
Immunopathogenesis of inflammatory bowel diseases: functional role of T cells and T cell homing

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ABSTRACT

Inflammatory bowel diseases (IBD) are believed to arise from a complex interplay of environmental factors, genetic susceptibility, epithelial barrier defects and dysregulation of the intestinal immune system. Although the exact mechanisms of contribution and interference of these players are still not clear, significant advances have been achieved in understanding the immunopathogenesis of IBD in recent years resulting in novel and targeted therapeutic strategies.

We will begin this review by giving a brief outline of current pathogenetic concepts of IBD and then focus on the description of the present knowledge of T cell function and regulation in the context of IBD. Moreover, we will summarise the progress on the emerging field of gut homing and delineate some implications for future therapeutic approaches.

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the main entities of inflammatory bowel disease (IBD). While both of them are relapsing inflammatory disorders mainly involving the human gut and sharing many symptoms, they are distinguished by differences in terms of intestinal distribution, histological appearance and some clinical complications (1, 2).

Up to now, there is no comprehensive conception of IBD etiopathogenesis, which would be able to clearly explain the development of these diseases. Instead, it is agreed, that IBDs result from multifactorial events, which combine and interfere in a sophisticated manner. Lately, significant progress has been made in understanding many of these contributors.

For example, the role of genetic susceptibility is becoming more and more elucidated as novel techniques are

available for identifying single nucleotide polymorphisms (SNPs). Since 2001, when the NOD2 locus was the first to be associated with an increased risk for CD (3, 4), the list of candidate genes is constantly growing and a recent international study comprising over 75.000 samples reported a total of 163 susceptibility loci (5). Interestingly, 53 of these loci were specific for either UC or CD, while the others entailed a risk for both IBD phenotypes, therefore supporting the clinical observation that both disorders are distinct entities in spite of considerable overlap. Interestingly, a remarkable proportion of the proteins encoded by these genes, such as IL-23 receptor, IL-10, IFN- γ or STAT3, is implicated in T cell function, which will be the centre of this review.

Empirical observations have identified a number of environmental factors affecting the risk for developing IBD, among them smoking, lifestyle, hygiene, diet and the use of antibiotics and non-steroidal anti-inflammatory drugs (6). Many of these seem to influence the 'internal environment' of the gut microbiome. Consistently, significant changes in the intestinal microbiota like a decrease in the overall biodiversity and an enrichment of selected commensal organisms can be observed, promoting the idea that alterations in the interaction of gut bacteria and the mucosal immune system are a key event in IBD pathogenesis (7). Furthermore, evidence suggests that defects in the intestinal epithelial barrier function contribute therein by facilitating the access of the antigens of this dysbalanced microbiome to mucosal immune cells (8).

In genetically predisposed hosts, this translocation of luminal antigens finally leads to a dysregulated immune response driven by excessive and altered cytokine signalling of mucosal mac-

Competing interests:

M.F. Neurath served as an advisor for AbbVie, Giuliani, Pentax and Takeda. Additionally, he is co-holder of a patent for the IL-12/IL-23p40 antibody strategy in Crohn's disease.

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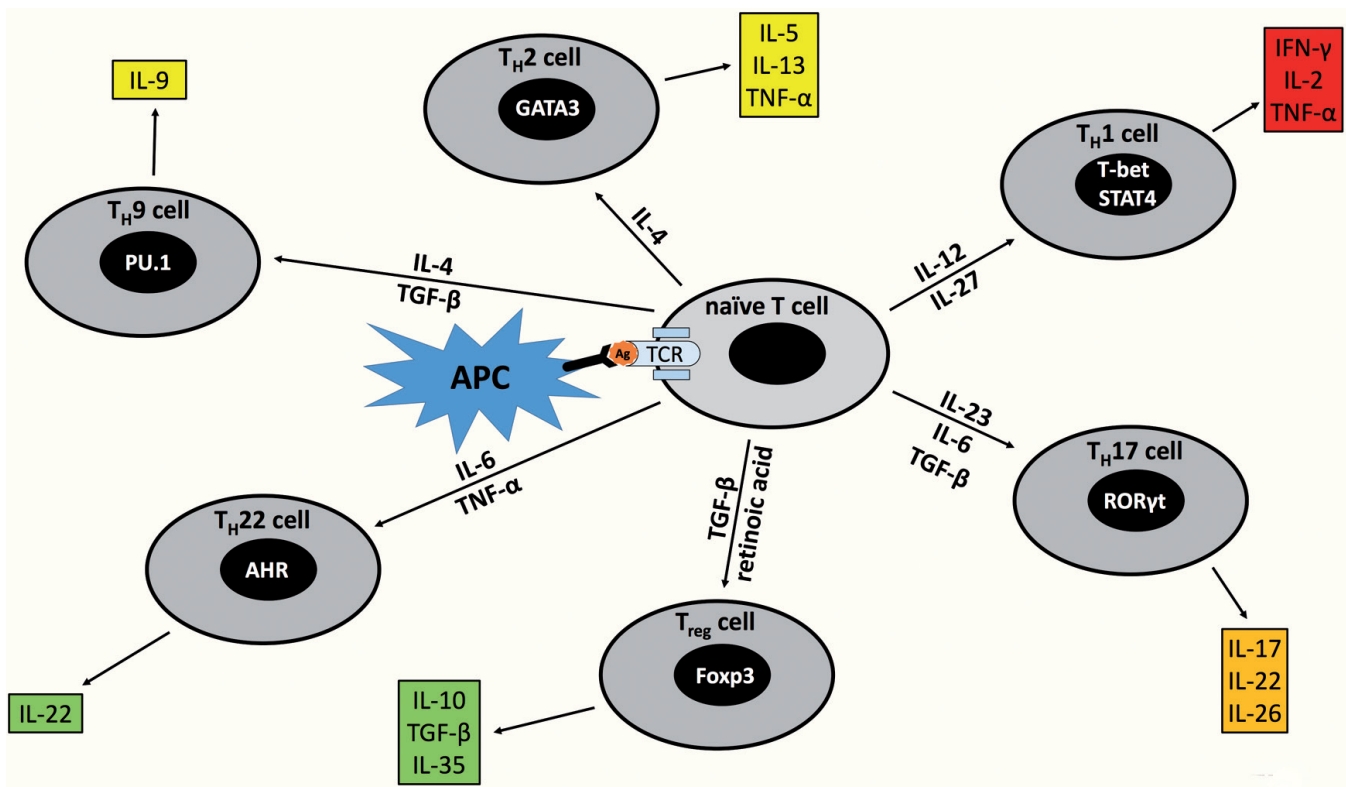


Fig. 1. CD4⁺ T cell subsets in IBD.

Upon encounter with their cognate antigen presented by antigen presenting cells (APCs) T cells differentiate into distinct subsets of effector T cells (T_H1, T_H2, T_H9, T_H17, T_H22) or regulator T cells (T_{reg}). This process is governed by the respective surrounding cytokine environment and goes along with the induction of specific transcription factors in each lineage as indicated. Thereupon, the secretion of specific cytokines or cytokine combinations is induced. T_H2 and T_H9 cells and their respective cytokines are believed to be predominantly involved in UC pathogenesis (yellow box), while T_H1 cells are thought to play a major role in CD (red box). T_H17 cells have been shown to be implicated in both conditions (orange box). Treg and T_H22 cells have rather protective functions in the context of intestinal mucosal inflammation (green box). TCR – T cell receptor.

rophages, T cells and innate lymphoid cells and resulting in mucosal inflammation with subsequent tissue injury and clinical symptoms (9).

While a detailed look at all the cellular players of the mucosal immune system would be beyond the scope of this review, we will focus on highlighting the role of T cells and their gut homing properties in the context of IBD.

T cells in IBD

Infiltration of the mucosa by T cells and the increased production of pro-inflammatory T cell cytokines are a hallmark of IBD (10). Blockade of TNF- α , which is produced by mucosal T cells as well as macrophages, fibroblasts and adipocytes (11, 12) is one of the most successful therapies for both CD and UC. Moreover, T cells are indispensable in many animal models of IBD (13).

Upon encounter with their cognate antigen, naïve T cells differentiate into ef-

factor (T_{eff}) or regulatory (T_{reg}) T cells depending on the present cytokine environment (14). A growing body of research indicates both an altered balance of different T cell lineages in IBD in general and differences between T cell signalling and function in CD and UC (Fig. 1). On the whole, CD is predominantly characterised by an enhanced aggregation and activation of the effector T cell lineages T helper (T_H)1 and T_H17, while counterregulatory T_{reg} function is inappropriately low. To the contrary, the profile of lamina propria T cells in UC mainly resembles T_H2 cells and T_H17 cytokines are also more frequently produced than in healthy controls (1, 2, 9, 10, 15–19). Collectively, even though many other cell types of the innate and adaptive immune system are indispensable for explaining the immune response in IBD, T cells are the key coordinators as they integrate and orchestrate signalling and functions of other cells (9).

T_H1 cells

T_H1 cells differentiate upon stimulation of naïve CD4⁺ cells with IL-12 and IL-27 under the control of transcription factors like T-bet and signal transducer and activator of transcription (STAT)4 and can be identified by the production of the T_H1 cytokines IFN- γ and IL-2 (16, 20, 21). Both these cytokines and the transcription factors have been found to be increased in CD compared to UC and healthy controls (10, 18, 19, 22), supporting the notion that CD might be a typical ‘T_H1-disease’. Findings in multiple animal models have encouraged this idea. For example, STAT4 deficiency and overexpression caused reduced and exacerbated experimental colitis respectively (23, 24). The blockade of IL-12/IL-23 p40 by a monoclonal antibody significantly ameliorated trinitrobenzene sulphonic acid (TNBS)-induced colitis (25) and similarly, antibody-induced neutralisation of IFN- γ prevented T_H1 responses

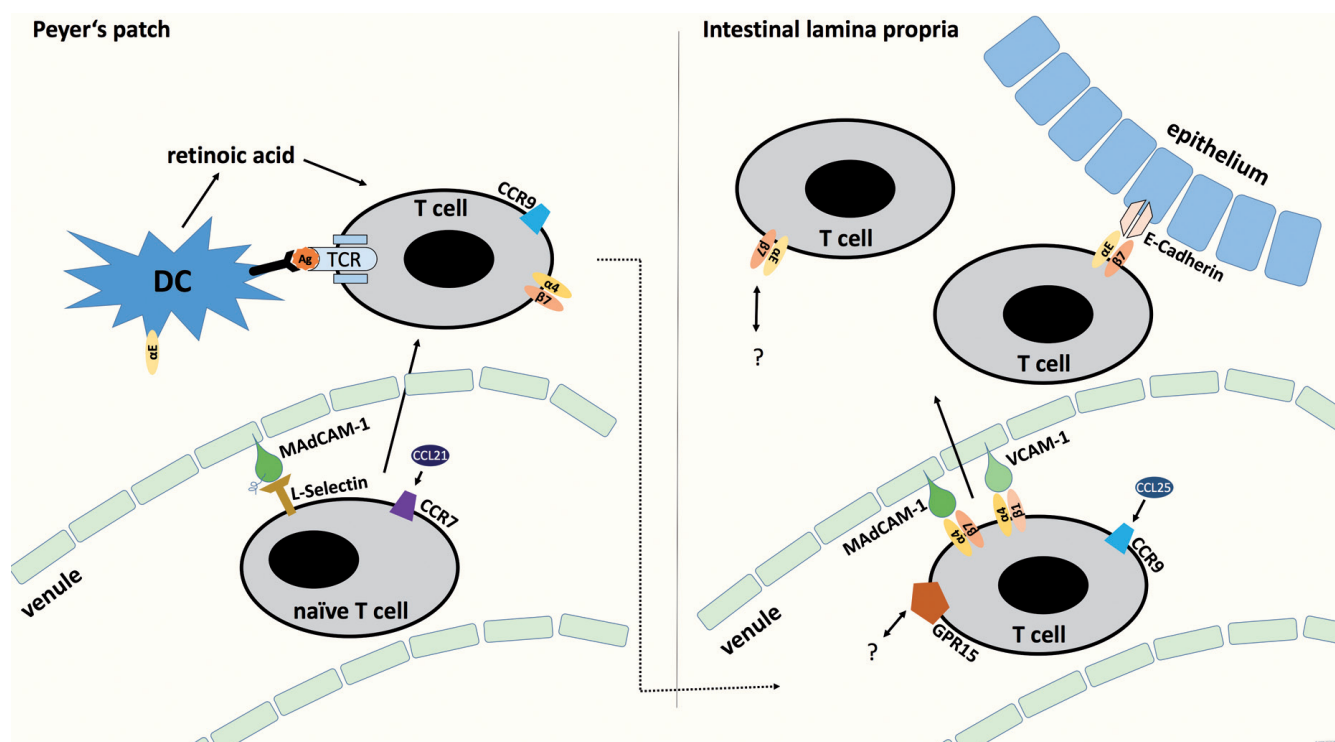


Fig. 2. Overview of gut homing of T cells.

Left side: Naïve T cells express L-Selectin and CCR7, which allow them to home to Peyer's patches via interaction with carbohydrate-modified MAdCAM-1 and CCL21. There, CD103 (α E)⁺ dendritic cells (DCs) not only function as antigen presenting cells but induce the expression of specific gut homing markers like α 4 β 7 and CCR9 at the same time. Retinoic acid produced by DC-derived retinal dehydrogenase importantly contributes to this upregulation.

Right side: Mature T cells that have been shaped like that are then able to home to the intestinal lamina propria. This homing process involves tethering to and rolling at the venular wall. Lymphocytes are then activated by chemokines, most importantly CCL25, which binds to CCR9, and come to a halt through interaction of integrins with their receptors, for example α 4 β 7 with the gut-specific MAdCAM-1 or α 4 β 1 with VCAM-1. GPR15 is a newly designated homing marker with an up to now unknown ligand. After extravasation, especially intraepithelial lymphocytes express α E β 7 to interact with epithelial E-Cadherin. The role of α E β 7 in lamina propria lymphocytes is still obscure.

and development of inflammation in a T cell transfer model of colitis (26).

When it was tried to translate these results from bench to bedside, however, the first attempts in targeting T_H1 signalling were quite disappointing. Namely, the anti-IFN- γ antibody fontolizumab failed to induce remission in CD (27). This confirms that it seems helpful, but not completely sufficient to categorise IBDs in a simple T_H1/T_H2 paradigm and emphasises that it is necessary to extend the view on other CD4⁺ T cell subsets.

T_H2 cells

The development of T_H2 cells occurs under the stimulus of IL-4 and subsequent upregulation of the transcription factors GATA3 and STAT6. Their cytokine profile is defined by the production of IL-4, IL-5 and IL-13 (28). As T cells from the mucosa of patients with UC have been demonstrated to secrete more IL-5 and IL-13 (but less IL-4) and

express more GATA3, UC is thought to constitute a (slightly atypical) T_H2-like disease with important contribution of IL-13-secreting natural killer (NK) cells (10, 29, 30, 31). Mechanistically, it seems that IL-13 negatively affects the intestinal epithelial barrier by increased apoptosis of intestinal epithelial cells (IECs), enhanced expression of pore-forming claudin-2 and decreased epithelial wound healing (30). Compatibly, STAT6-deficient mice were protected from oxazolone-induced colitis and displayed a marked reduction in T_H2 cytokines and a decrease in claudin-2 (32). Furthermore, a specific IL-13 antibody prevented the development of experimental colitis in this model (33) as well as blockade of the T_H2 response-inducing cytokine IL-25 or its receptor (34). In contrast, though, a recent study could not confirm an elevated IL-13 production in UC (35) and phase II studies of the IL-13 antibodies tralokinumab and anrukinzumab in UC

could not demonstrate clinical effectiveness (36, 37). Therefore, as applies for the T_H1-like milieu in CD, further studies will be necessary to clarify the exact contribution of the T_H2 cytokines to the pathogenesis of UC and to determine, whether alternative approaches in targeting T_H2 signalling might be therapeutically effective.

In 2005, it was shown that IL-33, which is recognised by its receptor ST2, induces T_H2 cells to produce T_H2-associated cytokines (38). Since then, several groups have found an upregulation of both IL-33 and ST2 in UC and proposed a role of this signalling axis in driving the T_H2-like response in this disorder (39, 40, 41, 42, 43). Interestingly, ST2 deficiency significantly improved colitis by promotion of mucosal healing in two experimental models and treatment with IL-33 led to epithelial barrier breakdown (44). In addition, IL-33 worsened dextran sodium sulphate (DSS)-induced colitis in an

IL-4-dependent manner (45). However, it has to be mentioned that a protective effect of IL-33 in TNBS-induced colitis has been described as well (46). Moreover, a recent study linked IL-33/ST2 signalling to T_{reg} differentiation, accumulation and maintenance rather than T_H2 responses in intestinal inflammation. Thus, the precise function of this axis has to be defined in future investigations, but yet it seems possible that novel therapeutic approaches might arise in this context.

T_H17 cells

The discovery of the IL-12 family member IL-23 in the year 2000 (47) and the demonstration of its ability to act independently of IL-12 (48) eventually led to the identification of IL-23-dependent T_H17 cells as a distinct T cell subset (49). IL-23, together with other cytokines like IL-6, IL-1 β , IL-21, TNF-like protein (TL)1A and transforming growth factor (TGF)- β (50-53) serves as inducer of T_H17 development. On transcription factor level, this is controlled by STAT3, retinoic acid orphan receptor (ROR) γ t, interferon regulatory factor (IRF)4 and basic leucine zipper transcription factor (Batf) (54). The secretion profile of T_H17 cells is mainly characterised by IL-17A, IL-17F, IL-22 and IL-26 (55, 56).

Meanwhile, the functional role of T_H17 cells in IBD has been extensively studied. Special interest has been dedicated to this T cell population as several genetic polymorphisms associated with IBD – for example IL-23R, IL-12p40, STAT3, JAK2 (5) – are related to T_H17 differentiation. Moreover, it seems that T_H17 cells contribute to the link between the intestinal microbiome and the dysregulated immune response in IBD, because a specific upregulation of T_H17 cell activity by intestinal bacteria could be demonstrated (57, 58). Further evidence for an important role of T_H17 cells in the context of IBD has been added by the finding that T_H17 cytokines are excessively produced by T cells in the lamina propria of UC and CD patients (15, 17, 59, 60). Additionally, surface markers of T_H17 cells (61) and the above mentioned transcription factors responsible for T_H17 develop-

ment could be demonstrated in the gut of IBD patients (15, 62).

The exact nature of T_H17 cells in IBD still needs to be clarified as different studies report both pro- and anti-inflammatory functions in mice as well as in human. The potential of T cells deficient for IRF4, ROR γ t or IL-23 to induce experimental colitis after T cell transfer is greatly decreased or even absent (63-65), indicating that T_H17 cells are a key driver of intestinal inflammation. To the contrary, deficiency or inhibition of the T_H17 cytokines IL-17A and IL-17F did not alter or even exacerbate colitis (64, 66, 67), which is consistent with the idea that T_H17 cytokines either have redundant effects or in some cases even exert protective function. The latter assumption was especially proposed for IL-17A (66). Other reports favouring a rather tissue-destructive role of T_H17 cytokines include an IL-17-mediated upregulation of pro-inflammatory cytokines such as IL-6, IL-8, IL-1 β and TNF- α (68, 69) and an increase in chemokine production and leukocyte infiltration (70). At the same time, T_H17 cells can also produce IL-22 (55), which seems to protect from mucosal inflammation and is discussed below in greater detail.

Furthermore, a clinical trial targeting IL-17A with the neutralising antibody secukinumab not only showed the inefficacy of this treatment for CD but also reported more adverse events (71). This impressively confirms that neither have T_H17 cells in human IBD been sufficiently characterised up to date nor can a single cytokine reflect the nature of a whole T cell subset. Thus, inhibiting or promoting several cytokines at the same time or targeting the underlying T cell population itself (*e.g.* on transcription factor level) might be a potentially successful strategy.

What further complicates the situation is that effector T cell lineages are plastic and can transdifferentiate into other T cell subsets. Particularly, T_H17 cells (and IFN- γ producing T_H17/T_H1 cells) were shown to be able to become T_H1 cells, when IL-12 and IL-23 is present, while TGF- β is lacking (72-74). Consistently, T_{reg} cells inhibited the transition of T_H17 cells to T_H1 cells (75).

Moreover, it has been recently shown, that T_H1 cells can also turn into T_H17 cells upon stimulation with TGF- β and IL-6 (76). It is therefore possible that such converted T cell populations that are clearly distinct from their precursors might critically contribute to maintenance of mucosal inflammation (73) and thereby make the identification of the right therapeutic targets even more difficult.

T_H9 cells

T_H9 cells have been recently recognised as an independent effector T cell subset (77). Their differentiation is controlled by IL-4 in combination with TGF- β , which induce the transcription factors purine-rich box 1 (PU.1), IRF4 and STAT6 (78-80). In turn, signalling via T-box expressed in T cells (T-bet) and GATA-binding protein 3 (GATA3) is suppressed, which would promote T_H1 and T_H2 development respectively (81, 82). T_H9 cells are characterised by producing IL-9 and sometimes also IL-10 (83). They are therefore believed to play a role in pathologic processes such as allergic airway inflammation, control of tumour growth and autoimmune encephalomyelitis (84-87).

Today, there is considerable evidence, that T_H9 cells are also implicated in the immunopathogenesis of IBD, especially of UC. In two recent studies, significantly more IL-9 producing and PU.1-expressing T cells could be detected in the mucosa of UC patients. Moreover, IL-9 receptor was upregulated on the intestinal epithelium of these patients (88, 89). Consistently, oxazolone-induced colitis in mice, an animal model mimicking UC, was crucially dependent on T_H9 cells as mice deficient for IL-9, treated with an IL-9 antibody or lacking PU.1 in CD4⁺ cells developed less severe colitis. Impairment of the intestinal epithelial barrier through downregulation of barrier proteins such as claudin 2 and inhibition of mucosal wound healing by IL-9 were demonstrated to be likely mediators of these findings (88). A later study revealed that IL-9 deficiency also protects from TNBS-induced colitis (90). Collectively, these results suggest, that IL-9 might become a future target for IBD treatment.

T_H22 cells

Like T_H9 cells, T_H22 cells have only been lately assigned the status of an independent effector T cell population. While their signature cytokine IL-22 was first identified to be produced by T_H17 cells, it is now clear that there exists a distinct subset of CD4⁺ T cells that produces IL-22, but not IL-17 or IFN- γ . T_H22 cells are further characterised by the expression of the C-C chemokine receptor type (CCR)4, CCR6 and CCR10, which are implicated in skin homing and were therefore initially believed to be important in skin pathologies (91). A T_H22 phenotype is promoted by stimulation of naïve CD4⁺ T cells with IL-6 and TNF- α and controlled by the aryl hydrocarbon receptor (AHR) as the most important transcription factor (92).

Increasingly, T_H22 cells are found to be of importance in the orchestration of T cell balance in IBD, although they are not the only source of IL-22 in the human intestine. Initial studies showed that IL-22 function reduces disease severity in animal models of colitis and identified STAT3 as potential mediator of this effect (93, 94). Later, it was demonstrated, that IL-22-induced STAT3 activation in intestinal epithelial cells (IECs) is vital for mucosal wound healing (95). Moreover, it seems to be necessary for the secretion of antibacterial peptides and mucus proteins (96, 97). A protective role for T_H22 was confirmed by the demonstration that an agonist of AHR is protective in different mouse models of colitis, while both an AHR antagonist and an IL-22-blocking antibody caused increased disease severity (98). Furthermore, it was found that the number of T_H22 cells is decreased in the lamina propria of UC patients and that increased TGF- β might lead to this depletion, therefore suggesting a pathogenetic relevance of T_H22 cells and also favouring protective functions. To the contrary, production of IL-22 by T cells contributed to intestinal inflammation in a memory T cell induced colitis model (99), indicating that T_H22 effects may vary depending on the inflammatory context.

Taken together, the exact function of T_H22 cells in human IBD remains to be

elucidated, but most findings point at a rather anti-inflammatory role, which advocates the idea that enhancing T_H22 function might be a prospective therapeutic strategy in IBD.

T_{reg} cells

Regulatory T cells (T_{regs}) are a T cell subset with marked immunosuppressive properties and have therefore attained particular interest in relation to IBD. They are found in two different forms: 'Natural' Tregs (nT_{regs}) and 'induced' Tregs (iT_{regs}), which are both characterised by expression of the transcription factor forkhead box protein 3 (Foxp3) (100, 101). The first development in the thymus upon high-affinity binding of antigens to their T cell receptor (TCR) and concomitant IL-2 stimulation leading to Foxp3 upregulation (102, 103). The latter emerge from naïve T cells in the periphery driven by TGF- β , which activates Smad 2, 3 and 4 molecules to induce Foxp3 (104–106). It has to be noted that TGF- β is also crucial for T_H17 development as discussed above. Yet, differentiation to T_H17 cells requires co-signalling of IL-6 and retinoic acid has been shown to be capable of suppressing T_H17 in favour of T_{reg} development (107, 108). Interestingly, bacterial metabolites such as the short-chain fatty acid butyrate have also been reported to promote intestinal iT_{reg} formation (109, 110). Similarly, iT_{regs} are induced by TGF- β , which is released from apoptotic cells (111). This suggests, that in intestinal tissues facing loads of bacteria and with a high turnover of self-antigens, a tight control of the T_{reg}/T_{eff} balance is necessary to prevent pathology.

T_{regs} exert their immunosuppressive role by different means. One important mechanism is the secretion of anti-inflammatory cytokines such as TGF- β , IL-10 or IL-35 (112, 113, 114). Another is based upon direct interaction with other cells through receptors like cytotoxic T lymphocyte-associated protein 4 (CTLA4), glucocorticoid-induced tumour necrosis factor receptor (GITR) or galectin-1 (115–117). The potential anti-colitogenic activity of T_{regs} has been demonstrated in different mouse

models. Mice that lack signalling through the T_{reg} cytokines TGF- β or IL-10 spontaneously develop colitis (118, 119). Co-transfer of T_{regs} in transfer colitis models suppresses colitis (120, 121) and TGF- β and IL-10 are essential mediators of this anti-inflammatory function (122, 123).

Different studies aiming at determining the presence and characterisation of T_{regs} in human IBD have shown that active IBD lesions contain more T_{regs} than appropriate controls and that the anti-inflammatory potential of these T_{regs} is preserved (124, 125). While this finding seems to contradict the perception of an undercontrolled inflammatory response in IBD, it can be explained by two approaches: First, it seems that not the absolute number of T_{reg} cells but the ratio of T_{eff} and T_{reg} cells is important (121, 124) and the increased T_{reg} population in IBD therefore fails to control the even more aggrandised T_{eff} accumulations. Accordingly, a first study evaluating the adoptive transfer of expanded T_{regs} in CD to extend the T_{reg} pool suggested potential efficacy (126). And second, there is strong evidence, that T_{eff} cells are resistant to T_{reg}-mediated suppression, e.g. by upregulation of inhibitory Smad7 (112). The relevance of this concept has already been proven by a clinical study exploring a Smad7 antisense oligonucleotide in the therapy of CD, which showed tremendous beneficial effects (127). Taken together, directly increasing the T_{reg} population by adoptive transfer or indirectly boosting its function are two very promising strategies that are currently evaluated for clinical therapy.

Gut homing

Before exerting their deleterious or protective functions within the lamina propria, T cells have to enter the gut mucosa in a complex process called homing, which takes place in postcapillary venules. A multistep model is used to explain the different events involved. First, mainly selectins initiate tethering to activated endothelial cells and rolling of lymphocytes at the venular wall, followed by chemokine-induced lymphocyte activation and eventually integrin-mediated arrest. After intensi-

fication of the adhesion and slow crawling along the epithelium, cells will then migrate paracellularly or transcellularly to the site of inflammation (128, 129). This sequence has attracted notable attention in the last years as specifically interfering with gut homing may be a promising extension of the therapeutic armamentarium in IBD. Consistently, the $\alpha 4$ integrin antibody natalizumab was successfully used to treat IBD patients (130) until some cases of progressive multifocal leukoencephalopathy (PML) were reported (131). These were believed to be due to inhibition of leukocyte trafficking to the central nervous system and have therefore lead to intensified efforts to develop selective gut homing strategies. As a result, the $\alpha 4\beta 7$ integrin blocking antibody vedolizumab has found entry into clinical practice recently (132, 133).

A gut homing phenotype is induced on naïve T cells in the mucosa associated lymphoid tissue (MALT) of the intestine (Fig. 2). Expression of CCR7 and L-selectin allows these naïve T cells to access intestinal secondary lymphoid tissues via interaction with chemokine C-C motif ligand (CCL)21 and carbohydrate-modified mucosal addressin cellular adhesion molecule (MAdCAM)-1 respectively (134, 135). Here, particularly CD103⁺ dendritic cells (DCs) function as antigen-presenting cells and induce the upregulation of specific gut-homing markers such as $\alpha 4\beta 7$ and CCR9 (136). Retinoic acid serves as transcription factor for $\alpha 4\beta 7$ and CCR9 and, interestingly, only gut DCs express retinal dehydrogenases, which process retinol to retinoic acid (137). Other receptors reported to be expressed on gut homing lymphocytes include CCR10, CCR5 or CXCR3. After T cells have been primed this way, they re-enter the circulation and are then able to specifically home to the gut lamina propria, where they may engage in the IBD immune response.

$\alpha 4\beta 7$ is the ligand of MAdCAM-1, which is exclusively found on venules in the intestine (138). In contrast, vascular cell adhesion molecule (VCAM)-1, which is the receptor for the integrin $\alpha 4\beta 1$ can also be detected in other tissues including the central nervous sys-

tem (131). Therefore, the latter interaction is believed to be responsible for the infectious complications observed with natalizumab. CCR9 is the receptor for CCL25, a chemokine which is mainly produced by epithelial cells of the small intestine, but is not found in the colon (139). While targeting $\alpha 4\beta 7$ by vedolizumab is now an established strategy in inhibiting T cell trafficking to the gut mucosa, targeting CCR9 with vernerin, an oral inhibitor, yielded rather disappointing results in clinical trials (140). Currently, several other compounds interfering with gut homing, are evaluated. One is PF-00547659, an antibody directed against MAdCAM-1, which was effective in moderate to severe UC in a recent phase II-trial (141). Moreover, the $\beta 7$ -antibody etrolizumab has shown promising results for the treatment of UC so far (142). As $\beta 7$ appears not only in combination with $\alpha 4$ but also with αE , etrolizumab might offer a dual mechanism of action. Though, the knowledge about $\alpha E\beta 7$ is scarce, but the picture which can be drawn today is that $\alpha 4\beta 7$ is downregulated on CD8⁺ T cells after they reach the intestinal lamina propria and $\alpha E\beta 7$ is upregulated in turn in a CCL25-mediated manner (143). $\alpha E\beta 7$ may then interact with E-Cadherin, its main ligand, on the basolateral side of the intestinal epithelium and therefore favour retention of lymphocytes in the epithelial compartment (139). Consistently, the vast majority of intraepithelial lymphocytes is $\alpha E\beta 7^{+}$ (144). What precise role $\alpha E\beta 7$ plays in the context of intestinal homing of CD4⁺ cells, however, has not been addressed so far. Moreover, αE knockdown in mice results in a reduced infiltrate of lymphocytes not only in the epithelium but also in the lamina propria, where E-Cadherin is not present (145), and $\alpha E\beta 7$ is expressed by lamina propria lymphocytes (LPL) in IBD patients (146). A possible explanation could be that $\alpha E\beta 7$ also plays a role in extravasation as it has been shown to promote adhesion of lymphocytes to endothelial cells in an E-Cadherin-independent fashion through a yet unknown receptor as well (147).

Recently, GPR15 has been proposed as another receptor which is specifically

involved in homing to the large intestine. In a GPR15-deficient mouse model, especially T_{reg} homing was down-regulated and resulted in aggravation of colitis (148). In contrast, almost none GPR15⁺ T_{regs} could be found in human LPL (149). Consistently, a first assessment of GPR15 function in human IBD favoured a role of GPR15 for homing of T_{eff} but not T_{reg} cells (150).

Thus, gut homing is an emerging field with a promising outlook for novel targeted therapies. Yet, considerable efforts have to be undertaken to clarify the lots of unresolved questions concerning this complex process.

Concluding remarks

While it is beyond doubt that T lymphocytes are key drivers of both UC and CD and many of the pro- and anti-inflammatory properties of different T cell subsets have been elucidated, most of the attempts to specifically target the involved cytokines, receptors or signalling pathways have failed or demonstrated only limited efficiency in recent years (9). Therefore, alternative approaches will be necessary to offer new therapies to the large portion of patients, who do still not respond to the currently available drugs. Inhibiting the gut homing of T cells and promoting T_{reg} populations or functions seem to be two such approaches with great potential. Others might be individualised medicine aiming at the identification of patients who will respond to a certain treatment (151), the targeting of several cytokines at one time (152) or sophisticated strategies to deliver drugs to the desired site of action (153, 154). Regarding these points, there is hope that the next years will bring forth new and successful strategies to control T cell-mediated inflammation in IBD.

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