activities. It both directly and indirectly causes the destruction of target tissues, and, in a succession of recent studies, IL-17 has been demonstrated to play a central role in many other chronic immune diseases in addition to EAE.

It now appears that TGF-β and IL-6 are essential for induction of Th17 cells in mice [31–33] and that IL-23 acts at the final maturation and maintenance step [34,35]. Actually, there is also a report that the Th17 cells that are induced *in vitro* by TGF-β and IL-6 alone produce both IL-17 and the inhibitory cytokine IL-10 and do not induce inflammation, whereas Th17 cells that have been stimulated with IL-23 after stimulation with TGF-β and IL-6 produce other pro-inflammatory cytokines and chemokines, but not IL-10, and are involved in inflammation [34]. The mechanism of Th17 induction in humans seems to be even more complex. Actually, initially there were many reports that it was difficult to induce human peripheral blood naive $CD4^+$ T cells to induce Th17 in the presence of TGF-β and IL-6 *in vitro*, and Acosta-Rodriguez *et al.* [36,37] reported that IL-1β and IL-6, not TGF-β, are important to induction of human Th17 and ruled out involvement of TGF-β in human Th17 production. However, several other groups [38••,39,40] recently demonstrated the role of TGF-β and the Th17 differentiation pathway in humans apparently resembles that of mice. There are already numerous detailed general review articles concerning Th17 [8–12].

As stated above, murine Th17 cells emerge when naive $CD4^+$ T cells are stimulated with antigen in the presence of TGF-β and IL-6. In contrast, in the presence of TGF-β alone, naive $CD4^+$ T cells differentiate into $Foxp3^+$ T_R cells, and retinoic acid has been found to further promote differentiation into T_R cells at that time. In the presence of IFN-γ, naive $CD4^+$ T cells differentiate into Th1 cells and into Th2 cells in the presence of IL-4 [26]. Moreover, the existence of new Th cell subpopulations has recently been suggested by differentiation into IL-10-producing Tr-1 cells in response to TGF-β and IL-27 [41,42] and into IL-9-producing Th9 cells in response to TGF-β and IL-4 [43,44], making T-cell immunity increasingly complex.

Intestinal Th17 cells

Well then, are Th17 cells a pathological cell population that is present only in individuals who have developed an immune disease? Ivanov *et al.* [45] showed that Th17 cells are always specifically present as resident cells in the small intestine of normal mice even in health and that the orphan nuclear receptor RORγt is a Th17-cell mouse gene. As indicated by the Th1 master gene being *t-bet* and the Th2 master gene being *GATA-3*, Th17 cells appear to be an independent T-cell population. RORγt was already known to be a molecule that is specifically expressed in the LTi cells that are present in the cryptopatches in the small intestine, and it may be possible to describe Th17 cells as unique cells that arise in the small intestine [45,46]. Actually, RORγt knockout mice lack cryptopatch cells, and their intestine is devoid of Th17 cells [45]. Atarashi *et al.* [21••] also showed that because Th17 cells gradually increase in number after birth and dramatically decrease in germ-free mice, they are enteric-bacteria-dependent cells. Moreover, they found that under specific pathogen free (SPF) conditions, they are equally present in $MyD88^{-/-} \times Trif^{-/-}$ mice, the same as in normal mice. Finally, they also found that the ATP produced by certain intestinal bacteria induces intestinal Th17 cells by instructing $CD70^+$ dendritic cells [21••]. Moreover, they also showed that Th17 cells are present in the normal large intestine and that when ATP was administered to a model of chronic colitis, the number of Th17 cells increased and worsening of the colitis was observed [21••]. However, the function of the naturally occurring Th17 cells that are enteric-bacteria-dependently present in healthy mice is still unknown. Zaph *et al.* [47] reported inducing IL-25 as a result of intestinal bacteria-stimulating intestinal epithelial cells and that the IL-25 inhibited Th17 induction. IL-25, also called IL-17E, is a cytokine that belongs to the IL-17 family. As a result of the above, the inhibitory function of IL-25 is lost in the germ-free environment in which no intestinal bacteria are present, and the number of Th17 cells in the mucosa of the large intestine increases. Th17 cells increase in the mucosa of the large intestine of IL-25 knockout mice.

Th17 cells and inflammatory bowel disease

A succession of studies conducted in human IBD and various models of IBD has reported the central role of Th17 cells. Fujino *et al.* [48] conducted immunohistochemistry studies and observed stronger IL-17 protein expression in the inflamed mucosa in both ulcerative colitis and Crohn's disease than in healthy volunteers or at noninflamed sites in IBD. Seiderer *et al.* [49] observed stronger IL-17 mRNA expression in inflamed mucosa than in noninflamed mucosa in Crohn's disease. Nielsen's group [50], on the other hand, found that IL-17 mRNA was strongly expressed in the intestinal mucosa in Crohn's disease regardless of the degree of disease activity and that it was more strongly expressed at active sites in the intestinal mucosa in ulcerative colitis than in healthy volunteers. Similarly, Hölttä *et al.* [51] found increased expression of IL-23 protein as well as IL-17 protein in immunohistological studies of the intestinal mucosa in Crohn's disease, regardless of the degree of disease activity. By contrast, we detected significantly increased IL-17 mRNA expression in the intestinal mucosa in ulcerative colitis in comparison with normal mucosa [52]. On the other hand, in contrast to published reports, though there was a tendency to increase in

mucosa in which Crohn's disease was active, the difference was not significant [52]. Moreover, when $CD4^+$ T cells isolated from inflamed sites were stimulated with anti-CD3/anti-CD28 antibodies, a significant increase in IL-17 secretion was observed in the ulcerative colitis group [52]. On the other hand, though a tendency for IL-17 protein secretion by $CD4^+$ T cells isolated from active sites in the mucosa in Crohn's disease to increase was observed to be the same as in an assessment of IL-17 mRNA, the difference was not significant [52]. It is interesting that significantly higher expression of the IL-23 component units p40 and p19 as well as of retinoid-related orphan receptor C (RORC) and IL-23R was observed in active mucosa than in normal mucosa in both ulcerative colitis and Crohn's disease [52]. Furthermore, our own research group has demonstrated local increases in $CD14^+CD209^+$ special macrophages in the intestine in Crohn's disease [53]. The $CD14^+$ macrophages in Crohn's disease produce excessive IL-23 in response to exposure to enteric bacteria, and it has also been found that IL-23 acts on T cells and natural killer (NK) cells promoting IFN-γ production. Interestingly, high production of IFN-γ was confirmed by stimulating lamina propria mononuclear cells (LPMCs) from the intestine of Crohn's disease patients with IL-23 or enteric bacteria, but it was impossible to confirm production of IL-17. In view of the above, it is possible that IL-23 production by macrophages is increased locally in the intestine in Crohn's disease and it acts on both Th1 and Th17 cells, but that IL-17 production is inhibited by other humoral factors, especially by the Th1 cytokine IFN-γ.

Inflammatory bowel disease therapy by targeting Th17 cells

As the involvement of the IL-23/IL-17 axis in IBD was being elucidated, investigation of various IBD models that used IL-17-deficient mice, p19-deficient mice and p40-deficient mice and even attempts to prevent and treat IBD with IL-17/IL-23 inhibiting monoclonal antibodies was undertaken by many groups. Alex *et al.* [54] reported increased production of IL-17 in both dextran sodium sulfate (DSS) colitis and trinitrobenzene sulfonic acid (TNBS) colitis. Ito *et al.* [55] reported attenuation of DSS colitis in IL-17-deficient mice, and Ogawa *et al.* [56] reported suppression of the development of DSS colitis in inhibition experiments with IL-17-neutralizing antibody. Yen *et al.* [20] showed that double-deficient $IL\text{-}10^{-/-} \times IL\text{-}19^{-/-}$ mice obtained by crossing IL-10-deficient mice (which spontaneously develop chronic colitis) with P19-deficient mice did not develop colitis; on the other hand, $IL\text{-}10^{-/-} \times p35^{-/-}$ mice developed colitis, the same as the control $IL\text{-}10^{-/-}$ mice; thus, it might be possible that $IL\text{-}10^{-/-}$ mice, which have long been considered a Th1 Crohn's disease model, are actually a Th17-mediated model. IL-17 production was markedly decreased in the $IL\text{-}10^{-/-} \times IL\text{-}19^{-/-}$ mice without having any effect on IFN-γ production. Moreover, though there was a tendency toward suppression of colitis in the $CD4^+CD45RB^{high}$ T-cell transfer colitis model by anti-IL-6 and anti-IL-17 neutralizing antibodies when each of them was administered alone, the inhibitory effect was not significant; in contrast, marked suppression of colitis was observed when anti-IL-6 and anti-IL-17 antibodies were administered together [20]. The above results appear to support two conclusions. The first is that colitis disorder depends on the integrated actions of Th17 family cytokines other than IL-17, including Th17 cytokines IL-17F, IL-22, etc. The second is that IL-6 is involved in the induction of Th17 cells, thereby suggesting that inhibiting Th17 cytokines as a whole is important to suppressing the development of colitis, and that is thought to be important from the standpoint of considering treatment strategies for IBD in the future. On the other hand, Elson *et al.* [57] established a bacterium-specific $CD4^+$ T-cell line isolated from C3H/HeJBir mice, which are a model of naturally occurring IBD, and developed a model of colitis transferable to SCID mice. In this model, significantly more IL-17-producing cells than IFN-γ-producing cells infiltrated the inflamed intestine. In addition, when Th1-type and Th17-type bacteria-specific $CD4^+$ T-cell lines were established *in vitro* and transferred into SCID mice, more severe colitis was induced by transfer of fewer Th17-type cells than Th1-type cells, and Th17-type colitogenic $CD4^+$ cells were shown to be the dominant etiological factor in this model [57]. Moreover, the development of colitis as a result of transfer of the bacteria-specific $CD4^+$ T-cell line was inhibited by an anti-IL-23 (p19) mAb, supporting the importance of the IL-17-mediated immune response in chronic colitis [57].

Similarity of Th17 and $Foxp3^+$ T_R cells and chronic colitis

Research on regulatory T (T_R) cells has been vigorously expanded in recent years, just as it occurred for Th17 cells. Some regulatory T cells, $CD4^+CD25^+$ T_R cells, which express the Foxp3 molecule [58], Tr-1 cells, which produce IL-10 [59], and Th3 cells, which produce TGF-β [60], have already been studied independently. Research on $CD4^+CD25^+Foxp3^+T_R$ cells has been particularly active, and initially the cells were thought to be produced by natural generation in the thymus and were called naturally occurring $CD4^+CD25^+Foxp3^+T_R$ cells. On the basis of their property of suppressing a variety of immune responses, these cells have gradually been demonstrated to play a major role in the pathology of various chronic immune diseases, including IBD [61,62]. With respect to IBD, when $CD4^+CD45RB^{high}$ T cells from which $CD4^+CD25^+Foxp3^+T_R$ cells had been removed were transferred into immunodeficient mice,

they developed Crohn's disease-like chronic colitis [14,63]. Moreover, as the onset of chronic colitis was suppressed when $CD4^+CD25^+Foxp3^+T_R$ cells were transferred together with $CD4^+CD45RB^{high}$ T cells, $CD4^+CD25^+Foxp3^+T_R$ cells appear to act in an inhibitory manner against the development of IBD [14,63]. Furthermore, as transfer of $CD4^+CD25^+Foxp3^+T_R$ cells even into mice that had already developed IBD was able to steer the colitis in the direction of healing [64], it may be possible to use these cells for cell therapy [63]. There have been reports of impaired functions of $CD4^+CD25^+Foxp3^+T_R$ cells in other models of IBD [3], and even in IBD in humans, decreases in $CD4^+CD25^+Foxp3^+T_R$ cells have been reported in the peripheral blood of active ulcerative colitis and Crohn's disease patients [65].

The existence of inducible $CD4^+CD25^+Foxp3^+T_R$ cells that are induced in the periphery and distinct from thymus-dependent naturally occurring $CD4^+CD25^+Foxp3^+T_R$ cells has also recently been demonstrated [66]. Interestingly, TGF-β is essential to inducing them from naive $CD4^+$ T cells in the periphery. This is similar to Th17 requiring TGF-β and IL-6 as described above, and this similarity is extremely fascinating. In other words, the fate of naive $CD4^+$ T cells may be determined by just one molecule, IL-6 (perhaps IL-1β or IL-21 in humans). There have been several very interesting reports in this regard, and they have the following points in common. The first is that a certain number of Th17 and $CD4^+CD25^+Foxp3^+T_R$ cells are present in the intestine even in healthy states [45,67]. The second is that the presence of enteric bacteria favors the production of Th17 and $CD4^+CD25^+Foxp3^+T_R$ cells in the intestine [46,68] (as yet unconfirmed [47,69]) and the third is that dendritic cells in the intestine or mesenteric lymph nodes actively promote the production of both Th17 and $CD4^+CD25^+Foxp3^+T_R$ cells in the intestine [21••,70–73]. However, there are points of divergence. The first is that the retinoic acid produced by dendritic cells in the intestine induces only $CD4^+CD25^+Foxp3^+T_R$ cells [70,74–76]. The second is that the IL-2 that is essential to the maintenance of $CD4^+CD25^+Foxp3^+T_R$ cells has an inhibitory effect on Th17 cell production instead [77]. The third point of divergence is that Th17 cells, not $CD4^+CD25^+Foxp3^+T_R$ cells, are induced in the presence of pro-inflammatory cytokines, in addition to TGF-β [31–33]. The fourth point, in relation to the TLR9 molecule mediated by the DNA of enteric bacteria, is that $CD4^+CD25^+Foxp3^+T_R$ cells increase, and Th17 cells decrease in the intestine of TLR9-deficient mice [78]. The situation is made even more complicated by the possibility of conversion between $CD4^+CD25^+Foxp3^+T_R$ cells and Th17. Xu *et al.*'s [79] group has reported that $CD4^+CD25^+Foxp3^+T_R$ cells express membrane-type TGF-β and that in the presence of IL-6 they convert to Th17 cells all by themselves. This could be an important warning regarding cell therapy with $CD4^+CD25^+Foxp3^+T_R$ cells to treat chronic immune diseases, including IBD, because when T_R cells are injected into IBD patients during inflammation, there is a chance that they may convert to pathologic Th17 cells in an environment in which IL-6 is abundant. However, we found a significant increase in $CD4^+CD25^+Foxp3^+T_R$ cells in active-phase IBD mucosa in comparison with the mucosa of healthy volunteers [80]. At first, we thought that this phenomenon represented a feedback loop associated with an increase in the T_R cell maintenance cytokine IL-2, which is produced locally at sites of inflammation, but, on the other hand, an increase in Th17 cells in response to an increase in production of pro-inflammatory cytokines, including IL-6 and IL-21, was postulated, and the Th17/$CD4^+CD25^+Foxp3^+T_R$ cell balance appeared to play a very important role in the disorder.

Conclusion

From a clinical perspective, IBDs are chronic, persistent diseases characterized by repeated relapses and remissions. One explanation could be that colitogenic memory $CD4^+$ T cells created at the time of disease development persist in the body, including during remission, in a manner that is dependent on the homeostatic cytokine IL-7. On the other hand, other effector cytokines may induce inflammation at the time of the initial episode and during relapses. In recent years, Th17-type $CD4^+$ T cells, primarily Th17 cells, have been shown to play a central role in murine and human IBD. Inhibition of the Th17 pathway may hold promise as a treatment for IBD, though we need to clarify the respective roles of other subsets of $CD4^+$ T cells, such as Th1 and Th2 cells. Thus, in the same way that there are periods of remission and relapse clinically, it may be important to attack different immune mediators, that is, homeostatic as well as effector cytokines to achieve an optimal treatment strategy for IBD. Finally, Th17 cells appear to be closely related to inducible T_R cells, and the similarities and divergences in generation, balance, conversion, etc., between pathogenic Th17 cells and inhibitory T_R cells need also to be aggressively explored.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 381).

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