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Environmental control of Th17 differentiation

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Abstract

Th17 cells participate in the control of extracellular bacteria and fungi, but dysregulated Th17 cell activity can result in immunopathology. Thus, the generation and the activity of Th17 cells should be tightly regulated, and simultaneously it should be able to respond to the challenges presented by a changing environment. In this viewpoint, we discuss some of the mechanisms by which microbes, dietary components and environmental toxins influence the Th17 response.

Keywords

Diet; Environment; Microbes; Th17; Toxins

Background

Th17 cells have been recently identified as a subset of helper T cells characterized by the production of IL-17 and the expression of the transcription factor RORγt [1]. The differentiation of Th17 cells is closely related with that of Foxp3$^+$ Treg; Treg differentiation is induced by TGF-β, but TGF-β in combination with IL-6 or IL-21 results in the generation of Th17 cells whose phenotype is later on stabilized by IL-23 [1]. Several mechanisms operate to maintain the equilibrium between these two cell subsets [1]. Foxp3 and RORγt, the transcription factors that drive the differentiation of Treg and Th17 cells, respectively, establish a physical interaction that results in the inactivation of RORγt and favors Treg differentiation [2]. Signaling *via* the receptors for IL-6 or IL-21, however, inhibits the suppressive effect of Foxp3 on RORγt and results in the generation of Th17 cells [2]. Conversely, signaling triggered by IL-2 [3] or retinoic acid (RA) [4] interferes with the Th17 differentiation program and promotes the generation of Treg. This cross-regulation of the signaling pathways that drive Treg and Th17 differentiation is influenced by environmental factors, affecting our ability to fight off pathogens and our susceptibility to autoimmune disorders. In this viewpoint we will focus on a few examples that highlight the effects that microbes, vitamins and environmental toxins have on the Th17 subset.

Microbial control of Th17 immunity

Microbes have been long known to influence the susceptibility and the course of autoimmune diseases [5]. Although several mechanisms have been invoked to explain the

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effect of infections on autoimmunity [5] here we will focus on their effects on Th17 immunity.

IL-27 is a heterodimeric cytokine that belongs to the IL-12 family and is produced by activated DC. Stumhofer *et al*. [6] have reported that chronic inflammation of the CNS with *Toxoplasma gondii* triggers the local expression of IL-27, dampening Th17 immunity to *Toxoplasma. In vitro* experiments showed that IL-27 suppressed the differentiation of Th17 cells triggered by IL-6 and TGF-β by a STAT1-dependent pathway [6]. Although this work clearly shows the direct effects of IL-27 on the Th17 subset *in vitro*, IL-27 might also control the Th17 subset by indirect mechanisms *in vivo*. Indeed, IL-27 in combination with TGF-β promotes the generation of suppressive T cells that produce IL-10 [7, 8]. Whether these IL-10-secreting T cells can directly control the Th17 subset has not been formally proven as yet, but these observations potentially add another level of regulation to the activity of IL-27 on the Th17 subset. Considering that exaggerated immune responses are also observed in IL-27 receptor-deficient mice infected with *Leishmania donovani, Trypanosoma cruzi*, or after helminth challenge, these studies provide a potential mechanism for the control of Th17-driven autoimmune diseases by parasitic infections.

In healthy animals Th17 cells are mainly localized in mucosal surfaces [9]; thus interactions with the commensal flora are likely to modulate the Th17 response. These interactions are especially important for the integrity of the gut, where a delicate balance between Th17 cells fighting pathogens and Treg that suppress the immune response to normal intestinal flora and food antigens should be constantly re-adjusted. Thus, it is not surprising that our interactions with the intestinal flora have both pro-and anti-inflammatory effects [10, 11].

IL-25 (IL-17E) is a member of the IL-17 family of cytokines with anti-inflammatory properties. Through an IL-13-dependent mechanism, IL-25 inhibits the production of IL-23, IL-1 and IL-6 by DC inhibiting Th17 differentiation [12]. While searching for bacterial signals involved in the control of intestinal Th17 cells, Zaph and coworkers found that Th17 cell numbers are increased in the large intestine in the absence of commensal bacteria [13]. The study of the molecular mechanism behind this observation showed that the commensal flora triggers IL-25 secretion by intestinal epithelial cells, which then interferes with the differentiation of Th17 by DC [13]. Strikingly, the effect of IL-25 on Th17 differentiation in the gut was independent of IL-13 [13].

Commensal microbes can also promote Th17 differentiation in the gut. Atarashi *et al.* 14] recently found that the ATP secreted by commensal bacteria acts on $CD70^{high}$ $CD11c^{low}$ DC to stimulate the secretion of IL-6, IL-23, TGF-β and favor the generation of Th17 cells. The bacterial TLR5 ligand flagellin has also been recently shown to promote Th17 differentiation by $CD11c^{high}CD11b^{high}$ DC [15]. These results were complemented by a study from Belkaid and coworkers, which demonstrated that DNA from commensal bacteria interferes with the intestinal conversion of Treg, facilitating the differentiation of Th17 and Th1 cells [16]. Strikingly, this effect was restricted to TLR9 ligands, and no effect on Treg was seen upon activation of TLR2, TLR4 or TLR5 signaling pathways [16].

All in all, these data highlight the promoting and inhibitory effects of microbes on Th17 differentiation. Parasites and commensal flora can dampen Th17 immunity by IL-25- and IL-27-dependent mechanisms, but microbes can also boost Th17 immune responses. These seemingly opposing effects of microbes on Th17 immunity are likely to result from microbe- and tissue-specific mechanisms. The characterization of those mechanisms and the identification of the microbial ligands involved will provide the molecular basis to understand the role of infections on immune disorders.

Vitamins in the control of Th17 differentiation

Vitamin A is metabolized to RA by retinal dehydrogenase enzymes present in gut APC. The RA produced by intestinal DC [4] and macrophages [17] has been shown to control the balance between Th17 and Treg at multiple points. Xiao *et al.* 18] demonstrated that RA enhances TGF-β driven SMAD3 signaling and inhibits IL-6 and IL-23 receptor expression. RA also suppresses a population of $CD44^{high}CD4^{+}$ T cells that directly interferes with Treg generation [19]. Finally, RA directly boosts the differentiation of Treg mediated by gut DC [4] and macrophages [17]. Thus, by directly interfering with the expression of the IL-6 and IL-23 receptors needed for Th17 differentiation, and by simultaneously boosting the differentiation of Treg, RA has a potent inhibitory role in the differentiation of Th17 cells. Strikingly, it has been recently reported that the activation of lamina propria $CD11c^{high}CD11b^{high}$ DC by the TLR5 ligand flagellin results in the differentiation of Th17 and Th1 cells in an RA-dependent manner [15]. The reasons for the discrepancy of these results with the well-characterized inhibitory activity of RA on Th17 differentiation are currently unknown. Although the authors attributed their observation to dose-dependent effects on RA signaling [15], it is also possible that exposure of the DC to microbial ligands modifies their ability to promote Treg differentiation by the secretion of RA. Indeed, this interpretation would be in agreement with the decreased ability to induce Treg differentiation displayed by TLR9-activated DC [16].

Vitamin D is also known to influence the immune response, but its effects on Th17 and Treg differentiation have not been characterized in detail. Skin DC express the enzymatic machinery needed to generate active metabolites of Vitamin D. Thus, it is conceivable that similarly to what has been described for vitamin A in the gut, vitamin D drives the generation of functional Treg in the skin. Indeed, Vitamin D metabolites have been described to favor the expansion of Treg [20, 21] and boost their activity [22], while it interferes with the Th17 cell response. Whether vitamin D directly inhibits the differentiation of Th17 cells or indirectly controls them by boosting the generation of suppressive Treg [20, 21] and Tr1 [23] cells is yet not known.

Toxin receptors in the differentiation of Th17 cells

The aryl hydrocarbon receptor (AHR) is a ligand activated transcription factor with a promiscuous binding site that allows it to interact with a broad array of synthetic and natural ligands [24]. AHR was initially identified as a receptor for dioxins such as the 2,3,7,8-tetracholrodibenzo-*p*-dioxin; however, it was later on found that tryptophan derivatives such as 6-formylindolo[3,2-b]carbazole and dietary compounds such as the indole-3 carbinol derivatives, flavones, flavonols an isoflavones, present in vegetables and fruits can also activate AHR. [24]. Upon activation by its ligands, AHR translocates to the nucleus and controls the transcription of its target genes. AHR is known to act on the immune system at multiple levels with sometimes opposing results. As an example, AHR signaling has been linked with both pro- and anti-inflammatory responses [25–28]. Recently, it was reported that AHR expression was up-regulated in Th17 cells [29, 30]. Indeed, AHR ligands can boost the differentiation of Th17 cells triggered *in vitro* with IL-17 and IL-6 in the absence of APC [29, 30]. The activation of AHR *in vivo* by its ligand 6-formylindolo[3,2-b]carbazole resulted in an increased Th17 response and a worsening of experimental CNS autoimmunity [29, 30]. Strikingly, AHR activation with 2,3,7,8-tetracholrodibenzo-*p*-dioxin or other ligands can also result in the control of the pro-inflammatory response and the expansion of the T_{reg} compartment [25, 29, 31, 32]. Thus, the control of TH17 differentiation by AHR seems to be complex and might involve the modulation of TGF-β-dependent signaling [33], interactions with other transcription factors such as the RA receptor [34] and STAT1 [32], and its effects on regulatory cells [25, 29, 31, 32]. However,

the broad diversity of ligands bound by AHR, and its ability to interact with viral proteins [35] and other transcription factors, positions AHR as a nexus between environmental toxins, dietary compounds and infections and Th17 cells.

Concluding remarks

The recurrent infections that afflict patients with impaired Th17 immunity underline the importance of Th17 cells for the control of extracellular bacteria and fungi [36]. However, dysregulated Th17 activity can result in immunopathology and thus the generation of Th17 cells is tightly controlled. The examples discussed herein suggest that the environment operates at multiple levels to control Th17 immunity: it acts on Th17 cells, APC and Treg. Vitamin A and AHR ligands act directly on T cells to influence Th17 differentiation [18, 29, 30, 32]. Bacterial flagellin and ATP, however, modify the ability of APC to differentiate Th17 cells [14, 15]. Finally, RA, AHR ligands and bacterial DNA influence the generation of Th17 cells by affecting the reciprocal differentiation of Treg cells [4, 16, 29, 32]. Note that each one of these environmental factors operates at multiple levels: RA and AHR ligands, for example, can act on both T cells and APC influencing both Treg and Th17 differentiations [4, 16, 29, 31, 32]. In addition, the pathways triggered by different factors cross-talk to influence each other's effects on Th17 cells: the RA receptor and AHR can dimerize and modulate each other's activity [34], and both the RA receptor and the AHR can influence TGF-dependent signaling [18, 33]. The characterization of these complex interactions will shed light on the effects of the environment on the immune response and might result in the development of new drugs for the treatment of autoimmunity.

Abbreviations

AHR	aryl hydrocarbon receptor
RA	retinoic acid

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