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Role of Endogenous and Induced Regulatory T Cells During Infections

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Abstract

Background—Various populations of regulatory cells, including Foxp3+ T_{Reg}, have been shown to play a central role in the maintenance of peripheral homeostasis and establishment of controlled immune responses.

Objective—In this review, we discuss current hypotheses and points of polemic associated with the origin, mode of action, and antigen specificity of both endogenous and induced regulatory T cells during infections.

Keywords

Regulatory T cells; peripheral homeostasis; controlled immune response

Introduction

In order to sustain their transmission and/or reproduction, a large number of microbes have to establish long-term interactions with their host. During this coexistence, the microbe must avoid elimination by the host immune response and sustain its life cycle, while at the same time delaying or preventing host destruction. Microbe-mediated modulation of innate and acquired immune responses of the persistently infected host has to meet these requirements and restore a “homeostatic” environment. Failure to establish or maintain homeostatic conditions usually causes disease. This is clearly the case of the microflora that invade our gut or our skin, as well as for “pathogenic” microbes that establish chronic infections. Regardless of the final outcome of these long-term interactions, all persistent microbes obey the same principle: the immune system constitutes their ecological niche and they have coevolved with their host to learn how to dictate an immune response appropriate to insure their survival. For instance, microbes have been shown to induce a large array of regulatory cells to insure their own survival [1]. From the point of view of the host, surviving an infection requires the generation of a controlled immune response that recognizes and controls microbial expansion while limiting collateral damage to self-tissues that may result from an exuberant immune response. This implies that induction of regulatory T cells also arise as a result of the host response to the infectious process in a bid to maintain or restore a homeostatic environment [1].

Every microenvironment requires a specific set of immunoregulatory mediators, including regulatory T cells, to maintain its integrity at steady state condition or in the face of infection

or inflammation. Several types of CD4⁺ regulatory T cell have been described on the basis of their origin, generation, and mechanism of action with two main origins identified: thymically derived Foxp3⁺ T_{reg} cells whose presence precedes microbial exposure, and inducible regulatory T cells, which are comprised of IL-10-producing Tr1 cells [2], transforming growth factor- β (TGF- β)producing T_H3 cells [3] and inducible Foxp3⁺ T cells [4]. Both types of regulatory T cell, by virtue of their capacity to control the intensity of effector responses, have been shown to play a major role in the control of host–microbial interactions.

Role of Foxp3⁺ T_{Reg} Cells During Infection in Experimental Models

Foxp3⁺ T_{Reg} cells (T_{Reg}) were initially described as a unique population of CD4⁺ T cells that prevent the expansion of self-reactive lymphocytes and subsequent autoimmune disease [5]. Some of the earliest studies of T_{Reg} cells emphasized that such cells control the extent of immune-mediated pathology. Activated T_{Reg} cells efficiently control self-reactive T cells and innate responses in mouse models of colitis, thereby minimizing collateral tissue damage [6]. A similar scenario can occur during some chronic infections, whereby T_{Reg} cells are required to monitor the constant immune response by the host and to prevent detrimental tissue damage. Experimental evidence supports the idea that T_{Reg}-cell-mediated control of immunopathology may be particularly important for protecting immune-privileged environments or tissues with highly specialized functions, such as the liver or eyes [7, 8]. Even when T_{Reg} cells successfully preserve homeostasis in the host by controlling excessive immune responses, one consequence of such control is enhanced pathogen survival [9] and, in some cases, long-term pathogen persistence. T_{Reg} cells that accumulate at the site of Leishmania infection regulate the function of local effector cells, which prevents efficient elimination of the parasite [10]. In this model of infection, parasite persistence, as a result of immune suppression by T_{Reg} cells, is necessary for the maintenance of protective immunity against the parasite [7, 10]. So, in some instances, T_{Reg} cells can control the fine balance that is established between the pathogen and its host, thus mediating an equilibrium that can become mutually beneficial. In other cases, regulatory control is excessive, allowing the pathogen to replicate without restraint and overwhelm the host, thereby compromising the survival of the host [11].

Natural T_{Reg} Cells and Human Infections

In humans, the establishment of a role for T_{Reg} cells during infection has been complicated by the fact that human Foxp3⁺ T_{Reg} constitutes a more heterogeneous population than in mice. Furthermore, most published studies in humans were conducted by analyzing T_{Reg} frequency or function in peripheral blood. However, in some chronic infections, such as that due to HIV, T_{Reg} cells can accumulate in infected tissues [12], potentially depleting the relevant cells from this compartment. Despite these caveats, some reports provide solid evidence for a role of T_{Reg} cells in many human infections [13]. In most published studies, the removal of CD4⁺CD25⁺ T cells from cultures of peripheral or lymphoid leukocytes from HIV-, HCV-, or HBV-infected patients results in an increase in virus-specific immune responses in vitro [14, 15]. These findings suggest that T_{Reg} cells by suppressing virus-specific immunity may contribute to uncontrolled viral replication, therefore potentially playing a detrimental role in human viral infection. On the other hand, the inverse correlation between HCV-specific TGF- β response by CD4⁺CD25⁺ T cells and liver damage strongly support the idea that T_{Reg} cells also have a role in controlling chronic inflammatory responses and liver damage in HCV carriers [16]. Interestingly, patients who are chronically infected with HCV and go on to develop autoimmunity have fewer peripheral T_{Reg} cells [17]. However, the link between chronic infection, autoimmune disorders, and dysregulation of T_{Reg}-cell function requires further analysis.

Possible Mechanism of Action of Foxp3⁺ T_{reg} During Infection

Despite extensive studies in various models, the mechanism by which Foxp3⁺ T_{reg} cells limit effector responses during the infection process remains largely unknown. While IL10, TGF- β , and CTLA-4 have been shown to potentially contribute to their function in both experimental models and human infections, a role for recently identified molecules such as adenosine, cAMP, or IL-35 and their contribution to T_{reg} function has not yet been evaluated [18–21]. It is important to keep in mind that regulatory T cells are likely to utilize several mechanisms in a manner specific to a given situation. Furthermore, regulation of infected tissues usually arises from the coordinated action of various populations of regulatory cells and varies according to the site of infection or the degree of inflammation. In addition, the mechanisms by which T_{Reg} exert their function are likely to be complementary, as shown in the context of experimental colitis.

Dendritic cells (DCs) appear to be one of the targets of Foxp3⁺ T_{reg} suppressive function. T_{reg} cells directly interact with DCs in vivo [22]. T_{reg} cells, which are more mobile than naïve T cells in vitro, out-compete the latter in aggregating around DCs via a mechanism dependent on LFA-1 [23]. After forming aggregates, T_{reg} cells specifically down-regulate the expression of CD80/86, but not CD40 or class II MHC, on DCs in both a CTLA-4- and LFA-1-dependent manner [23]. T_{reg} exert this CD80/86-down-modulating effect even in the presence of strong DC-maturing stimuli. A consequence of this interaction is the induction of infectious tolerance, which is believed to allow the expansion of the regulatory environment in a bystander manner. The interaction of T_{reg} with DCs impairs the capacity of the antigen-presenting cell (APC) to establish a lasting interaction with effector T cells [24], and CTLA-4 appears to play an important role in this process [25]. Importantly, T_{reg} via CTLA-4 interaction can initiate the immunoregulatory pathway of tryptophan catabolism in DCs. The mechanisms by which IDO downregulates immune responses are still elusive and may involve multiple pathways. In particular, CD4⁺ T cells, exposed to low tryptophan and kynurenin produced increased amounts of IL-10 and TGF- β but little IFN- γ and IL-4 [26]. Thus, independently of their direct control of microbe-specific immune responses, following activation, T_{reg} can suppress unrelated immune responses in a non-antigen-specific manner either through cell contact or through the regulatory cytokines they produce—a mechanism known as bystander suppression.

A few years ago, the concept of the “hygiene hypothesis” emerged, stating that increasing incidences of allergy and asthma in Western countries are a consequence of reduced infectious stresses during early childhood [27]. The mechanistic explanations appear to be associated with a “counter-regulatory” model involving the induction of various regulatory T-cell populations during infection. For example, during gastrointestinal infection, helminth-driven T_{Reg}-cell suppression of effector function is responsible for protection against subsequent airway inflammation [28]. It is likely that some of these mechanisms have evolved as a result of our symbiotic relationship with gut flora. Thus, the presence of symbiotic and pathogenic microorganisms, in the gut or other peripheral tissues, could lead to the maintenance of a pool of activated regulatory T cells (both natural and inducible) that would maintain host immune homeostasis and enhance the threshold required for immune activation and induction of an immune response [29]. The benefit of such deactivation would be to decrease the instances of aberrant immune responses, such as allergic and autoimmune disorders.

Role of IL-10 Producing T cells During Infections

The role of IL-10 as an immunoregulatory cytokine in infection has been mainly documented in the context of chronic infections [30]. IL-10 can inhibit the immune

responses [mediated by both T helper 1 (T_H1) cells and T_H2 cells] (Fig. 1) to many pathogens in experimental models [31–33] and in human infectious diseases, such as tuberculosis, malaria, hepatitis C, filariasis, leishmaniasis, and schistosomiasis [34–39]. The most remarkable example of this control is illustrated by its crucial role during acute infection of mice with *Toxoplasma gondii*. In this model, IL-10 production by T cells is the key regulator of effector-cell responses, as IL-10-deficient mice can control parasite number but they succumb to lethal immunopathology driven by unrestrained effector-cell responses [40]. During T_H2-dominated helminths infection, the majority of IL-10 is produced by T_H2 cells [30]. Besides T cells, IL-10 can be produced by numerous cell types, including B cells, natural killer cells, macrophages, and DCs (reviewed in [30]). During acute *Plasmodium yoelii* infection, a subset of regulatory DC expressing CD11c^{low} CD45RB^{hi} that induces IL-10 secreting T cells becomes the predominant DC population in the spleen [41]. IL-10 can also be produced by natural T_{reg} and, in some cases, is associated with their function. However, in most cases, the inducible T_R1-cell population is the relevant source of this cytokine during infection. During various infections, T_R1 cells develop from conventional T cells after encountering certain signals, such as exposure to deactivated or immature APCs, repeated exposure to antigen, or IL-10 itself (reviewed in [2, 42]). Of note, these conditions prevail during chronic infection in which APC functions are often targeted by the pathogen and there is chronic exposure to microbial antigens. Consistent with a role for these cells in human disease, T_R1-cell clones can be isolated from patients who are chronically infected with HCV [34]. Interestingly, these regulatory clones had similar viral antigen specificity to the protective T_H1-cell clones isolated from the same patient [34]. Additionally, defined microbial products can manipulate DCs to favor the induction of regulatory T cell populations [43]. For example, filamentous haemagglutinin from *Bordetella pertussis* was shown to induce IL-10 production by DCs; these DCs favored the differentiation of naïve T cells into T_R1 cells [44]. Similarly, T_R1 cells can be generated from naïve T cells in the presence of DCs stimulated with phosphatidylserine from *Schistosoma mansoni* [45].

Although T_R1 cells define a population of T cells that can produce IL-10 and/or TGF- β , some IL-10-producing T cells can also produce IFN- γ . The autocrine regulation by IL-10 of Th1 and Th2 cells was initially described in human clones [46]. In the context of an infectious disease, IFN- γ /IL-10 double producers were first described in the bronchoalveolar lavage of patients with tuberculosis [47] and in individuals chronically infected with *Borrelia burgdorferi* [48]. Indeed, in many chronic infections in humans and experimental animals, the presence of CD4⁺ T cells that produce high levels of both IL-10 and IFN- γ have been documented (reviewed in [49]).

Recently, it was shown that IFN- γ and IL-10-producing CD4⁺ T cells emerge during experimental infection with *T. gondii* and in a model of nonhealing Leishmaniasis [50, 51]. These cells were reported to share many features with T_H1 cells and were the main source of protective IL-10. Furthermore, these T cells were identified as activated T-bet⁺ T_H1 cells and were distinct from T_H2 cells, natural T_{Reg} cells, or other subsets of inducible regulatory T cells. Unlike IFN- γ production, IL-10 production was transiently observed in only a fraction of the IFN- γ -producing cells and was produced more rapidly by recently activated T cells than by resting T cells [50]. The instability of IL-10 synthesis, which was observed only when the T_H1 cells were fully activated, is probably necessary to prevent sustained suppression of effector functions. Thus, it appears that, in some cases, cells with regulatory properties could arise from fully differentiated T_H1 cells as a negative-feedback loop. It is likely that numerous previous studies of T_R1 cells were in fact incriminating similar populations. These IFN- γ -and IL-10-producing T cells may represent a dominant regulatory response to infections induced during a highly polarized T_H1-cell response.

Potential Role for Converted FOXP3⁺ Regulatory T Cells During Infection

Until recently, the expression of Foxp3 on CD4⁺ T cells was believed to indicate the thymic origin of these cells. However, there is mounting evidence that Foxp3⁺ T_{Reg} cells can also develop extrathymically. In vitro studies have shown that conversion of naïve peripheral CD4⁺ CD25⁻ into Foxp3⁺ regulatory T cells could be achieved through ligation of the T-cell receptor in the presence of TGF- β [4]. Such conversion can be mimicked in vivo by delivering antigen under subimmunogenic conditions [52] or by targeting antigen to DCs via the regulatory receptor DEC205 [53]. Targeting or manipulating DCs, as well as chronic exposure to low doses of antigen, is characteristic of many chronic infections. During infection, the downstream effects of inflammatory responses are also often associated with anti-inflammatory processes including TGF- β production. Furthermore, some pathogens target sites in the body in which TGF- β is abundant, such as the gastrointestinal tract, the skin, and the eye [54]. TGF- β can also be produced by infected cells or cells that are in contact with the microorganisms. Interestingly, following malaria infection of humans, enhanced TGF- β and Foxp3⁺ T_{Reg}-cell responses in peripheral blood correlate with an enhanced parasitic growth rate [55]. One intriguing observation is that only a fraction of infected individuals displayed this TGF- β burst. Whether there is a genetic predisposition in the capacity of individuals to produce cytokines known to promote regulatory T-cell induction and how this could potentially correlate with their susceptibility to infectious diseases remains to be addressed. This may not be the case in acute infection scenarios, such as with *Listeria monocytogenes* infection in mice that failed to induce Foxp3 by conventional CD4⁺ T cells [56]. Thus, a highly inflammatory environment will prevail during acute infection and not favor the emergence of Foxp3⁺ T cells. This hypothesis is supported by the observation that T_H1 or T_H2 polarizing cytokines can interfere with the induction of these cells [57]. On the other hand, we speculate that chronic infections may require an additional layer of regulation, which would be provided by converted Foxp3⁺ regulatory T cells. To support this, we have found that BCG can specifically induce new populations of Foxp3⁺ T cells that accumulate at the dermal site of infection (Blank and Belkaid, unpublished observation). Some pathogens that target highly regulated environments, such as the gut, may also utilize this pathway to their own advantage.

The gut is a major mucosal barrier, constantly exposed to both pathogenic and commensal microorganisms along with ingested dietary antigens. It is, therefore, a highly regulated immunologic site that must generate both tolerogenic and immunogenic responses. Immune reactivity against nonpathogenic gut elements is not only wasteful but dangerous to the host and is known to lead to severe tissue damage (e.g., inflammatory bowel disease). On the other hand, the development of active immunity is required to protect the host against invasive pathogens. Different subsets of regulatory T cells have been shown to be instrumental in the maintenance of this complex homeostasis. Additionally, several subsets of DCs with regulatory properties have been described with the capacity to induce IL-10 secretion from T cells or induce oral tolerance at steady state conditions [58–60] reviewed in [61]. In fact, no other tissue is submitted to greater levels of antigenic pressure than the gut. The adult human intestine contains up to 100 trillion microorganisms [62]. At birth, the massive exposure to these neoantigens, as well as the remodeling of the gut flora following infection, imposes a unique challenge to this environment. Thus, the gastrointestinal tract requires additional levels of control to maintain the delicate balance between tolerance to commensal bacteria and food products and the capacity to mount an effective immune response against ingested pathogens. Induction of Foxp3⁺ T_{Reg} in this environment appears to be one of these regulatory mechanisms.

We and others have recently demonstrated that the gut-associated lymphoid tissue (GALT) is a preferential site for the peripheral induction of Foxp3⁺ T_{Reg} cells [63–66]. A role for

local DCs in this conversion process is supported by the observation that DCs from the lamina propria of the small intestine and from MLNs are noticeably better than splenic DCs at inducing the expression of Foxp3 in naïve T cells in the presence of exogenous TGF- β [63, 64]. Similarly, lamina propria macrophages can efficiently induce Foxp3⁺ T cells [67]. In particular, DCs expressing CD103⁺ in these two compartments can induce Foxp3⁺ T cells in the absence of any exogenous factors [63, 64]. This conversion process was associated with their capacity to release bioactive TGF- β , which could further be linked with their capacity to activate latent TGF- β [64]. A compelling hypothesis would be that these gut-converted T_{Reg} cells could become part of the peripheral T_{Reg}-cell pool. Therefore, over time, the gut flora, oral pathogens, or food may have an important role in shaping the repertoire of peripheral Foxp3⁺ T_{Reg} cells. The relative contribution of these converted T_{Reg} cells to peripheral tolerance and the outcome of infections, as well as how pathogens can utilize or interfere with this pathway to favor their own survival, remains to be addressed. Currently, in the absence of definitive markers to distinguish endogenous vs converted Foxp3⁺ regulatory T cells, these questions will remain difficult to answer.

It is becoming clear that nutrient status can impact an individual's susceptibility to intestinal pathologies [68]. In the case of vitamin A, and in particular, its transcriptionally active metabolite, retinoic acid (RA), prolonged insufficiency not only disrupts the integrity of the intestinal epithelial barrier but also prevents the proper deployment of effector lymphocytes into the GALT following priming. Indeed, the capacity of GALT DCs to imprint gut homing receptor to lymphocytes is associated with their capacity to release RA [68–70]. More recently, it was demonstrated that RA and cytokines produced by DCs in the Peyer's patches synergized to promote IgA secretion by gut activated B cells [70]. Importantly, a recent report demonstrated that the addition of RA to naturally occurring T_{Reg} in vitro can promote their expression of gut tropism receptors and subsequently favor their migration to the GALT [71]. Another effect of RA on immune regulation of the gastrointestinal (GI) tract is associated with its capacity to enhance the TGF- β -mediated generation of Foxp3⁺ T_{Reg} from naïve T cells by gut DCs [63–65, 67, 72–75]. The induction of Foxp3 observed in the presence of small-intestinal lamina propria DCs and CD103⁺ MLN DCs can be inhibited by a retinoic-acid receptor antagonist [63, 64]. Conversely, incubation of splenic or CD103[−] MLN DCs with both TGF- β and RA enhanced their capacity to induce Foxp3⁺ T_{Reg} [63–65]. RA produced by intestinal macrophages can also synergize with TGF- β to induce Foxp3⁺ T_{Reg} [67]. Importantly, RA can also induce the conversion of naïve CD4⁺ T cells purified from human cord blood into Foxp3⁺ T_{Reg} cells [72]. Reciprocally, RA can inhibit the generation of Th-17 [65, 72, 74, 75]. Taken together, this suggests that RA may play an important role in maintaining the balance between effector and regulatory populations in the GI tract. The mechanism by which RA produced by DCs can enhance the capacity of TGF- β to induce Foxp3 on naïve T cells remains unclear but is likely due to a conjunction of effects on both T cells and DCs. Thus, defined microenvironments may have evolved self-containing strategies in which local mediators can imprint homing properties while at the same time favoring the induction or function of T_{Reg}. Sitespecific cells or factors such as neurons or hormones can also favor the induction of Foxp3⁺ T_{Reg} [76, 77]. It is therefore tempting to speculate that a link between homing and regulatory T cell induction may represent a more general mechanism. Such a strategy could allow the constant generation and migration of T_{Reg} to defined compartments. Thus, these T_{Reg} would be expected to have the prerequisite antigen specificities (e.g., flora antigens), status of activation, and survival requirement, allowing them to regulate a defined microenvironment.

Manipulation of Foxp3⁺ T_{Reg} by the Gut Flora

The tissues of the GI tract are constantly exposed to TLR ligands harbored by the commensal gut flora [78]. These microflora play a central role in the maintenance and

control of host homeostasis. In addition to promoting development of the immune system and control of metabolic functions, intestinal microflora play a major protective role by displacing pathogens and enhancing barrier fortification [79, 80]. TLRs are widely expressed by cells of hematopoietic origin, including professional APCs, DC and macrophages, T and B lymphocytes, and nonhematopoietic cells, including the epithelial cells lining the intestinal tract [81]. The initial identification of TLRs in the splenic and peripheral blood leukocyte compartments paved the way for our understanding of how engagement of these molecules by invasive pathogens can activate inflammatory cascades that initiate adaptive immunity [82]. However, mucosal tissues via their interaction with commensals are the only environments in constant contact with TLR ligands.

Yet, the purpose of TLR signaling by the commensal flora has only recently begun to be elucidated. For example, it is now clear that TLR signaling in the intestinal epithelial compartment is crucially involved in the maintenance of intestinal homeostasis and tissue repair [83]. Furthermore, these signals positively regulate the sampling of luminal contents by DC from the underlying lamina propria compartment [84]. Commensal floral interactions with TLRs have also been shown to mediate tolerance to food antigens [85].

Recent evidence suggests that $\text{Foxp3}^+ \text{T}_{\text{reg}}$ also mediate intestinal homeostasis. Their absence or failure to properly patrol the GALT leads to reactivity against the commensal flora and subsequent colitis [86]. TLR signaling has been shown to impact T_{reg} homeostasis [87]. T_{reg} themselves selectively express TLRs, including 2, 4, 5, and 8 [87]. Interaction with some of these ligands, such as those binding TLR2, can favor T_{reg} expansion both in vitro and in vivo [88, 89]. Accordingly, in TLR2-deficient mice, T_{reg} frequencies in both gut and secondary lymphoid tissues are decreased [88, 89]. In TLR9-deficient mice, on the other hand, we observed increased T_{reg} frequencies in all of the intestine effector tissues (Hall and Belkaid, submitted). Together, these findings indicate that TLR ligands can exert differential effects on T_{reg} homeostasis, which may explain why Myd88-deficient mice or germ-free mice have unaltered T_{reg} frequencies [83, 88, 90]. This suggests that the interaction with persistent microbes does not always lead to the induction or increase of T_{reg} function. For instance, DCs activation that can be mediated by TLR ligands impairs T_{reg} conversion [73]. Indeed, we found that gut flora derived DNA, but not other TLR agonists, strongly constrained the capacity of lamina propria DCs to induce T_{reg} conversion in vitro and can act as a natural adjuvant for priming intestinal responses via modulation of $\text{T}_{\text{reg}}/\text{T}_{\text{eff}}$ equilibrium (Hall and Belkaid, unpublished data). This would suggest that, in some highly regulated environment, persistent microbes might limit peripheral conversion by modulating APC function in order to preserve the capacity of their host to protect themselves from pathogenic infection.

In some circumstances, the regulation exerted by regulatory T cells is excessive, thus preventing the establishment of protective immune responses, whereas in other circumstances, this control is not sufficient to prevent immunopathology. At both extremes, manipulation of regulatory T cells has been shown to potentially offer therapeutic potential. Because T_{Reg} cells offer an opportunity for microorganisms to generate favorable conditions for persistence, their induction and survival can also be manipulated by microbes. Indeed, some recent reports suggest that some pathogens may provide survival/proliferative signals to T_{Reg} . In addition, microbe-associated DC maturation [91], stimulation of TLRs, other pattern-recognition receptors [87], and induction of cytokine production can all favor T_{Reg} -cell activation (or induction) and thereby support survival of the pathogen. These concepts now provide the basis for new therapeutic approaches in which microbial strategies could be utilized to induce or manipulate regulatory T cells to control allergic and autoimmune diseases.

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Fig. 1. Origins and specificities of regulatory T cells during infections

The origin and antigen specificity of regulatory T cells (TReg cells) may vary according to the site and the nature of the infection. In acute infection, tissue damage may be associated with enhanced presentation of self-antigens. In this case, self-reactive natural TReg cells may be activated and could, in a bystander manner, limit effector responses against the pathogen. At sites of infection, various populations of microbe-specific regulatory T cells can be induced [e.g., induced Foxp3⁺ Treg (iFoxp3⁺), Th3⁺, Th1⁺, or Th2⁺-producing IL-10 or Tr1 cells]. In some chronic infections, there is evidence that natural Treg cells derived from the thymus may also accumulate at sites of infection and can recognize microbial antigens. In an environment that is rich in transforming growth factor-β (TGF-β) and the vitamin A metabolite, retinoic acid (RA), such as the gut, peripheral conversion of naïve CD4⁺ T cells into Foxp3⁺ Treg cells may occur in response to food or gut flora antigen or during oral infection. This conversion may be favored by specialized population of DCs expressing CD103 or resident macrophages. These induced Foxp3⁺ T cells (iFoxp3⁺Treg) migrate back to the gut via their expression of gut homing receptor (α4β7 and CCR9) and could potentially limit immune responses. Some of these induced iFoxp3⁺ Treg may be able to recirculate and could contribute to the control of peripheral homeostasis. Blue arrows indicate induction. Red arrows indicate limitation of immune responses