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Regulation of Th17 cells in the mucosal surfaces

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Abstract

The mucosal surfaces represent the main intersection between jawed vertebrates and the environment. The mucosal surface of the intestine alone forms the largest surface that is exposed to exogenous antigens as well as the largest collection of lymphoid tissue in the body. Therefore, a protective immune activity must coexist with efficient regulatory mechanisms in order to maintain a health status of these organisms. The discovery of a new lineage of helper T cells that produce interleukin (IL)-17 has provided valuable new insight into host defense and the pathogenesis of inflammatory diseases at the mucosal surfaces. Of particular interest for these surfaces, it has been reported that peripherally-induced regulatory T cells and Th17 effector cells arise in a mutually exclusive fashion, depending on whether they are activated in the presence of TGF-β or TGF-β plus inflammatory cytokines such as IL-6. This review will address the protective and pathogenic roles of Th17 cells in the mucosal surfaces and potential regulatory mechanisms that control their development.

Keywords

Intestine; Lung; Mucosal; TH17; T regulatory cells

The mucosa as the main environmental interface

The main intersection sites between the environment and our organism are the mucosal surfaces, represented by the gastrointestinal, respiratory, and genital tract. The majority of contacts established at the mucosal surfaces are with non-pathogenic microbial antigens, dietary antigens and air-borne antigens. The mucosal surfaces also contain a diverse and large immune system. For example, the gut-associated-lymphoid-tissue (GALT) harbors more lymphocytes than all remaining lymphoid tissues together [1]. In contrast to the peripheral lymphoid tissue, the GALT consists of 70% constitutively activated T cells bearing an antigen-experienced phenotype ($CD45RB^{lo}$, $CD44^{hi}$, $CD69^{hi}$, $CD62L^{lo}$) [1]. A large proportion of these T cells can be classified as memory T cells, based on their phenotype and functional capacity to display immediate cytotoxicity and the prompt ability to secrete cytokines such as IFN-γ, IL-4, and TNF-α [1]. In the past few years, it has become clear that the GALT also naturally contains a population of T cells that constitutively produce pro-inflammatory cytokines such as IL-17A, IL-17F, TNF-α and IL-22.

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Introduction to Th17 cells

Th17 cells were recently defined as a distinct lineage that does not share developmental pathways with either Th1 or Th2 cells [2]. In fact, both IFN-γ and IL-4 are able to inhibit the differentiation of IL-17 producing T cells, while blocking antibodies to IFN-γ and IL-4 facilitate [3, 4]. Moreover, overexpression of either T-bet (main Th1 transcription factor) or c-Maf, (transcription factor important for IL-4 expression), reduced IL-17 production [4, 5]. Another cytokine involved in both Th1/Th2 and Treg development that negatively regulates Th17-differentiation is IL-2. IL-2 is essential for the TGF-β-mediated iTreg induction but its signaling via Stat5 constrains Th17 generation, while IL-2 deficiency was also shown to be associated with increased Th17 generation in vivo [6]. Finally, the cytokine IL-27, another member of the IL-12 cytokine family, is composed by Epstein-Barr virus-induced gene 3 (EBI3) and p28 chains and also suppresses Th17 development [2]. Although IL-27 signal activates several different pathways, including IL-6-related STAT3, the suppression of Th17 development is dependent on Stat1 [7, 8].

In contrast to the Th1/Th2 subsets, which are inhibited by TGF-β, Th17 cells rather require TGF-β, along with the pro-inflammatory cytokines IL-6 or IL-21, for their differentiation from naïve precursors [2, 9–11]. Data originated from Cua and Littman's laboratory pointed to the retinoic acid-related orphan receptor (ROR)γt as the key transcription factor for generation of Th17 cells [2]. Accordingly, RORγt-deficient naïve CD4 T cells have reduced ability to differentiate into IL-17-producing cells, whereas forced expression of RORγt in naïve CD4 T cells is sufficient to induce expression of IL-17, IL-17F and IL-22 [12]. Current dogma proposes that initial steps are driven by TGF-β and IL-6 and/or IL-21, while IL-23 plays a fundamental role in stabilizing the phenotypic features of the Th17 lineage [13]. Similar TGF-β-dependent pathway also operates in human Th17 cell-differentiation from naïve CD4 T cells [14].

Th17 cells have been linked to several autoimmune disorders (reviewed elsewhere [2, 13]) but are physiologically found in the lamina propria of the intestine. In the mucosal surfaces, the production of Th17-related cytokines such as IL-22 and IL-17 itself is crucial for host protection against several extracellular pathogens, but is also related to the development of pathological inflammatory disorders. In this review we will focus on the role of these cells in the mucosal surfaces of the gut and the lung and discuss the potential mechanisms that govern their efficient generation and regulation at these sites.

Role of Th17 cells in the gut

IL-17 producing cells are present at high numbers at steady state in the mucosal surfaces, being represented mostly by $CD4^{+}TCR\alpha\beta$ and $CD8\alpha\alpha TCR\gamma\delta$ T cells in lamina propria of the small intestine [15]. New studies have started to elucidate physiological factors that influence this spontaneous production of IL-17 in the intestinal lamina propria. In a recent study, Ivanov et al. reported that commensal bateria are required for IL-17 production in the small intestine, since germ-free mice from three different strains contained virtually no Th17 cells in the lamina propria. Surprisingly, neither *Trif* nor *Myd88* were required for this "spontaneous" IL-17 production in the lamina propria, indicating that toll-like receptor signaling was not involved in this phenomenon [15]. An explanation for these findings could be found in a recent report by Atarashi and coworkers, who have shown that adenosine 5′-triphosphate (ATP) derived from commensal bacteria can activate a subset of lamina propria antigen-presenting cells ($F4/80^{+}CD11b^{+}CD70^{hi}CD11c^{lo}$cells) that are able to produce IL-6, IL-23 and TGF-β, triggering the differentiation of Th17 cells [16].

Curiously, a different regulation seems to occur in large intestine. In contrast to what was described for the small intestine [15], Zaph and coworkers showed that large intestine from germ-free mice contains more IL-17 producing cells than mice reared in *specific-pathogen-free* (SPF)

conditions [17]. The authors found that the microbiota present in the large intestine is responsible for the production of IL-17-family cytokine IL-25 (IL-17E), which counter-regulates IL-17 production through inhibition of IL-23 production by lamina propria macrophages. Small and large intestines are indeed very different sites regarding the immune system. First, there are more IELs per epithelial cell and more LPLs in the small intestine and the lymphocyte migration to these sites is differentially regulated [1]. Peyer's patches and M cells are also mostly found in the small intestine, although the large intestine contains a similar structure, the cecal patch. The composition of lymphocytes is distinct between these two anatomical sites. For example, the so-called unconventional lymphocytes such as CD8αα TCRαβ and CD8ααTCRγδ IELs are more frequent in the small than in the large intestine [1]. Additionally, the great majority of commensal bacteria are found in the large intestine and possibly the composition of bacteria species is distinct from the small intestine. Finally, "spontaneously" producing Th17 cells are present at higher frequency in the small intestine [15].

Therefore, different regulation of small and large intestine is plausible. Nonetheless, the findings by Atarashi and coworkers [16] differ from those by Zaph et al.[17] since the first found a dramatic decrease while the latter found an increase in the frequency of IL-17 producing cells in the large intestine of germ-free mice. These discrepancies could be related to different genetic background, although consistent data with the conclusion reached in each of the three mentioned studies (either increased [17] or decreased [15, 16] IL-17 production in the lamina propria of mice maintained under germ-free conditions) were reported when comparing various conventional and germ-free mouse strains. Considering that germ-free mice should not harbor any microbiota, one reason for the divergent results might be related to alterations in the microbiota of conventional mice maintained in different facilities. For instance, Ivanov et al. described that mice originated from Taconic Farms contain significantly higher population of IL-17 producing cells in the lamina propria than from mice Jackson Laboratory [15].

The IL-23/IL-17 axis plays multiple roles in the intestinal immune system, being protective against certain extracellular pathogens while detrimental in different models of inflammatory bowel diseases [2]. Genome-wide association studies from patients with inflammatory bowel diseases have pointed to IL-23R as one of the main genes associated with risk of developing Crohn's disease and ulcerative colitis [18]. IL-23 has been shown to mediate T-cell independent colitis and innate inflammatory responses induced by agonist CD40 antibodies or by *Helicobacter hepaticus*-infection of RAG-deficient mice [19, 20]. Although Th17 cells were not required for the development of the disease in these models, predominantly mediated by IL-23 production, IL-17 expression by innate cells was found significantly inhibited upon IL-23p19 blockade [20]. In T cell dependent models of colitis, induced either by *Helicobacter hepaticus*-infection associated with anti-IL10R treatment, or by naïve T cell transfer into RAG-deficient mice, IL-23 but not IL-12 was associated the intestinal pathology [20, 21]. The involvement of IL-23 in the inflammatory process appeared to have strictly innate-immunity as well as a Th17-mediated components [20, 21]. A recent study directly linked the Th17 lineage-differentiation with colitis development. Using the transfer model of colitis, Leppkes and coworkers showed that naïve $CD4^+$T cells from wild type, but not from RORγ-deficient mice, induce colitis upon transfer into RAG-deficient mice. Additionally, by using blocking antibodies to IL-17A and naïve $CD4^+$T cells from IL-17F-deficient mice, the authors showed that IL-17A and IL-17F redundantly trigger intestinal inflammation [22].

The above data underscores the importance of the IL-23/IL-17 axis in mediating detrimental intestinal inflammation, but in many cases inflammatory processes triggered by these cytokines is crucial for host protection. Mangan and coworkers have shown that although IL-23p19-deficient mice are able to mount a vigorous Th17 response after *Citrobacter rodentium* infection, this response is not efficient enough, since $p19^{-/-}$, but not WT mice, succumb shortly after infection with uncontrolled bacterial growth and dissemination, suggesting that IL-23 is

important for a full differentiation and for an efficient Th17 response against this intestinal pathogen [11]. The production of IL-23 has been recently linked also with the induction of IL-22-producing mucosal NK-cells (NK-22) in mice and humans [23, 24]. This population of $CD56^{hi}$NK cells seems to constitute another important branch of the immune response against intestinal pathogens and also requires stimulus from the microbiota and RORγt expression for their development [23, 25, 26]. Furthermore, although in some inflammatory contexts IL-22 production by Th17-cells can exert proinflammatory effects, IL-22 produced either by Th17 cells or by NK-22 cells was shown to protect mice from IBD, probably exerting protective effects on responding intestinal epithelial cell (IEC) in the colon [25].

A recent report extended the protective role of Th17 cells to oropharyngeal fungus (*C. albicans*) infection. Conti et al. showed that IL23p19 and IL-17RA-deficient mice, but not IL-22 or IL-12p35-deficient mice are susceptible to oral candidiasis [27]. The role played by IL-17- producing T cells in controlling invading pathogens, including *Candida* infection, is of special interest in infections that cause immune deficiency. Both simian and human immunodeficiency virus (SIV and HIV, respectively) were shown to massively deplete intestinal memory $CD4^+$T cells at all stages of infection [28]. Raffatellu et al. extended these observations by demonstrating that SIV infection of rhesus macaques resulted in a severe depletion of Th17 cells in the ileal mucosa. As a consequence of deprived Th17 responses, the macaques displayed blunted responses against *Salmonella typhimurium*, resulting in bacterial dissemination [29].

Role of Th17 cells in the lungs

In addition to their role in the intestinal immune system, IL-17-producing $CD4^+$ T cells also constitute an important arm of adaptive immune responses against airborne-pathogens [30]. For instance, IL-17-producing cells play an important role in the establishment of effective immune responses to *Mycobacterium tuberculosis* mainly through the recruitment of protective IFN-γ-producing $CD4^+$ T cells [31]. Increasing evidence suggests that IL-17, acting either directly or indirectly, significantly stimulates neutrophil maturation, migration, and function in the lung tissue and airways. IL-17 induction of neutrophil activation and migration is important in defense against a variety of organisms that infect the lung [32, 33]. It was reported that *Klebsiella pneumoniae*-pulsed dendritic cells led to IL-17 production in an IL-23-dependent manner [34]. Accordingly, IL-23 p19-deficient and IL-17R-deficient mice where shown to be more susceptible to lung infection with *Klebsiella pneumoniae* [34, 35]. The increased bacteremia and mortality observed in these mice was associated with reduced levels of CXCL1, CXCL2, G-CSF, and subsequent neutrophillic influx in the lung upon challenge with *Klebsiella pneumoniae*. Likewise, in mice infected with *Mycoplasma pneumoniae*, infiltration of the lungs by neutrophils is dependent upon IL-23-induced upregulation of IL-17 [36]. Another important respiratory pathogen *Bordetella pertussis*, the cause of whooping cough, employs multiple pathways to elicit IL-17 response. Protection of mice by pertussis vaccine requires production of IL-17, IL-23, and IL-1 [37]. In addition to regulation of chemokines and cytokines, IL-17 regulates antimicrobial peptide production of beta defensins in human bronchial epithelial cells [32, 37]. Taken together, these data support the idea that Th17 cells are critical for normal immunity against bacterial infections in the airways.

In some circumstances, however, IL-23 and/or IL-17 may also be associated with an unfavorable outcome to infection. A recent study by Zelante et al. demonstrated that the Th17 pathway acted as a negative regulator of the Th1-mediated immune resistance to both *Candida albicans* and *Aspergillus fumigatus*, and played an inflammatory role previously attributed to uncontrolled Th1 responses [38]. IL-23 acted as a molecular connection between uncontrolled fungal growth and inflammation, being produced by DC in response to high fungal burden and counter regulating IL-12p70 production. Both IL-23 and IL-17 impaired antifungal effector

activities of neutrophils even in the presence of IFN-γ. In addition, both cytokines activated the inflammatory program of neutrophils by inducing the release of MMP9 and MPO, which likely contributes to the high inflammatory pathology and tissue destruction associated with Th17 cell activation. Together, these results imply that the relative contribution of IL-17 to host defense against respiratory pathogens might vary depending on the infectious setting.

There is growing evidence from clinical studies that exaggerated recruitment and activation of neutrophils in the airways is linked to the clinical course of several inflammatory diseases in the airways and lungs, such as asthma, nonspecific bronchial hyperreactivity (BHR), chronic bronchitis, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and acute respiratory distress syndrome [32, 39]. The precise role of Th17 cells in lung diseases is still largely unclear, but there is growing clinical and experimental evidence to suggest that they may be important for neutrophilic influx in acute and chronic airway inflammation. In asthmatic patients, IL-17 expression was increased in the lungs, sputum, BALF, or sera, and severity of airway hypersensitivity in patients correlated with the level of IL-17 expression [40]. Human bronchial fibroblasts cells, airway smooth muscle cells, and lung epithelial cells respond to stimulation with IL-17 in vitro by producing IL-6, IL-8, and GRO-α. IL-8 and GRO-α are known chemoattractants for neutrophils, and IL-6 is a neutrophil activating cytokine [41]. Thus, the increased expression of IL-17 in the lung during allergic responses may explain the increased accumulation and activation of lung neutrophils. Consistent with this, Hellings et al. in a mouse model of allergic asthma showed that acute allergen provocation is followed by a rapid increase in IL-17 mRNA in mouse lungs, which correlated with an increase in neutrophilic influx in the airways [42]. Neutralizing anti-IL-17 mAb treatment ablated bronchial neutrophilia in parallel with reduction of bone marrow and blood neutrophilia. Moreover, IL-23 and Th17 cells not only induce Th17-cell mediated neutrophil recruitment but can also upregulate Th2-mediated eosinophilic airway inflammation and hyperresponsiveness [43, 44]. Recently, using a well-established murine model of hypersensitivity pneumonitis and pulmonary fibrosis, Simonian et al. repeatedly exposed C57BL/6 mice to *Saccharopolyspora rectivirgula* and demonstrated that CD4 T cells expressing IL-17 and IL-22 are recruited in to the lung [45]. Importantly, after exposure of IL-17Ra$^{-/-}$ mice to *S. rectivirgula*, a significantly decreased T cell alveolitis was seen, with an associated decrease in collagen deposition. These data highlight a role for Th17 cells in the immune response directed against bacterial pathogens and for the subsequent development of lung fibrosis. Thus, in contrast to Th1 and Th2 cells, Th17 cells may be involved in the pathogenesis of various inflammatory and allergic responses in the lung in part by supporting neutrophil recruitment and survival and inducing proinflammatory cytokines by structural cells.

Similar to the intestine, IL-17 producing cells are present at high numbers at steady state in the airways, mostly represented by invariant NKT cells, TCRγδ T cells and non-T cells [15]. Although many studies have characterized pathways that induce and regulate Th17-related cytokines in the intestine, very few studies have attempted to describe how these pathways operate in the airways. For example, are there microbial or endogenous stimuli required for the spontaneous production of IL-17 in the lungs? Since intestinal and lung-associated lymphoid tissue share characteristics typically found at mucosal sites, such as predominant induction of tolerance at steady state, it is plausible that parallel regulatory mechanisms to the intestine can be found in the airways (*discussed below*).

Regulation of Th17 cells in the mucosa: IL-25 and TSLP

The cytokine, IL-25, is expressed by lung epithelial cells and activated eosinophils and basophils. It mediates early T-cell differentiation towards a Th2-phenotype and development of airway hyperactivity and allergic diseases. This characteristic, associated with the ability to suppress Th17 differentiation suggested that IL-25 could be an important regulatory

mechanism to suppress the development of different inflammatory diseases. Additionally, IL-25 promotes Th2-cell differentiation upon thymic stromal lymphopoietin (TSLP)-activated DC stimulation [46]. This IL-25/TSLP pathway seems to operate in the intestinal mucosa as well. Mice with an IEC-specific deletion of the NF-κB-related kinase, IKKβ, show a reduced expression of TSLP in the intestine and fail to develop a protective Th2 response against the intestinal parasite *Trichuris*. Moreover, these mice develop exaggerated IFN-γ and IL-17 responses [47]. These results underscore the importance of mechanisms that regulate Th17 responses under pathogen-induced or autoimmune and allergic diseases-induced inflammation in the mucosal surfaces.

Regulation of Th17 cells in the mucosa: Reciprocal development of Th17 and Treg cells

In addition to its effects on Th17-differentiation, TGF-β has multiple roles in both systemic and mucosal immune-regulation, among them is the ability to convert naïve CD4 cells into Foxp3-expressing regulatory T cells (iTreg) [48]. This contrasting deviation underscores a central role of TGF-β in orchestrating the pro- and anti-inflammatory nature of adaptive immunity. This pathway has particular relevance at mucosal surfaces such as the intestine, where both intense microbial load and production of TGF-β are constant under physiological conditions. How is the balance of pro- and anti-inflammatory responses achieved in the highly stimulated surface of the intestinal mucosa?

It was recently found that Foxp3 can directly inhibit Th17 differentiation by direct interaction with RORγt [49–51]. Actually, RORγt and Foxp3 may coexist in the same cell [50, 52]. Eberl's group reported that RORγt-expressing T cells contain a sizeable population of cells with regulatory properties, including IL-10 producing Foxp3$^+$Treg cells in vivo [52]. The balance between IL-17 producing RORγt$^+$ T cells and IL-10 producing Foxp3$^+$ cells depends on factors such as inflammatory cytokines and the expression of Foxp3 itself. IL-6-deficient mice show decreased IL-17 producing RORγt cells in various tissues, including the airways and mesenteric lymph nodes. Remarkably, the relative frequency of IL-17-producing RORγt$^+$ or IL-10-producing Foxp3$^+$ RORγt$^+$ T cells remained constant during chronic intestinal inflammation as well as after lung infection with influenza A-virus [52]. The authors proposed the existence of a robust mechanism maintaining the equilibrium between Th17 and Tregs within RORγt cells during infection [52]. Keeping the balance of IL-17 versus IL-10 production would promote inflammation while limiting collateral damage, a necessary compromise between maintaining effective immunity and tissue integrity.

The constant exposure to luminal antigens creates a so-called "physiological chronic inflammation" in the gut, which could easily favor the TGF-β driven effector differentiation at the expense of iTreg. The high amounts of IL-17 producing T cells at steady state correlates with the fact that inflammatory cytokines are produced physiologically in the intestine [12, 15, 52]. At the same time, the intestine is highly regulated, containing several different mechanisms to control pathological inflammation. In normal circumstances, previous exposure to antigens via oral or nasal routes efficiently inhibits the development of immune responses to subsequent challenges with the same antigen [53, 54]. The intestinal and airway mucosa are highly effective at inducing iTregs [48, 54]. Lafaille's group has shown that Tregs are induced after oral or nasal exposure to the cognate antigen and these iTregs are sufficient and required for mucosal tolerance in this system [48, 54]. Belkaid and Powrie's groups confirmed and extended these findings by demonstrating that iTregs were preferentially induced in MLN and lamina propria by a subpopulation of DCs, rather than in spleen or peripheral lymph nodes, reinforcing that the intestine is a privileged site for Treg induction [55, 56]. Importantly, these intestinal DC subpopulations specifically produce a "co-factor" for Treg development, the vitamin-A metabolite retinoic acid [55–58].

Regulation of Th17 cells in the mucosa: Retinoic acid

Mucosal APCs, especially $CD11b^+CD11c^+$ or $CD103^-CD11c^+$ DCs, are able to help the development of the Th17 cells in the lamina propria of the intestine [55, 58]. On the other hand, important regulatory functions can also be ascribed to DCs present in the mucosal sites. For example, antigen-presentation by mucosal DCs in the MLN plays crucial roles in the development of oral tolerance [59]. Also, mucosal plasmacytoid $CD8\alpha\alpha^+$ DCs are inefficient at inducing CD4 T helper proliferation but instead can induce their differentiation to IL-10-producing CD4 cells [60]. Recently, the $CD103^+$ DC-population was shown to be the main population involved in the production of retinoic acid (RA). Importantly, the production of RA by mucosal APCs, including lamina propria macrophages, was associated with their high efficiency in converting naïve $CD4^+$ T cells into $FoxP3^+$ T cells in a TGF-β-dependent fashion [55–58]. In contrast to the effect on Treg cells, RA potently constrains Th17 conversion [57]. Different groups have shown that RA signaling through RAR receptors in the T cells is able to block the inhibitory effects of inflammatory cytokines, such as IL-6, on the TGF-β mediated Foxp3 induction and consequently suppressing the development of IL-17-producing CD4 and CD8 T cells [57, 61]. Additionally, RA directly inhibits TGF-β and IL-6-induced RORγt on naïve $CD4^+$ T cells [57, 62], possibly through the inhibition of IL-6Rα and IL-23R expression [63].

The dose of RA associated with toll-like receptor (TLR) agonists was also suggested to play a role on the suppression of Th17 differentiation. Although previous studies have described that RA has suppressive effects on Th17 development in all doses examined, including spontaneous production of RA by mucosal DCs in T/DC co-cultures [57, 62], Uematsu and coworkers have recently suggested that production of RA by $CD11c^{hi}CD11b^{hi}$ LP DCs, when stimulated by TLR5-ligand flagellin, promoted a modest differentiation of antigen-specific Th17 and Th1 cells, suggesting that innate stimuli may induce contrasting effects of RA on either DCs or T cells.

Clinically, vitamin-A derivatives have been used to treat certain types of cancer and skin-related diseases such as psoriasis [64]. Interestingly, the production of IL-6 and IL-23 and differentiation of IL-17 and IL-22-producing Th17 cells has been implicated with the pathogenesis of autoimmune psoriasis [65]. Several clinical trials currently investigate potential application of the inhibition of Th17 development, for example, using antibodies against IL-23, in the treatment of autoimmune diseases [66]. In fact, retinoic acid and other vitamin-A derivatives were previously shown to suppress experimental models of autoimmune diseases recently linked to a Th17 phenotype, such as experimental autoimmune encephalomyelitis [67]. Is possible that part of the mechanism of action of retinoids in the treatment of psoriasis and EAE is related to suppression of Th17 development. Therefore, it is of utmost interest to dissect the mechanism of action of retinoic acid-mediated suppression of these inflammatory processes as well as to evaluate possible therapeutic applications for retinoic acid in Th17-related diseases.

Concluding remarks

The discovery of Th17 cells represents a major step in our understanding of protective and pathological responses at the mucosal surfaces. However, there are still many unanswered questions, such as how endogenous and/or microbiota-derived stimuli trigger RORγt and consequently Th17 development in the mucosa. Additionally, it is not know which type/strains of commensal bacteria trigger natural production of Th17 in the intestine. A great deal of work needs to be done with regards to the precise regulatory mechanisms that govern the efficient generation, persistence, and reactivation of Th17 cells at different mucosal sites. The relationship between Tregs and Th17 cells as well as the possible pro-inflammatory role of

Tregs that lose Foxp3 expression or co-express Foxp3 and RORγt are also of great interest. A largely unexplored topic is also the role of IL-17 production by cells other than $CD4^+$ T cells. IL-17 can also be produced by $CD8^+$ T cells, γδT cells, and in some cases even natural killer T (NKT) cells, macrophages, neutrophils, and eosinophils. Lastly, a critical direction for future studies of Th17 cells will be to determine what roles these cells play in human disease, and ultimately how useful or safe they will be as a therapeutic target.

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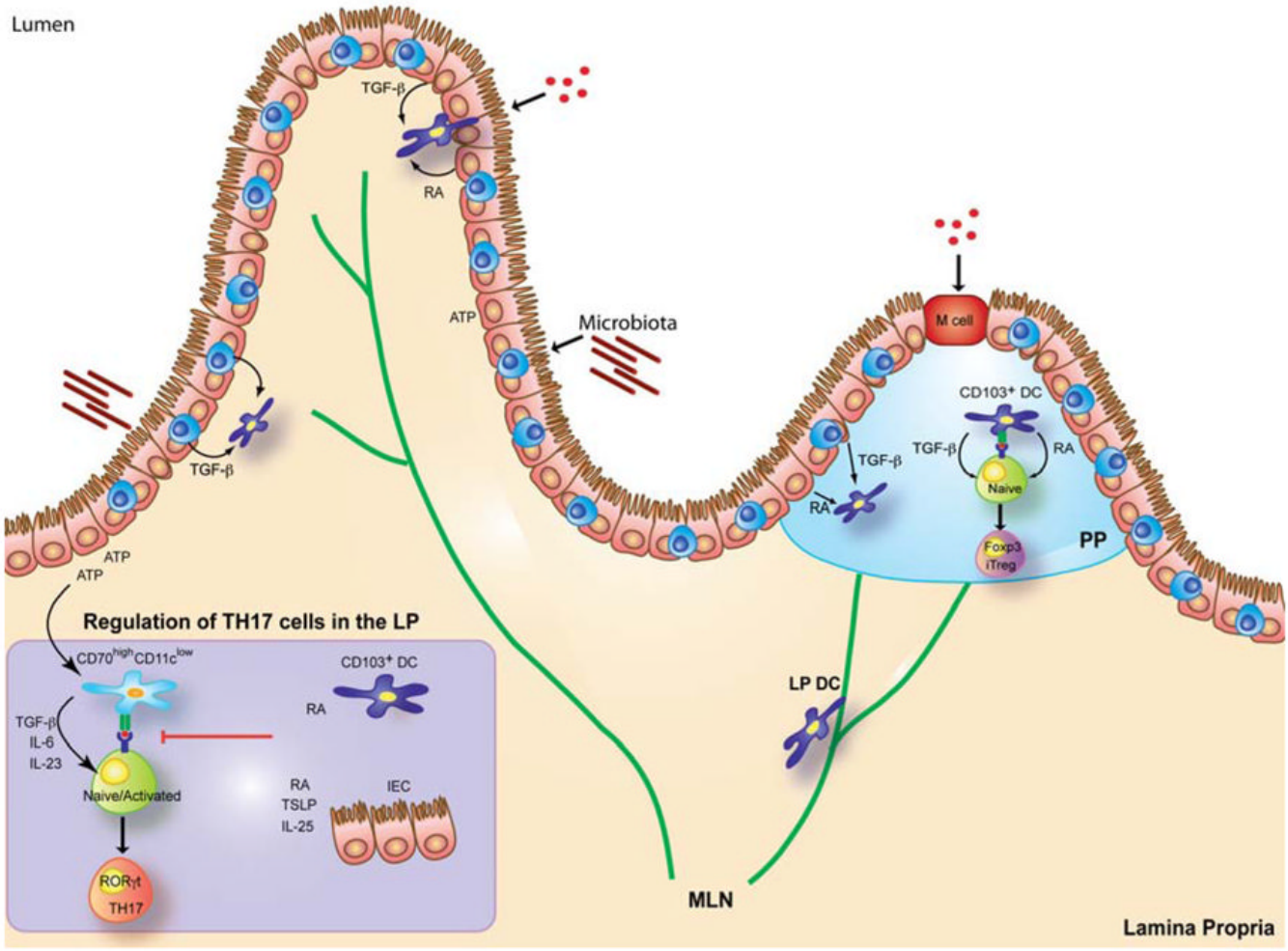

Figure 1. Generation and regulation of Th17 responses in the intestine

Under the influence of microbial-derived stimuli and ATP, *lamina propria* (LP) $CD70^{high}$ and/or $CD103^{-}$ DCs induce Th17 differentiation through the production of TGF-β, IL-6 and IL-23. Production of TGF-β by LP cells also promote the anti-inflammatory $Foxp3^{+}$ induced regulatory T cells (iTreg). The balance between Th17 and Treg cell development is favored towards Treg cells upon the influence of retinoic acid (RA) produced by LP and Peyer's patch $CD103^{+}$ DCs, LP macrophages and intestinal epithelial cells (IEC). Besides RA, *thymic stromal lymphopoietin* (TSLP) expressed by IEC and the cytokine IL-25 were reported to suppress Th17 development in the intestine.