover to promote the 'epithelial escalator', which functions together with epithelial secretions to dislodge resident parasites [30, 31]. Another Th2 associated cytokine, namely IL-9, promotes the release of mast cell protease that can depredate tight junctions and in turn increase the fluid flow in the intestine. All together these mechanisms are part of the “weep and sweep” response, which is key for the control of a helminth invasion.

2.3. Differentiation and function of Th17 cells

The signature cytokines of Th17 cells are IL-17A and IL-17F. Th17 cells produce also, IL-22 and TNF-α. TGF-β, IL-1β, IL-6, and IL-23 are the cytokines, which are important for Th17 cell differentiation. IL-6 can activate STAT3, which induces IL-23R and RORγt [32-34], the master transcriptional regulator of Th17 cells. This master transcriptional regulator leads to the production of IL-17A and IL-17F [1, 4, 35, 36]. IL-6 also promotes the release of IL-21 [33], which synergizes with TGF-β, IL-6, and IL-1β, for the induction of IL-23 receptor expression [37]. In the presence of IL-23, CD4+ RORγt+ IL-17A+ T cells can expand and fully mature in Th17 cells [38, 39].

Human and mouse Th17 cells are rare in a non-pathological state [2, 40]. A specific member of commensal microbiota, known as segmented filamentous bacteria (SFB), attracts Th17 cells in the terminal ileum of mice [41]. Therefore in steady state condition most of the few Th17 cells accumulate mainly in the intestine. The commensal microbiota promotes the release of serum amyloid A [41] and adenosine 5′-triphosphate (ATP), which activates lamina propria mononuclear phagocytes. These phagocytes in turn promote Th17 cell differentiation [42]. Among all cytokines known to induce the differentiation of Th17 cells, the presence of IL-1β rather than IL-6 is essential in the intestine [43]. TGF-β 1 is also not essential for the differentiation of Th17 cells in the intestine, but may influence the phenotype of Th17 cells together with IL-1β [44]. Th17 cells, which have been differentiated in the presence of TGF-β1 are less pathogenic and produce more IL-10 compared to Th17 cell differentiated in the presence of IL-1β [45, 46].

Th17 cells also produce several other cytokines besides IL-17A and IL-17F. Cytokine production by Th17 cells is also modulated by environmental factors in the intestine. For example, the activation of the environmental chemical receptor and transcription factor aryl hydrocarbon receptor in Th17 cells is important for the production of IL-22 [47-49]. IL-22 is a critical cytokine for antimicrobial immunity exerted by Th17 cells [50]. On the other hand, the induction of c-maf upon stimulation with IL-27, promotes the release of IL-10 from Th17 cells [51], and these IL-10 producing Th17 cells are also particularly induced in the intestine [40]. Therefore Th17 cells can have different cytokine profiles depending on environment factors.
In the absence of pathology, Th17 cells are very rare. However pathogenic infections, such as fungi infection with *Candida albicans*, or bacterial infection with gram positive or gram negative extracellular bacteria, such as *Citrobacter rodentium* or *Klebsiella pneumoniae* lead to a dramatic increase of the number of Th17 cells [52-56]. Viral infection also promotes a Th17-cell mediated immune response [40]. In line with this, Th17 cells and their effector cytokines IL-17A, IL-17F, and IL-22 are critical for proper host defense against various infections, especially against extracellular bacteria and fungi. The receptors for IL-17A, IL-17F and IL-22 are broadly expressed throughout the intestinal epithelial tissue. Therefore Th17 cells can provide crosstalk between immune system and tissues [2, 57].

IL-17A and IL-17F strongly induce the recruitment of neutrophils to the inflammatory site. The subsequent induction of the chemokine CCL20 attracts even more Th17 cells via CCR6, the chemokine receptor of CCL20, which is highly expressed by Th17 cells [58]. Additionally, both IL-17A and IL-17F promote β-defensin production [56, 59, 60]. β-defensins play an important role in the immune responses against bacterial infections. Interestingly, IL-17A and IL-17F can compensate each other during the host defense against *S. aureus* [56]. However during other infections, such as *Citrobacter rodentium*, IL-17A and IL-17F are both required in order to control the bacterial dissemination [56].

At the mucosal surface IL-22 has a crucial function for host defence and tissue homeostasis. IL-22 induces the expression of antimicrobial peptides from epithelial cells and limits bacterial replication and dissemination during *Citrobacter rodentium* infection [57, 61]. Furthermore IL-22 can promote epithelial cell proliferation, survival, and tissue repair in the intestine [62-64].

However it should be noted that several other immune cells besides Th17 cells can produce IL-17A and IL-22, thereby also contributing to the defense against pathogens (for review see [50]).

### 2.4. Differentiation and function of Foxp3+ Treg cells

In 1995 Sakaguchi et al. first described a subpopulation of regulatory T cells characterized by the constitutive expression of the IL-2 receptor α-chain (CD25). These regulatory T cells were called CD4+CD25+ Treg [65]. Foxp3 was identified later on as the master transcriptional regulator of CD4+CD25+ Treg cells, which have been called Foxp3+ Treg cells thereafter [66, 67]. Foxp3+ Treg cells can be generated within the thymus (tTreg) [65]. However, Foxp3+ Treg cell numbers are also regulated in peripheral lymphoid organs both by expansion of pre-existing Foxp3+ Treg and by de novo generation of induced regulatory T cells (iTreg). The combination of the cytokines IL-2 and TGF-β1 are key for the differentiation of naïve T cells into Foxp3+ iTreg cells [68-73]. Foxp3+ Treg cells are essential to control auto-reactive T cells, which can react to self-antigens and cause damage to the host. The key role of Foxp3+ Treg cells in the peripheral immune response is evident in murine models [74] and in humans [75]: scurfy mice [74] and IPEX...
(immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) patients [75] lacking the master transcriptional factor of regulatory T cells - Foxp3 - consequently develop strong autoimmune disorders. Importantly, a severe form of autoimmune enteropathy is characteristic for scurfy mice and IPEX patients [75]. This underlines the importance of Foxp3+ Treg cells for controlling the immune response in the intestine. Foxp3+ Treg cells have different mechanism to suppress effector T cells. Some of these are mediated via soluble factors (i.e. IL-10, TGF-β [76, 77]) and others are cell contact dependent (i.e. CTLA-4, cAMP [78, 79]). Recent studies have demonstrated that Foxp3+ Treg cells can acquire some features of effector T helper cells in order to better control them (see paragraph 4.3).

2.5. Differentiation and function of Tr1 cells

In 1994, T regulatory type 1 (Tr1) cells were isolated from severe combined immunodeficiency (SCID) patients transplanted with allogeneic haematopoietic stem cells (HSCT). Subsequently it was possible to test the regulatory capacity of this new type of T cells directly in murine IBD models. To date Tr1 cells lack a defined cell surface signature, and their identification relays therefore on their unique cytokine profile. Tr1 cells secrete high levels of IL-10 as compared to IL-4 and IL-17A, the hallmark cytokines of Th2 and Th17 cells respectively. Depending on the milieu Tr1 cells can produce variable levels of IFN-γ, the key cytokine produced by Th1 cells [80]. However, Tr1 cells posses the capacity to suppress inflammatory T cell responses and, therefore are distinct from bona fide Th1, Th2 and Th17 cells that largely promote rather than suppress the inflammatory responses.

Tr1 cells are induced in the periphery, and they respond selectively to persistent foreign and self-antigens under steady-state conditions [81].

After the discovery of Foxp3 as the master transcriptional regulator of Foxp3+ Treg cells, it became a key point, if also Tr1 cells express a master regulator. The double reporter mouse model for IL-10 and Foxp3 was instrumental in order to demonstrate that these two types of regulatory T cells are distinct. Indeed, Tr1 cells do not constitutively express Foxp3 [82, 83] and can be induced from IPEX patients who lack Foxp3 [84]. However the master transcriptional regulator for Tr1 cells has not been identified so far.

IL-10 has been considered to be the driving force for Tr1-cell generation on the basis of experiments in which antigen-specific Tr1 cells are induced in vitro by repeated TCR stimulation in the presence of high doses of IL-10 [85, 86]. However, the frequency of Tr1 cells in IL-10 deficient mice is not altered. Several recent publications have demonstrated a key role of IL-27, which can even synergize with TGF-β, in the induction of Tr1 cells. During the induction of Tr1 cells by IL-27, the ligand-activated transcription factor hydrocarbon receptor (AhR) physically associates with c-avian musculoaponeurotic fibrosarcoma (c-Maf) and transactivates the Il10 and Il21 promoters. The secretion of IL-21 acts as an autocrine growth factor for Tr1 cells (Reviewed in [87]).
Tr1 cells can control Th1, Th2 and Th17 cell, and regulate immune responses mainly through the secretion of the immunosuppressive cytokines IL-10 and TGF-β1 [88]. The antigen-specific activation of Tr1 cells is important to potentiate their regulatory function [86]. IL-10 acts by limiting the magnitude of immune responses, as proved by mice that lack IL-10 and that exhibit spontaneous enterocolitis. IL-10 down-regulates the expression of costimulatory molecules, such as CD80, CD86, and MHC Class II, and pro-inflammatory cytokine production by APCs and inhibits the secretion of IL-2, TNF-α and IL-17 by effector T cells [89]. In particular, Tr1-cell supernatant diminishes the capacity of monocytes to stimulate Th1-cell responses and blocks the differentiation and maturation of DCs via IL-10 [90]. TGF-β down-regulates the functions of APCs [91] and inhibits the proliferation and cytokine production by T cells [92]. Therefore, the suppressive effects of Tr1 cells are reversed by the addition of anti-IL10 and anti-TGF-β neutralizing antibodies [85, 93, 94], but additional mechanisms may also contribute. Human Tr1 cells generated in vitro by crosslinking CD3 with CD46 can kill target cells through a granzyme B/ perforin dependent mechanism [95] [96]. Accordingly human Tr1 cells selectively kill myeloid cells (i.e., DC and monocytes) through granzyme B/ perforin [97]. This selective cell-killing is mediated by CD226, which is expressed on Tr1 cells. Only myeloid cells express the CD226-ligand (CD155). Thus, this type of regulatory mechanism by Tr1 cells requires a cell-cell contact with APCs.

3. The immune homeostasis in the intestine

The immune system has to respond selectively to harmful non-self pathogens and at the same time needs to minimize reactions against self and not-harmful antigens. This highly fine-tuned mechanism is possible due to a strict selection process, which happens in the thymus. Potentially auto-reactive CD4+ T cell progenitors, which recognize self-antigens with their T cell receptor (TCR), are either deleted or converted into thymic-derived CD4+ regulatory T cells (tTreg) with anti-inflammatory properties. This process, called central tolerance, is essential for the education of CD4+ T cells to respond selectively against foreign antigens. However this thymic control appears still to be insufficient. Therefore the immune system developed several other mechanisms to control potentially auto-reactive T cells, which take places in the periphery (peripheral tolerance). Among these mechanisms, the action of CD4+ regulatory T cells, which can be either selected in the thymus, (tTreg) or induced in the periphery (iTreg)[98], is one of the most studied. Treg cells are essential to control auto-reactive T cells, which can react to self-antigens and cause damage to the host.

The intestine is not only a source of self-antigens, but also contains a vast collection of non-self antigens, such as commensal bacteria. These antigens can promote the activation of naïve T cells causing immune-pathology such as inflammatory bowel disease (IBD). Therefore the immune system has established a second checkpoint in the intestine where naïve T cells, which are potentially able to respond to non self-antigens, are educated to be tolerant. There are important differences between thymus and intestine in tolerance induction. The driving force for the selection in the thymus is the affinity of TCRs to
MHC, while the flora and cytokines are crucial to determine the fate of naïve T cells in the intestine. Accordingly different commensal bacteria can selectively drive a tolerogenic or pro-inflammatory response. In line with this, the bacterial composition of the intestine has a substantial impact on the balance between pro-inflammatory and regulatory T cells in the intestine, and can also affect other organ specific diseases [41, 99-101]: For example mice lacking an innate sensor, which controls the intestinal micro-flora, are more susceptible to develop colitis [100]. Another interaction between the gut flora and an autoimmune disease was found in EAE (experimental autoimmune encephalomyelitis, a mouse model for multiple sclerosis). Multiple sclerosis is caused by an attack by auto-reactive T cells against brain white matter. Interestingly it was shown that the commensal gut flora can trigger these auto-reactive T cells, which then drive the disease. Finally it is known that the bacterial colonization between neonates born vaginally or by cesarean delivery differs, and interestingly these differences have been linked to an increased risk for atopic diseases such as allergic rhinitis and asthma in children born by cesarean delivery [102].

Considering the amount of self- and none self-antigens present in this organ and with it the potential to generate an unwanted immune response, different players are required to control the immune homeostasis in the intestine. The first one is a specialized subset of DC, which through the release of TGF-β and retinoic acid, is able to induce iTreg cells [103]. These iTreg cells represent then the second players. It is also known that naïve T cells migrate to the intestine in order to acquire an iTreg cell phenotype [104, 105]. Interestingly, these iTreg cells have a TCR repertoire, which is specific to an individuals microflora. Based on these results, one could hypothesize that iTreg cells have an advantage over tTreg cells (3rd player), which are also present in the intestine, but are obviously non-bacteria specific. However, it was shown that specific commensal bacteria can directly activate tTreg cells bypassing the antigen specificity [106]. Both tTreg and iTreg are able to suppress effector T cells in the intestine, thereby curing or preventing colitis development [68, 98, 107-110]. It seems that tTregs and iTreg can also supplement the function of each other partially by expanding the TCR diversity [111]. Tr1 cells (4th players) are expanded in the absence of iTregs, and can at least partially compensate the absence of iTregs [112, 113]. Consistent with this, Tr1 cells and Treg cells can compensate each other to suppress effector T cells in the intestine [114].

In conclusion, commensal antigens in the intestine play an essential role in the regulation of the immune homeostasis. Naïve T cells, which could be potentially auto-reactive, are converted into different types of regulatory T cells, which in turn control other effector T helper cells. The regulatory T cells originated in the thymus (nTregs) also participate in this regulatory environment by expanding the antigen specificity of the immune response.

4. Breakdown of the immune homeostasis in the intestine

Imbalance between pro- and anti-inflammatory T helper cells can cause intestinal pathology, such as IBD in humans. Crohn’s disease (CD) and ulcerative colitis (UC) are the two main
forms of IBD. CD can attack any part of the digestive tract. It typically manifests in the ileum, although it can also selectively affect the large intestine. Histological Crohn’s disease shows a transmural inflammation. This inflammation is characterized by focal infiltration of neutrophils into the epithelium. These neutrophils, along with mononuclear cells, can infiltrate the crypts, leading to inflammation or abscess. Granulomas, aggregates of macrophage derivatives, known as giant cells, are found in CD and are specific for the disease. Ulceration can also be seen in highly active CD. On the other hand, UC is a disease mainly of the colon that includes ulcerations. UC normally begins in the rectum, and can continuously affect the whole colon and also the terminal ileum. The pathology in ulcerative colitis involves distortion of crypt architecture, inflammation of crypts and hemorrhage. The inflammation is more superficial compared to CD and affects the mucosa and submucosa.

The aetiology of IBD is still unknown, but it seems that genetic and environmental factors contribute to disease development. Initial studies suggested that CD and UC are mediated by Th1 and Th2 cells respectively. This was based on the cytokine profile seen in CD (IL-12 and IFN-γ) and UC (IL-5, IL-13) [115]. However more recent work has shown that Th17 cells also infiltrate the intestine in CD and UC patients as well [116-118]. Accordingly the signature cytokines of Th17 cells (IL-17A, IL-17F, IL-22) are produced in the intestine of CD and UC patients [116, 118-120]. Additionally, genome wide association studies have linked polymorphism in Th17-related genes, such as IL-23R and STAT3 with IBD [121-124]. In line with these associations murine studies have also shown that Th17 cells are involved in numerous autoimmune and chronic inflammatory diseases [2], and IBD is one of these diseases [125]: RORγt deficient mice, which lack Th17 cells, exhibit attenuated experimentally induced autoimmune disease [4]. Adoptive transfer of in vitro or in vivo differentiated Th17 cells into lymphopenic hosts leads to the development of colitis [114, 126-128]. IL-23, which is important for the maintenance, expansion and pathogenicity of Th17 cells [38, 39], is essential for the induction of colitis in mouse models. All together, these data argue for an important role of Th17 cells in IBD. However, Th17 cells produce several factors. And it is currently not completely understood, which of these is/are responsible for the pathogenicity of Th17 cells in the intestine [129-132].

One key feature of Th17 cells is their plasticity, which might also contribute to the pathogenic potential of Th17 cells. Epigenetic studies have shown that Th17 cells are more plastic compared to Th1 and Th2 cells [56, 133-135]. Th17 cells have bivalent domains of histone modifications in the Tbx21 locus, which encodes for T-bet, the key transcriptional factor for Th1 cells. On the contrary, Th1 cells have only repressive markers in both Rorc and Il17a loci. These differences might account for the higher plasticity of Th17 cells relative to Th1 cells [133]. In line with these data, CD4+ T cells, which express both the key transcriptional factors and cytokines of Th17 and Th1 cells, have been found in the colon of mouse colitis models and moreover in colon of human IBD patients. They are also suggested to play an important role for the development of chronic disease [39, 114, 118].

Human IBD is characterized by a mixture of effector T cells. Therefore it is difficult to assess the relative contribution of a specific T helper cell subset in patients. However there are mouse IBD models, which are dominated by one specific T helper cells subset: Selective
deficiency in iTreg cells causes Th2 dominated intestinal pathology, which is characterized by gastritis and plasmacytic enteritis with increased frequencies of plasma cells in the intestinal lamina propria [113]. Another mouse model of colitis, which is induced by the transfer of naïve T cells into a lymphopenic host, is dominated by Th1 cells. This colitis model is characterized by IFN-γ dependent mucosal ulceration in the colon [136, 137]. Th17 cell-dominated intestinal pathology is characterized by mucosal hyperplasia but not ulceration [76, 136, 138]. IL-22, a signature cytokine of Th17 cells, can promote epithelial cell survival and proliferation. It is also important for the repair of the intestinal mucosa [63, 136, 139]. Accordingly, IL-22 induces the hyperplasia in the Th17 dominated colitis models [136]. On the contrary IL-22 is beneficial in Th1 dominated colitis models, which are characterized by ulceration [62]. Of note, the histomorphology in these Th1, Th2, or Th17 cell dominated mouse IBD models features only some characteristics of human IBD. But still these models are useful to evaluate the function of specific T helper cell subsets.

5. Control of pro-inflammatory T helper cells in the intestine

There are three ways to control effector T cells. First, inhibition of the differentiation of naïve T cells into effector T cells. Second, endogenous mechanism limiting the pathogenic potential of effector T cells. Third, control of effector T cells through regulatory T cells.

5.1. Inhibition of the de novo differentiation of effector T cells

One possibility is to inhibit the de novo differentiation of naïve T cells into effector T cells and generate regulatory T cells in stead. Such a reciprocal development pathway has been described for Th17 cells: High concentrations of TGF-β and/or retinoic acid up-regulate Foxp3 [140, 141], which in turn inhibits the induction of RORγt [37], thereby preventing the differentiation of Th17 cells. Moreover, IL-2 together with TGF-β1 promotes the induction of Foxp3⁺ regulatory T cells (iTregs) instead of Th17 cells [142]. Interestingly, IL-2 blocks Th17 cell differentiation by directly inhibiting Il17a transcription. This second mechanism is largely independent of Foxp3 or RORγt expression, but dependent on the induction of STAT5, which competes with STAT3 for the common sites across the locus encoding IL-17A [143]. Finally, IL-27 through the activation and interaction of AhR and c-maf promotes the induction of type 1 regulatory T cells (Tr1) and efficiently counteracts the effects of TGF-β and IL-6 on CD4⁺ T cells, resulting in the inhibition of Th17 development in a STAT1-dependent manner (Reviewed in [144]).

5.2. Endogenous control of effector T cells

All effector T cell subsets (Th1, Th2, Th17) have the ability to acquire IL-10 production, thereby limiting their own pathogenicity [145]. This mechanism of self control has been very well described for Th17 cells (Figure 2): During particular bacterial and viral infection, naïve T cells maturate in effector Th17 cells and contribute to the eradication of infections. However, if the Th17 response is too strong and potentially life threatening, Th17 cells are redirected to the small intestine in order to be controlled [40]. The reason why mature Th17
cells migrate mainly to the small intestine is because of the high expression of the chemokine receptor CCR6 [146]. The highest concentration of CCL20, the ligand of CCR6, is indeed in the small intestine [40]. Interestingly, IL-17A and IL-17F promote the release of CCL20 from epithelial cells in the duodenum. The recruited Th17 cells also produce CCL20, furthermore amplifying CCL20 production. This suggests that Th17 cells implement through a positive feedback loop the recruitment of other Th17 cells to the small intestine. Once effector Th17 cells migrated to the intestine, two complementary mechanisms occur in order to control them. First, effector Th17 cells are washed out and eliminated via the intestinal lumen due to the strong tissue destruction and diarrhoea. Secondly, Th17 cells are reprogrammed in regulatory Th17 (rTh17) cells. This last mechanism relays on the plasticity of these cells. In the intestine, effector Th17 cells acquire the capacity to produce IL-10 [40] and in parallel express IL-10Rα. If Th17 cells cannot respond to IL-10, they acquire a “promiscuous” phenotype co-expressing IFN-γ and promote the inflammation in the small intestine [114].

![Diagram of Th17 cell control](image)

**Figure 2. Endogenous control of Th17 cells in the intestine.** A strong Th17 response leads to the redirection of effector Th17 (eTh17) cells to the small intestine. Once eTh17 cells migrated to the intestine, two complementary mechanisms occur in order to control them. First, eTh17 cells are washed out and eliminated via the intestinal lumen due to the strong tissue destruction and diarrhoea. Secondly, Th17 cells are reprogrammed in regulatory Th17 (rTh17) cells.

### 5.3. Exogenous control of effector T cells via regulatory T cells

Importantly, other control mechanisms, which do not rely on the “sense of responsibility” of effector T helper cells, are also present (Figure 3). Regulatory T cells play an essential role for controlling T helper cells. The two most studied regulatory T cell subsets are Foxp3+ Treg and Tr1 cells. Foxp3+ Tregs can be induced in the periphery (Foxp3+ iTregs) or in the thymus (Foxp3+ tTregs). Interestingly, Foxp3+ iTregs are induced in the intestine by TCR recognition of commensal antigens [101, 104, 105, 147]. Foxp3+ iTregs cells are obviously non-bacteria specific, but nevertheless can be activated by some bacterial species in the intestine [106]. It
is also important that Foxp3\(^+\) iTregs and Foxp3\(^+\) tTregs perform complementary functions, in part by expanding the TCR diversity [111].

**Figure 3. Control of effector T helper cells in the intestine.** Different regulatory T cells can efficiently suppress specific T helper cell subsets in the intestine.

Although different types of regulatory T cells can partially compensate each other, it seems that regulatory T cells can also have a more specialized function, and suppress specific types of effector T cells more potent then others: mice with a selective deficiency in iTreg cells develop spontaneous intestinal inflammation, which is characterized by an expansion of Th2 cells [113], indicating that iTregs play an important role in controlling Th2 cells in the intestine. Moreover expression of GATA-3 and IRF-4, master regulators of Th2 cells, by Foxp3\(^+\) Treg cells is important for the control of Th2 cells [148, 149]. Additionally, some
Foxp3+ Treg cells can express T-bet the master transcriptional regulator of Th1 cells. These T-bet+Foxp3+ Tregs express CXCR3, which is also highly expressed by Th1 cells. Thanks to the expression of the same chemokine receptor T-bet+Foxp3+ Tregs can better “follow” and in turn suppress Th1 cells [150]. Finally, it was shown that IL-10 can induce IL-10 production by Foxp3+ Treg via STAT3 activation, and Foxp3+IL-10+ Tregs are particularly important to control Th17 cells [76, 138, 151]. In addition to Foxp3+ Treg the immune system uses an alternative type of regulatory T cell, which can compensate a possible paucity of Foxp3+ Treg in order to avoid immune pathology in the intestine [112]. These cells, Tr1 cells, which are characterized by an abundant production of IL-10 and by the absence of Foxp3 expression, exert an efficient regulation of Th17 cells in the intestine [114]. Interestingly, IL-10 seems to play a non-redundant role in controlling Th17 cells: acting on both Th17 cells and regulatory T cells. Th17 cells are suppressed directly via IL-10, which is produced by Tr1 and Foxp3+Treg cells [114, 136]. Additionally, IL-10 acts on Foxp3+Treg. It activates STAT3 in Foxp3+Tregs, which is crucial to enable them to suppress Th17 cells [138, 151]. Moreover IL-10 signalling in Foxp3+Treg cells is required to promote IL-10 production [138] (Figure 3).

In conclusion Foxp3+ Treg cells can have different phenotypes. This feature allows Foxp3+ Tregs to suppress specific effector T cells more efficiently. Additionally Foxp3+ Tregs can team up with Tr1 cells to maintain the immune homeostasis in the intestine.

However, regulatory T cells do not only suppress effector T cells but can also promote effector T cell function in some settings [152, 153], indicating that the immune system aims to maintain a proper balance between regulatory and effector T cells rather then uncontrolled suppression of effector T cells.

6. Conclusions

CD4+ T helper cells have important physiological functions at the large intestinal mucosal surface: they secrete cytokines thereby attracting other immune cells, inducing antimicrobial peptides, and promoting tissue repair. Therefore effector CD4+ T helper cells play an important ‘border patrol’ function, and protect the body against infections. Thymic derived naïve CD4+ T cells express bacterial antigen specific TCRs. Encounter with these bacterial derived foreign antigens in the colon can drive the differentiation of regulatory T cells or pro-inflammatory effector T cells dependent on the bacteria and the environmental milieu. If effector CD4+ T helper cells are uncontrolled, they can elicit tissue damage and induce disease such as IBD. Therefore the immune system has established several mechanisms in order to control pro-inflammatory T helper cells. These mechanisms are primarily important to avoid immune pathology and in turn to maintain tolerance in the intestine. However a growing body of evidence suggests that these mechanisms can also be used to suppress other organ specific diseases. One example for this interaction between the intestine and another organ is that the commensal gut flora can trigger a T-cell mediated immune response, which leads to autoimmune disease in the brain [99]. Therefore one
possible strategy for the treatment of autoimmune diseases in future would be to specifically target the gut flora. Although the mechanisms controlling effector T cells in the intestine work well in most humans, the frequency of autoimmune and chronic inflammatory disease is steadily increasing. Unfortunately, there are currently no curative treatments for these diseases available. Therefore the patients suffer from the side effects of the drugs and from the relapses of their disease. The challenge will be to better understand the mechanisms controlling effector T cells in order to establish new and potentially curative treatments for autoimmune and chronic inflammatory diseases. The intestine has the potential to serve as the key target organ of these therapies.

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7. References

[1] Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK (2006) Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 7090: 235-8.

[2] Korn T, Bettelli E, Oukka M, Kuchroo VK (2009) IL-17 and Th17 Cells. Annu Rev Immunol. 485-517.

[3] Zheng W, Flavell RA (1997) The transcription factor GATA-3 is necessary and sufficient for Th2 cytokine gene expression in CD4 T cells. Cell. 4: 587-96.

[4] 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. 6: 1121-33.

[5] Szabo SJ, Kim ST, Costa GL, Zhang X, Fathman CG, Glimcher LH (2000) A novel transcription factor, T-bet, directs Th1 lineage commitment. Cell. 6: 655-69.

[6] Zhu J, Yamane H, Paul WE (2010) Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol. 445-89.

[7] Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL (1986) Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. J Immunol. 7: 2348-57.

[8] Hsieh CS, Macatonia SE, Tripp CS, Wolf SF, O'Garra A, Murphy KM (1993) Development of TH1 CD4+ T cells through IL-12 produced by Listeria-induced macrophages. Science. 5107: 547-9.

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[9] Usui T, Preiss JC, Kanno Y, Yao ZJ, Bream JH, O'Shea JJ, Strober W (2006) T-bet regulates Th1 responses through essential effects on GATA-3 function rather than on IFNG gene acetylation and transcription. J Exp Med. 3: 755-66.

[10] Usui T, Nishikomori R, Kitani A, Strober W (2003) GATA-3 suppresses Th1 development by downregulation of Stat4 and not through effects on IL-12Rbeta2 chain or T-bet. Immunity. 3: 415-28.

[11] 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. 5553: 338-42.

[12] Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL (2006) Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol. 6: 347-61.

[13] Le Gros G, Ben-Sasson SZ, Seder R, Finkelman FD, Paul WE (1990) Generation of interleukin 4 (IL-4)-producing cells in vivo and in vitro: IL-2 and IL-4 are required for in vitro generation of IL-4-producing cells. J Exp Med. 3: 921-9.

[14] Seder RA, Boulay JL, Finkelman F, Barbier S, Ben-Sasson SZ, Le Gros G, Paul WE (1992) CD8+ T cells can be primed in vitro to produce IL-4. J Immunol. 6: 1652-6.

[15] Swain SL, Weinberg AD, English M, Huston G (1990) IL-4 directs the development of Th2-like helper effectors. J Immunol. 11: 3796-806.

[16] Kaplan MH, Schindler U, Smiley ST, Grusby MJ (1996) Stat6 is required for mediating responses to IL-4 and for development of Th2 cells. Immunity. 3: 313-9.

[17] Shimoda K, van Deursen J, Sangster MY, Sarawar SR, Carson RT, Tripp RA, Chu C, Quelle FW, Nosaka T, Vignali DA, Doherty PC, Grosveld G, Paul WE, Ihle JN (1996) Lack of IL-4-induced Th2 response and IgE class switching in mice with disrupted Stat6 gene. Nature. 6575: 630-3.

[18] Takeda K, Tanaka T, Shi W, Matsumoto M, Minami M, Kashiwamura S, Nakanishi K, Yoshida N, Kishimoto T, Akira S (1996) Essential role of Stat6 in IL-4 signalling. Nature. 6575: 627-30.

[19] Kurata H, Lee HJ, O'Garra A, Arai N (1999) Ectopic expression of activated Stat6 induces the expression of Th2-specific cytokines and transcription factors in developing Th1 cells. Immunity. 6: 677-88.

[20] Zhu J, Guo L, Watson CJ, Hu-Li J, Paul WE (2001) Stat6 is necessary and sufficient for IL-4’s role in Th2 differentiation and cell expansion. J Immunol. 12: 7276-81.

[21] Zhang DH, Cohn L, Ray P, Bottomly K, Ray A (1997) Transcription factor GATA-3 is differentially expressed in murine Th1 and Th2 cells and controls Th2-specific expression of the interleukin-5 gene. J Biol Chem. 34: 21597-603.

[22] Zhu J, Min B, Hu-Li J, Watson CJ, Grinberg A, Wang Q, Killeen N, Urban JF, Jr., Guo L, Paul WE (2004) Conditional deletion of Gata3 shows its essential function in T(H)1-T(H)2 responses. Nat Immunol. 11: 1157-65.

[23] Zhu J, Cote-Sierra J, Guo L, Paul WE (2003) Stat5 activation plays a critical role in Th2 differentiation. Immunity. 5: 739-48.
[24] Urban JF, Jr., Noben-Trauth N, Donaldson DD, Madden KB, Morris SC, Collins M, Finkelman FD (1998) IL-13, IL-4-alpha, and Stat6 are required for the expulsion of the gastrointestinal nematode parasite Nippostrongylus brasiliensis. Immunity. 2: 255-64.

[25] Anthony RM, Rutitzky LI, Urban JF, Jr., Stadecker MJ, Gause WC (2007) Protective immune mechanisms in helminth infection. Nat Rev Immunol. 12: 975-87.

[26] Anthony RM, Urban JF, Jr., Alem F, Hamed HA, Rozo CT, Boucher JL, Van Rooijen N, Gause WC (2006) Memory T(H)2 cells induce alternatively activated macrophages to mediate protection against nematode parasites. Nat Med. 8: 955-60.

[27] Hasnain SZ, Evans CM, Roy M, Gallagher AL, Kindrachuk KN, Barron L, Dickey BF, Wilson MS, Wynn TA, Gencris RK, Thornton DJ (2011) Muc5ac: a critical component mediating the rejection of enteric nematodes. J Exp Med. 5: 893-900.

[28] Herbert DR, Yang JQ, Hogan SP, Groschwitz K, Khodoun M, Munitz A, Orekov T, Perkins C, Wang Q, Brombacher F, Urban JF, Jr., Rothenberg ME, Finkelman FD (2009) Intestinal epithelial cell secretion of RELM-beta protects against gastrointestinal worm infection. J Exp Med. 13: 2947-57.

[29] Artis D, Wang ML, Kelbaugh SA, He W, Brenes M, Swain GP, Knight PA, Donaldson DD, Lazar MA, Miller HR, Schad GA, Scott P, Wu GD (2004) RELMbeta/FIZZ2 is a goblet cell-specific immune-effector molecule in the gastrointestinal tract. Proc Natl Acad Sci U S A. 37: 13596-600.

[30] Akiho H, Blennerhassett P, Deng Y, Collins SM (2002) Role of IL-4, IL-13, and STAT6 in inflammation-induced hypercontractility of murine smooth muscle cells. Am J Physiol Gastrointest Liver Physiol. 2: G226-32.

[31] Cliffe LJ, Humphreys NE, Lane TE, Potten CS, Booth C, Gencris RK (2005) Accelerated intestinal epithelial cell turnover: a new mechanism of parasite expulsion. Science. 5727: 1463-5.

[32] Zhou L, Ivanov, II, Spolski R, Min R, Shenderov K, Egawa T, Levy DE, Leonard WJ, Littman DR (2007) IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. Nat Immunol. 9: 967-74.

[33] Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, Schluns K, Tian Q, Watowich SS, Jetten AM, Dong C (2007) Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. Nature. 7152: 480-3.

[34] Yang XO, Panopoulos AD, Nurieva R, Chang SH, Wang D, Watowich SS, Dong C (2007) STAT3 regulates cytokine-mediated generation of inflammatory helper T cells. J Biol Chem. 13: 9358-63.

[35] Veldhoen M, Hocking RJ, Atkins CJ, Locksley RM, Stockinger B (2006) TGF-beta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells. J Exp Med. 2: 179-89.

[36] Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR, Weaver CT (2006) Transforming growth factor-beta induces development of the T(H)17 lineage. Nature. 7090: 231-4.

[37] Zhou L, Lopes JE, Chong MM, Ivanov, II, Min R, Victora GD, Shen Y, Du J, Rubtsov VP, Rudensky AY, Ziegler SF, Littman DR (2008) TGF-beta-induced Foxp3 inhibits T(H)17 cell differentiation by antagonizing RORgammat function. Nature. 7192: 236-40.
[38] McGeachy MJ, Chen Y, Tato CM, Laurence A, Joyce-Shaikh B, Blumenschein WM, McClanahan TK, O’Shea JJ, Cua DJ (2009) The interleukin 23 receptor is essential for the terminal differentiation of interleukin 17-producing effector T helper cells in vivo. Nat Immunol. 3: 314-24.

[39] Ahern PP, Schiering C, Buonocore S, McGeachy MJ, Cua DJ, Maloy KJ, Powrie F (2010) Interleukin-23 drives intestinal inflammation through direct activity on T cells. Immunity. 2: 279-88.

[40] 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. 7357: 514-8.

[41] Ivanov, II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, Wei D, Goldfarb KC, Santee CA, Lynch SV, Tanoue T, Imaoka A, Itoh K, Takeda K, Umesaki Y, Honda K, Littman DR (2009) Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 3: 485-98.

[42] Atarashi K, Nishimura J, Shima T, Umesaki Y, Yamamoto M, Onoue M, Yagita H, Ishii N, Evans R, Honda K, Takeda K (2008) ATP drives lamina propria T(H)17 cell differentiation. Nature. 7214: 808-12.

[43] Shaw MH, Kamada N, Kim YG, Nunez G (2012) Microbiota-induced IL-1beta, but not IL-6, is critical for the development of steady-state TH17 cells in the intestine. J Exp Med. 2: 251-8.

[44] Zielinski CE, Mele F, Aschenbrenner D, Jarrossay D, Ronchi F, Gattorno M, Monticelli S, Lanzanocechia A, Sallusto F (2012) Pathogen-induced human T(H)17 cells produce IFN-gamma or IL-10 and are regulated by IL-1beta. Nature.

[45] 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. 7318: 967-71.

[46] 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. 12: 1390-7.

[47] Veldhoen M, Hirota K, Christensen J, O’Garra A, Stockinger B (2009) Natural agonists for aryl hydrocarbon receptor in culture medium are essential for optimal differentiation of Th17 T cells. J Exp Med. 1: 43-9.

[48] Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld JC, Stockinger B (2008) The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature. 7191: 106-9.

[49] Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF, Bettelli E, Caccamo M, Oukka M, Weiner HL (2008) Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. Nature. 7191: 65-71.

[50] O’Connor W, Jr., Zenewicz LA, Flavell RA (2010) The dual nature of T(H)17 cells: shifting the focus to function. Nat Immunol. 6: 471-6.
[51] Apetoh L, Quintana FJ, Pot C, Joller N, Xiao S, Kumar D, Burns EJ, Sherr DH, Weiner HL, Kuchroo VK (2010) The aryl hydrocarbon receptor interacts with c-Maf to promote the differentiation of type 1 regulatory T cells induced by IL-27. Nat Immunol. 9: 854-61.

[52] Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, Ho AW, Hai JH, Yu JJ, Jung JW, Filler SG, Masso-Welch P, Edgerton M, Gaffen SL (2009) Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med. 2: 299-311.

[53] Huang W, Na L, Fidel PL, Schwarzenberger P (2004) Requirement of interleukin-17A for systemic anti-Candida albicans host defense in mice. J Infect Dis. 3: 624-31.

[54] Ye P, Garvey PB, Zhang P, Nelson S, Bagby G, Summer WR, Schwarzenberger P, Shellito JE, Kolls JK (2001) Interleukin-17 and lung host defense against Klebsiella pneumoniae infection. Am J Respir Cell Mol Biol. 3: 335-40.

[55] Iwakura Y, Nakae S, Saijo S, Ishigame H (2008) The roles of IL-17A in inflammatory immune responses and host defense against pathogens. Immunol Rev. 57-79.

[56] Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, Fujikado N, Tanahashi Y, Akitsu A, Kotaki H, Sudo K, Nakae S, Sasakawa C, Iwakura Y (2009) Differential roles of interleukin-17A and -17F in host defense against mucoeithelial bacterial infection and allergic responses. Immunity. 1: 108-19.

[57] Ouyang W, Kolls JK, Zheng Y (2008) The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 4: 454-67.

[58] Pelletier M, Maggi L, Micheletti A, Lazzeri E, Tamassia N, Costantini C, Cosmi L, Lunardi C, Annunziato F, Romagnani S, Cassatella MA (2010) Evidence for a cross-talk between human neutrophils and Th17 cells. Blood. 2: 335-43.

[59] Kao CY, Chen Y, Thai P, Wachi S, Huang F, Kim C, Harper RW, Wu R (2004) IL-17 markedly up-regulates beta-defensin-2 expression in human airway epithelium via JAK and NF-kappaB signaling pathways. J Immunol. 5: 3482-91.

[60] Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, Fouser LA (2006) Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. J Exp Med. 10: 2271-9.

[61] Zheng Y, Valdez PA, Danilenko DM, Hu Y, Sa SM, Gong Q, Abbas AR, Modrusan Z, Ghilardi N, de Sauvage FJ, Ouyang W (2008) Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. Nat Med. 3: 282-9.

[62] Zenewicz LA, Yancopoulos GD, Valenzuela DM, Murphy AJ, Stevens S, Flavell RA (2008) Innate and adaptive interleukin-22 protects mice from inflammatory bowel disease. Immunity. 6: 947-57.

[63] Pickert G, Neufert C, Leppkes M, Zheng Y, Wittkopf N, Warntjen M, Lehr HA, Hirth S, Weigmann B, Wirtz S, Ouyang W, Neurath MF, Becker C (2009) STAT3 links IL-22 signaling in intestinal epithelial cells to mucosal wound healing. J Exp Med. 7: 1465-72.

[64] Sugimoto K, Ogawa A, Mizoguchi E, Shimomura Y, Andoh A, Bhan AK, Blumberg RS, Xavier RJ, Mizoguchi A (2008) IL-22 ameliorates intestinal inflammation in a mouse model of ulcerative colitis. J Clin Invest. 2: 534-44.

[65] Sakaguchi S, Sakaguchi N, Asano M, Itoh M, Toda M (1995) Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25).
Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases. J Immunol. 3: 1151-64.

[66] Fontenot JD, Gavin MA, RudenskyAY (2003) Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. Nat Immunol. 4: 330-6.

[67] Hori S, Nomura T, Sakaguchi S (2003) Control of regulatory T cell development by the transcription factor Foxp3. Science. 5609: 1057-61.

[68] Huber S, Schramm C, Lehr HA, Mann A, Schmitt S, Becker C, Protschka M, Galle PR, Neurath MF, Blessing M (2004) Cutting edge: TGF-beta signaling is required for the in vivo expansion and immunosuppressive capacity of regulatory CD4+CD25+ T cells. J Immunol. 11: 6526-31.

[69] Schramm C, Huber S, Protschka M, Czochra P, Burg J, Schmitt E, Lohse AW, Galle PR, Blessing M (2004) TGFbeta regulates the CD4+CD25+ T-cell pool and the expression of Foxp3 in vivo. Int Immunol. 9: 1241-9.

[70] Fantini MC, Becker C, Monteleone G, Pallone F, Galle PR, Neurath MF (2004) Cutting edge: TGF-beta induces a regulatory phenotype in CD4+CD25- T cells through Foxp3 induction and down-regulation of Smad7. J Immunol. 9: 5149-53.

[71] Chen W, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, McGrady G, Wahl SM (2003) Conversion of peripheral CD4+CD25- naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. J Exp Med. 12: 1875-86.

[72] Kretschmer K, Apostolou I, Hawiger D, Khazaie K, Nussenzweig MC, von Boehmer H (2005) Inducing and expanding regulatory T cell populations by foreign antigen. Nat Immunol. 12: 1219-27.

[73] Marie JC, Letterio JJ, Gavin M, RudenskyAY (2005) TGF-beta1 maintains suppressor function and Foxp3 expression in CD4+CD25+ regulatory T cells. J Exp Med. 7: 1061-7.

[74] Bennett CL, Christie J, Ramsdell F, Brunckow 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. 1: 20-1.

[75] Brunckow ME, Jeffery EW, Hjerrild KA, Paepers B, Clark LB, Yasayko SA, Wilkinson JE, Galas D, Ziegler SF, Ramsdell F (2001) Disruption of a new forkhead/winged-helix protein, scurfyn, results in the fatal lymphoproliferative disorder of the scurfy mouse. Nat Genet. 1: 68-73.

[76] Huber S, Gagliani N, Esplugues E, O’Connor W, Jr., Huber FJ, Chaudhry A, Kamanaka M, Kobayashi Y, Booth CJ, RudenskyAY, 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. 4: 554-65.

[77] Fahlen L, Read S, Gorelik L, Hurst SD, Coffman RL, Flavell RA, Powrie F (2005) T cells that cannot respond to TGF-[-beta] escape control by CD4+CD25+ regulatory T cells. J Exp Med. 5: 737-46.

[78] Annunziato F, Cosmi L, Liotta F, Lazzeri E, Manetti R, Vanini V, Romagnani P, Maggi E, Romagnani S (2002) Phenotype, localization, and mechanism of suppression of CD4(+)CD25(+) human thymocytes. J Exp Med. 3: 379-87.
[79] Bopp T, Becker C, Klein M, Klein-Hessling S, Palmetshofer A, Serfling E, Heib V, Becker M, Kubach J, Schmitt S, Stoll S, Schild H, Staege MS, Stassen M, Jonuleit H, Schmitt E (2007) Cyclic adenosine monophosphate is a key component of regulatory T cell-mediated suppression. J Exp Med. 6: 1303-10.

[80] Roncarolo MG, Gregori S, Battaglia M, Bacchetta R, Fleischhauer K, Levings MK (2006) Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol Rev. 28-50.

[81] Haringer B, Lozza L, Steckel B, Geginat J (2009) Identification and characterization of IL-10/IFN-gamma-producing effector-like T cells with regulatory function in human blood. J Exp Med. 5: 1009-17.

[82] Vieira PL, Christensen JR, Minae S, O'Neill DJ, Barrat FJ, Boonstra A, Barthlott T, Storkinger B, Wraith DC, 'Garra (2004) IL-10-secreting regulatory T cells do not express Foxp3 but have comparable regulatory function to naturally occurring CD4+CD25+ regulatory T cells. J Immunol. 10: 5986-93.

[83] Maynard CL, Harrington LE, Janowski KM, Oliver JR, Zindl CL, Rudensky AY, Weaver CT (2007) Regulatory T cells expressing interleukin 10 develop from Foxp3+ and Foxp3-precursor cells in the absence of interleukin 10. Nat Immunol. 9: 931-41.

[84] Passerini L, Di Nunzio S, Gregori S, Gambineri E, Ceconni M, Seidel MG, Cazzola G, Perroni L, Tommasini A, Vignola S, Guidi L, Roncarolo MG, Bacchetta R (2011) Functional type 1 regulatory T cells develop regardless of FOXP3 mutations in patients with IPEX syndrome. Eur J Immunol. 4: 1120-31.

[85] Groux H, O'Garra A, Bigler M, Rouleau M, Antonenko S, de Vries JE, Roncarolo MG (1997) A CD4+ T-cell subset inhibits antigen-specific T-cell responses and prevents colitis. Nature. 6652: 737-42.

[86] Gagliani N, Jofra T, Stabilini A, Valle A, Atkinson M, Roncarolo MG, Battaglia M (2010) Antigen-specific dependence of Tr1-cell therapy in preclinical models of islet transplant. Diabetes. 2: 433-9.

[87] Pot C, Apetoh L, Awasthi A, Kuchroo VK (2010) Molecular pathways in the induction of interleukin-27-driven regulatory type 1 cells. J Interferon Cytokine Res. 6: 381-8.

[88] Cobbold SP, Nolan KF, Graca L, Castejon R, Le Moine A, Frewin M, Humm S, Adams E, Thompson S, Zelenika D, Paterson A, Yates S, Fairchild PJ, Waldmann H (2003) Regulatory T cells and dendritic cells in transplantation tolerance: molecular markers and mechanisms. Immunol Rev. 109-24.

[89] Pestka S, Krause CD, Sarkar D, Walter MR, Shi Y, Fisher PB (2004) Interleukin-10 and related cytokines and receptors. Annu Rev Immunol. 929-79.

[90] Cavani A, Nasorri F, Prezzi C, Sebastiani S, Albaraez C, Girolomoni G (2000) Human CD4+ T lymphocytes with remarkable regulatory functions on dendritic cells and nickel-specific Th1 immune responses. J Invest Dermatol. 2: 295-302.

[91] Strobl H, Emshoff R, Rothler G (1999) Conservative treatment of unilateral condylar fractures in children: a long-term clinical and radiologic follow-up of 55 patients. Int J Oral Maxillofac Surg. 2: 95-8.

[92] Cerwenka A, Swain SL (1999) TGF-beta1: immunosuppressant and viability factor for T lymphocytes. Microbes Infect. 15: 1291-6.
[93] Levings MK, Gregori S, Tresoldi E, Cazzaniga S, Bonini C, Roncarolo MG (2005) Differentiation of Tr1 cells by immature dendritic cells requires IL-10 but not CD25+CD4+ Tr cells. Blood. 3: 1162-9.

[94] Gregori S, Tomasoni D, Pacciani V, Scirpoli M, Battaglia M, Magnani CF, Hauben E, Roncarolo MG (2010) Differentiation of type 1 T regulatory cells (Tr1) by tolerogenic DC-10 requires the IL-10-dependent ILT4/HLA-G pathway. Blood. 6: 935-44.

[95] Grossman WJ, Verbsky JW, Tollefsen BL, Kemper C, Atkinson JP, Ley TJ (2004) Differential expression of granzymes A and B in human cytotoxic lymphocyte subsets and T regulatory cells. Blood. 9: 2840-8.

[96] Grossman WJ, Verbsky JW, Barchet W, Colonna M, Atkinson JP, Ley TJ (2004) Human T regulatory cells can use the perforin pathway to cause autologous target cell death. Immunity. 4: 589-601.

[97] Magnani CF, Alberigo G, Bacchetta R, Serafini G, Andreani M, Roncarolo MG, Gregori S (2011) Killing of myeloid APCs via HLA class I, CD2 and CD226 defines a novel mechanism of suppression by human Tr1 cells. Eur J Immunol. 6: 1652-62.

[98] Huber S, Schramm C (2006) TGF-beta and CD4+CD25+ regulatory T cells. Front Biosci. 1014-23.

[99] Berer K, Mues M, Koutrolos M, Rasbi ZA, Boziki M, Johner C, Wekerle H, Krishnamoorthy G (2011) Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature. 7374: 538-41.

[100] Elinav E, Strowig T, Kau AL, Henao-Mejia J, Thaiss CA, Booth CJ, Peaper DR, Bertin J, Eisenbarth SC, Gordon JI, Flavell RA (2011) NLRP6 inflammasome regulates colonic microbial ecology and risk for colitis. Cell. 5: 745-57.

[101] Lathrop SK, Bloom SM, Rao SM, Nutsch K, Lio CW, Santacruz N, Peterson DA, Stappenbeck TS, Hsieh CS (2011) Peripheral education of the immune system by colonic commensal microbiota. Nature. 7368: 250-4.

[102] Decker E, Hornef M, Stockinger S (2011) Cesarean delivery is associated with celiac disease but not inflammatory bowel disease in children. Gut Microbes. 2: 91-8.

[103] Benson MJ, Pino-Lagos K, Roseblatt M, Noelle RJ (2007) All-trans retinoic acid mediates enhanced T reg cell growth, differentiation, and gut homing in the face of high levels of co-stimulation. J Exp Med. 8: 1765-74.

[104] Hadis U, Wahl B, Schulz O, Hardtke-Wolenski M, Schippers A, Wagner N, Muller W, Sparwasser T, Forster R, Pabst O (2011) Intestinal tolerance requires gut homing and expansion of FoxP3+ regulatory T cells in the lamina propria. Immunity. 2: 237-46.

[105] Cassani B, Villablanca EJ, Quintana FJ, Love PE, Lacy-Hulbert A, Blaneer WS, Sparwasser T, Snapper SB, Weiner HL, Mora JR (2011) Gut-Tropic T Cells That Express Integrin alpha4beta7 and CCR9 Are Required for Induction of Oral Immune Tolerance in Mice. Gastroenterology.

[106] Geuking MB, Cahenzli J, Lawson MA, Ng DC, Slack E, Hapfelmeier S, McCoy KD, Macpherson AJ (2011) Intestinal bacterial colonization induces mutualistic regulatory T cell responses. Immunity. 5: 794-806.

[107] Huber S, Schramm C (2011) Role of activin A in the induction of Foxp3+ and Foxp3-CD4+ regulatory T cells. Crit Rev Immunol. 1: 53-60.
[108] Huber S, Stahl FR, Schrader J, Luth S, Presser K, Carambia A, Flavell RA, Werner S, Blessing M, Herkel J, Schramm C (2009) Activin a promotes the TGF-beta-induced conversion of CD4+CD25- T cells into Foxp3+ induced regulatory T cells. J Immunol. 8: 4633-40.

[109] Fantini MC, Becker C, Tubbe I, Nikolaev A, Lehr HA, Galle P, Neurath MF (2006) Transforming growth factor beta induced FoxP3+ regulatory T cells suppress Th1 mediated experimental colitis. Gut. 5: 671-80.

[110] Mottet C, Uhlig HH, Powrie F (2003) Cutting edge: cure of colitis by CD4+CD25+ regulatory T cells. J Immunol. 8: 3939-43.

[111] Haribhai D, Williams JB, Jia S, Nickerson D, Schmitt EG, Edwards B, Ziegelbauer J, Yassai M, Li SH, Rolland LM, Wise PM, Chen A, Zheng YQ, Simpson PM, Gorski J, Salzman NH, Hessner MJ, Chatila TA, Williams CB (2011) A requisite role for induced regulatory T cells in tolerance based on expanding antigen receptor diversity. Immunity. 1: 109-22.

[112] 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. 7282: 808-12.

[113] Josefowicz SZ, Niec RE, Kim HY, Treuting P, Chinen T, Zheng Y, Umetsu DT, Rudensky AY (2012) Extrathymically generated regulatory T cells control mucosal TH2 inflammation. Nature. 7385: 395-9.

[114] 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. 4: 554-65.

[115] Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, Fiocchi C, Strober W (1996) Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn’s disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. J Immunol. 3: 1261-70.

[116] Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki K, Bamba T, Fujiyama Y (2003) Increased expression of interleukin 17 in inflammatory bowel disease. Gut. 1: 65-70.

[117] Rovedatti L, Kudo T, Biancheri P, Sarra M, Knowles CH, Rampton DS, Corazza GR, Monteleone G, Di Sabatino A, Macdonald TT (2009) Differential regulation of interleukin 17 and interferon gamma production in inflammatory bowel disease. Gut. 12: 1629-36.

[118] Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, Parente E, Fili L, Ferri S, Frosali F, Giudici F, Romagnani P, Parronchi P, Tonelli F, Maggi E, Romagnani S (2007) Phenotypic and functional features of human Th17 cells. J Exp Med. 8: 1849-61.

[119] Brand S, Beigel F, Olszak T, Zitzmann K, Eichhorst ST, Otte JM, Diepolder H, Marquardt A, Jagla W, Popp A, Leclair S, Herrmann K, Seiderer J, Ochsenkuhn T, Goke B, Auernhammer CJ, Dambacher J (2006) IL-22 is increased in active Crohn’s disease...
and promotes proinflammatory gene expression and intestinal epithelial cell migration.

Am J Physiol Gastrointest Liver Physiol. 4: G827-38.

[120] Seiderer J, Elben I, Diegelmann J, Glas J, Stallhofer J, Tillack C, Pfennig S, Jurgens M, Schmechel S, Konrad A, Goke B, Ochsenkuhn T, Muller-Myhsok B, Lohse P, Brand S (2008) Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn’s disease and analysis of the IL17F p.His161Arg polymorphism in IBD. Inflamm Bowel Dis. 4: 437-45.

[121] Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO, Schumm LP, Lee AT, Gregersen PK, Barnada MM, Rotter JL, Nicolae DL, Cho JH (2006) A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 5804: 1461-3.

[122] Franke A, McGovern DP, Barrett JC, Wang K, Radford-Smith GL, Ahmad T, Lees CW, Balschun T, Lee J, Roberts R, Anderson CA, Bis JC, Bumpstead S, Ellinghaus D, Festen EM, Georges M, Green T, Haritunians T, Jostins L, Latiano A, Mathew CG, Montgomery GW, Prescott NJ, Raychaudhuri S, Rotter JI, Schumm P, Sharma Y, Simms LA, Taylor KD, Whitman D, Wijmenga C, Baldassano RN, Barclay M, Bayless TM, Brand S, Buning C, Cohen A, Colombel JF, Cottone M, Stronati L, Denson T, De Vos M, D’Inca R, Dubinsky M, Edwards C, Florin T, Franchimont D, Gearry R, Glas J, Van Gossum A, Guthery SL, Halfvarson J, Verspaget HW, Hugot JP, Karban A, Laukens D, Lawrance I, Lemann M, Levine A, Libiolle C, Louis E, Mowat C, Newman W, Panes J, Phillips A, Proctor DD, Regueiro M, Russell R, Rutgeerts P, Sanderson J, Sans M, Seibold F, Steinhardt AH, Stokkers PC, Torkvist L, Kullak-Ublick G, Wilson D, Walters T, Targan SR, Brant SR, Rioux JD, D’Amato M, Weersma RK, Kugathasan S, Griffiths AM, Mansfield JC, Vermeire S, Duerr RH, Silverberg MS, Satsangi J, Schreiber S, Cho JH, Annese V, Hakonarson H, Daly MJ, Parkes M (2010) Genome-wide meta-analysis increases to 71 the number of confirmed Crohn’s disease susceptibility loci. Nat Genet. 12: 1118-25.

[123] Anderson CA, Boucher G, Lees CW, Franke A, D’Amato M, Taylor KD, Lee JC, Goyette P, Imielinski M, Latiano A, Lagace C, Scott R, Amininejad L, Bumpstead S, Baidoo L, Baldassano RN, Barclay M, Bayless TM, Brand S, Buning C, Colombel JF, Denson LA, De Vos M, Dubinsky M, Edwards C, Ellinghaus D, Fehrmann RS, Floyd JA, Florin T, Franchimont D, Franke L, Georges M, Glaser J, Glazer NL, Guthery SL, Haritunians T, Hayward NK, Hugot JP, Jobin G, Laukens D, Lawrance I, Lemann M, Levine A, Libiolle C, Louis E, McGovern DP, Milla M, Montgomery GW, Morley KL, Mowat C, Ng A, Newman W, Ophoff RA, Papi L, Palmieri O, Peyrin-Biroulet L, Panes J, Phillips A, Prescott NJ, Proctor DD, Roberts R, Rutgeerts P, Sanderson J, Sans M, Schumm P, Seibold F, Sharma Y, Simms LA, Seielstad M, Steinhart AH, Targan SR, van den Berg LH, Vatn M, Verspaget H, Walters T, Wijmenga C, Wilson DC, Westra HJ, Xavier RJ, Zhao ZZ, Ponsioen CY, Andersen V, Torkvist L, Gazouli M, Anagnou NP, Karslen TH, Kupcinskas L, Sventoraityte J, Mansfield JC, Kugathasan S, Silverberg MS, Halfvarson J, Rotter JI, Mathew CG, Griffiths AM, Gearry R, Ahmad T, Brant SR, Chamaillard M, Satsangi J, Cho JH, Schreiber S, Daly MJ, Barrett JC, Parkes M, Annese
V, Hakonarson H, Radford-Smith G, Duerr RH, Vermeire S, Weersma RK, Rioux JD (2011) Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. Nat Genet. 3: 246-52.

[124] Glas J, Stallhofer J, Ripke S, Wetzel M, Pfennig S, Klein W, Epplen JT, Griga T, Schiemann U, Lacher M, Koletzko S, Folwaczny M, Lohse P, Goke B, Ochesnkuhn T, Muller-Myhsok B, Brand S (2009) Novel genetic risk markers for ulcerative colitis in the IL2/IL21 region are in epistasis with IL23R and suggest a common genetic background for ulcerative colitis and celiac disease. Am J Gastroenterol. 7: 1737-44.

[125] Miossec P, Korn T, Kuchroo VK (2009) Interleukin-17 and type 17 helper T cells. N Engl J Med. 9: 888-98.

[126] Lee YK, Turner H, Maynard CL, Oliver JR, Chen D, Elson CO, Weaver CT (2009) Late developmental plasticity in the T helper 17 lineage. Immunity. 1: 92-107.

[127] Wang C, Kang SG, Lee J, Sun Z, Kim CH (2009) The roles of CCR6 in migration of Th17 cells and regulation of effector T-cell balance in the gut. Mucosal Immunol. 2: 173-83.

[128] Elson CO, Cong Y, Weaver CT, Schoeb TR, McClanahan TK, Fick RB, Kastelein RA (2007) Monoclonal anti-interleukin 23 reverses active colitis in a T cell-mediated model in mice. Gastroenterology. 7: 2359-70.

[129] Zhang Z, Zheng M, Bindas J, Schwarzenberger P, Kolls JK (2006) Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. Inflamm Bowel Dis. 5: 382-8.

[130] Ogawa A, Andoh A, Araki Y, Bamba T, Fujiyama Y (2004) Neutralization of interleukin-17 aggravates dextran sulfate sodium-induced colitis in mice. Clin Immunol. 1: 55-62.

[131] Yang XO, Chang SH, Park H, Nurieva R, Shah B, Acero L, Wang YH, Schluns KS, Broaddus RR, Zhu Z, Dong C (2008) Regulation of inflammatory responses by IL-17F. J Exp Med. 5: 1063-75.

[132] 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. 6: 603-9.

[133] Wei G, Wei L, Zhu J, Zang C, Hu-Li J, Yao Z, Cui K, Kanno Y, Roh TY, Watford WT, Schones DE, Peng W, Sun HW, Paul WE, O'Shea JJ, Zhao K (2009) Global mapping of H3K4me3 and H3K27me3 reveals specificity and plasticity in lineage fate determination of differentiating CD4+ T cells. Immunity. 1: 155-67.

[134] Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, Cuff J, Fry B, Meissner A, Wernig M, Plath K, Jaenisch R, Wagschal A, Feil R, Schreiber SL, Lander ES (2006) A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell. 2: 315-26.

[135] Azuara V, Perry P, Sauer S, Spivakov M, Jorgensen HF, John RM, Gouti M, Casanova M, Warnes G, Merkenschlager M, Fisher AG (2006) Chromatin signatures of pluripotent cell lines. Nat Cell Biol. 5: 532-8.

[136] Kamanaka M, Huber S, Zeneswicz LA, Gaglani N, Rathinam C, O'Connor W, Jr., Wan YY, Nakae S, Iwakura Y, Hao L, Flavell RA (2011) Memory/effecter (CD45RB(lo)) CD4 T
cells are controlled directly by IL-10 and cause IL-22-dependent intestinal pathology. J Exp Med. 5: 1027-40.

[137] Powrie F, Leach MW, Mauze S, Menon S, Caddle LB, Coffman RL (1994) Inhibition of Th1 responses prevents inflammatory bowel disease in scid mice reconstituted with CD45RBhi CD4+ T cells. Immunity. 7: 553-62.

[138] Chaudhry A, Samstein RM, Treuting P, Liang Y, Pils MC, Heinrich JM, Jack RS, Wunderlich FT, Bruning JC, Muller W, Rudensky AY (2011) Interleukin-10 signaling in regulatory T cells is required for suppression of Th17 cell-mediated inflammation. Immunity. 4: 566-78.

[139] Witte E, Witte K, Warszawsk a K, Sabat R, Wolk K (2010) Interleukin-22: a cytokine produced by T, NK and NKT cell subsets, with importance in the innate immune defense and tissue protection. Cytokine Growth Factor Rev. 5: 365-79.

[140] Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, Hall J, Sun CM, Belkaid Y, Powrie F (2007) A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. J Exp Med. 8: 1757-64.

[141] Elias KM, Laurence A, Davidson TS, Stephens G, Kanno Y, Shevach EM, O'Shea JJ (2008) Retinoic acid inhibits Th17 polarization and enhances FoxP3 expression through a Stat-3/Stat-5 independent signaling pathway. Blood. 3: 1013-20.

[142] Laurence A, Tato CM, Davidson TS, Kanno Y, Chen Z, Yao Z, Blank RB, Meylan F, Siegel R, Hennighausen L, Shevach EM, O'Shea J J (2007) Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. Immunity. 3: 371-81.

[143] Yang XP, Ghoreschi K, Steward-Tharp SM, Rodriguez-Canales J, Zhu J, Grainger JR, Hirahara K, Sun HW, Wei L, Vahedi G, Kanno Y, O'Shea JJ, Laurence A (2011) Opposing regulation of the locus encoding IL-17 through direct, reciprocal actions of STAT3 and STAT5. Nat Immunol. 3: 247-54.

[144] Pot C, Apetoh L, Awasthi A, Kuchroo VK (2011) Induction of regulatory Tr1 cells and inhibition of T(H)17 cells by IL-27. Semin Immunol. 6: 438-45.

[145] Saraiva M, O'Garra A (2010) The regulation of IL-10 production by immune cells. Nat Rev Immunol. 3: 170-81.

[146] Reboldi A, Coisne C, Baumjohann D, Benvenuto F, Bottinelli D, Lira S, Uccelli A, Lanzavecchia A, Engelhardt B, Sallusto F (2009) C-C chemokine receptor 6-regulated entry of TH-17 cells into the CNS through the choroid plexus is required for the initiation of EAE. Nat Immunol. 5: 514-23.

[147] Gagliani N, Huber S, Flavell RA (2012) The Intestine: where amazing things happen. Cell Res. 2: 277-9.

[148] Wang Y, Su MA, Wan YY (2011) An essential role of the transcription factor GATA-3 for the function of regulatory T cells. Immunity. 3: 337-48.

[149] Zheng Y, Chaudhry A, Kas A, deRoos P, Kim JM, Chu TT, Corcoran L, Treuting P, Klein U, Rudensky AY (2009) Regulatory T-cell suppressor program co-opts transcription factor IRF4 to control T(H)2 responses. Nature. 7236: 351-6.
[150] 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 I inflammation. Nat Immunol. 6: 595-602.

[151] Chaudhry A, Rudra D, Treuting P, Samstein RM, Liang Y, Kas A, Rudensky AY (2009) CD4+ regulatory T cells control TH17 responses in a Stat3-dependent manner. Science. 3955: 986-91.

[152] Chen Y, Haines CJ, Gutcher I, Hochweller K, Blumenschein WM, McClanahan T, Hammerling G, Li MO, Cua DJ, McGeachy MJ (2011) Foxp3(+) regulatory T cells promote T helper 17 cell development in vivo through regulation of interleukin-2. Immunity. 3: 409-21.

[153] Gutcher I, Donkor MK, Ma Q, Rudensky AY, Flavell RA, Li MO (2011) Autocrine transforming growth factor-beta1 promotes in vivo Th17 cell differentiation. Immunity. 3: 396-408.