Published in final edited form as:

Curr Pathobiol Rep. 2018 March ; 6(1): 29–34.

Regional control of regulatory immune cells in the intestine

Tina L. Morhardt, M.D.¹, Atsushi Hayashi, Ph.D.^{2,3}, John Y. Kao, M.D.², and Nobuhiko Kamada, Ph.D.²

¹Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of Michigan, Ann Arbor, MI

²Division of Gastroenterology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI

³Miyarisan Pharmaceutical Co., Ltd., Research Laboratory, Tokyo 114-0016, Japan

Abstract

Purpose of review—The intestine contains the largest compartment of immune regulatory cells which include T regulatory cells and IL-10 producing macrophages. These cell populations serve to restrain unnecessary immune responses of the intestine, which may lead to the pathogenesis of Crohn's disease or food allergy.

Recent findings—This review discusses the recent findings pertaining to the functional regulation of these cells which may provide insight into novel therapies. Both T regulatory cells and macrophages are regulated in microbiota-dependent and microbiota-independent manners, i.e., dietary antigens. Often, this is specific to regional specialization and environment in small intestine vs. colon.

Summary—These immune regulatory cells are largely regulated by microbiota in the colon, whereas in the small intestine, the microbiota has less affect, as seen in germ-free mice studies. Targeting these cells in their specific compartments may direct future treatment modalities for inflammatory bowel disease as ulcerative colitis and Crohn's are vastly different diseases.

Keywords

Gut immune system; regulatory T cells; macrophages; interleukin-10; gut microbiota; dietary antigen

Address correspondence to: Nobuhiko Kamada, Division of Gastroenterology, Internal Medicine, University of Michigan, 1150 W. Medical Center Drive, Ann Arbor, MI 48109. nkamada@umich.edu.

Disclosures:

T.L.M., J.Y.K., and N.K. have no financial conflicts of interest. A.H. is employed by Miyarisan Pharmaceutical Co., Ltd.

Conflict of Interest

The authors declare that they have no conflict of interest.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

Introduction

The gastrointestinal tract (GI) is incessantly exposed to resident antigens, including the gut microbiota and dietary factors. Although the stimulation from these resident antigens is critical for the host vital processes such as the maturation of GI immune system, unwanted immune responses to these antigens are harmful to the host and lead to the development of diseases, such as inflammatory bowel disease (IBD) and food allergy. To properly control the immune responses against resident antigens, the GI immune system is equipped with various regulatory immune cells, such as regulatory T cells (Treg) and interleukin (IL)-10-producing macrophages. Recently, it has become evident that the stimulations from resident antigens and related factors, such as commensal microbes, microbial metabolites, and dietary factors, have modulating effects on these regulatory immune cells. Likewise, there is increasing evidence that there are regional differences in regulation of these cells, depending on whether small or large intestine. The regional control of regulatory immune cells is due to the variation in environmental factors between the different sites of the intestine. For example, the density of commensal bacteria is higher in the large intestine compared to the small intestine. Likewise, the composition of dietary factors differs between the small and large intestine, as most of the micronutrients are absorbed in the small intestine and never reach the large intestine at high concentration, while the large intestine is enriched with indigestible fibers. In this review, we will discuss the region-specific control of the development and maintenance of regulatory immune cells.

Regulation of Treg development in the intestine

Tregs are one of the major regulatory immune cells in the intestine. Tregs are CD4⁺ regulatory cells characterized by their expression of transcription factor forkhead box P3 (Foxp3) (1). These cells regulate gene expression and modulate the activation of other leukocyte populations, thus contributing to their role in immune homeostasis. Tregs are further differentiated into two subsets. Tregs are developed either directly in the thymus, known as thymus-derived Tregs (tTregs) or from naïve T cells in the periphery, termed peripheral Tregs (pTregs) or induced Tregs (iTregs) *in vitro*. tTregs, making up the majority of Tregs, are developed from thymic T cells, prompted by T cell receptor (TCR) signals induced by self-antigens. tTregs accumulate in the intestine and undergo further maturation during interaction with resident antigens. pTregs are derived from naïve CD4⁺ T cells from the thymus, which differentiate in the periphery in the presence of TCR signaling in response to antigen stimulation along with cytokines such as transforming growth factor- β (TGF- β). TGF- β has a role in Treg differentiation by inducing *Foxp3* expression in naïve T cells (2). It is thought that both Treg populations act to maintain immune homeostasis.

Microbiota-dependent regulation of Tregs

In the colon, the development of Foxp3⁺ pTregs is tightly regulated by commensal microbiota (3–5). In the pioneer study in this field, Atarashi et al. showed that colonic Foxp3⁺ pTregs and its IL-10 production are markedly reduced in germ-free (GF) mice when compared to specific-pathogen-free (SPF) mice (3). Later studies have shown that the microbiota-dependent subset of pTreg expresses Retinoic acid-related orphan receptor

gamma t (ROR γ t) (6). In mice, Atarashi et al. identified 46 strains of the *Clostridium* genus belonging to clusters IV and XIVa (also known as *Clostridium leptum* and *coccoides* groups, respectively) as Treg-inducing bacteria (3). In humans, Atarashi et al. further identified 17 Treg-inducing *Clostridia* strains in the microbiota, which belong to the *Clostridium* clusters IV, XIVa, and XVIII (7). These *Clostridium* strains were found to preferentially induce colonic ROR γ t⁺ Tregs, which produce IL-10.

Clostridia strains contribute to short chain fatty acid (SCFA) production, by the fermentation of indigestible dietary fiber. SCFAs act upon colonic T cells via receptor GPR43. SCFAs, such as butyrate and propionate, have been found to enhance Treg generation (8–10). Butyrate, through GPR43, inhibits histone deacetylase (HDAC) to promote Treg accumulation to epigenetically regulate the *Foxp3* gene in Tregs (9–10). These SCFAs were able to induce TGF- β 1 production from epithelial cells *in vitro*, which in turn positively affects Treg expansion (7). Moreover, it is reported that SCFAs increase interleukin 10 (IL-10) production in T cells in an mTOR-dependent manner, which goes on to modulate the Treg population (11).

In addition to bacterial metabolites, bacterial cell wall components also have properties to elicit Treg differentiation via recognition by innate sensing receptors, such as TLRs. A capsular polysaccharide (PSA) of *Bacteroides fragilis* from humans stimulates IL-10 production by Foxp3⁺ Tregs in the colon (12, 13). *B. fragilis* releases outer membrane vesicles (OMVs) which produce PSA, which then acts upon colon dendritic cells to produce IL-10 by TLR2 (13). Moreover, several probiotic bacteria, such as *Bifidobacterium* and *Lactobacilli*, have also been shown to promote IL-10 production from colonic Tregs, enhancing production of TGF- β and IL-10 in colon dendritic cells and macrophages (14, 15).

Furthermore, the gut microbiota indirectly regulates the development of Foxp3⁺ Treg through activating innate immune cell cross-talk. There is evidence of interaction among mononuclear phagocytes and innate lymphoid cells (ILCs) in regulating the induction of Tregs in the large intestine. The cross-talk between mononuclear phagocytes and ILCs leads to the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) by ILCs, which in turn promotes the differentiation of Tregs in the intestine (16). Of note, commensal microbiota is required for the activation of mononuclear phagocytes, suggesting that the microbiota is a critical hub for the Treg induction by ILCs.

Thus, the microbiota, its metabolites and cell wall components play pivotal roles in the induction of Tregs, most likely Foxp3⁺ROR γ t⁺ pTreg in the large intestine (15) (Figure 1).

Microbiota-independent development of Tregs

Although the gut microbiota is critical for the induction of pTreg cells in the large intestine, the density of the microbiota is significantly lower in the small intestine (17). Moreover, the concentration of certain key Treg-inducing microbial metabolites, such as SCFAs, are markedly lower in the small intestine since the abundance of obligate anaerobes, which degrade dietary fibers and generate SCFAs, is significantly lower in the small intestine than

the colon (18). Consistent with this notion, the abundance of Foxp3⁺ Treg is not decreased in the small intestine of GF mice compared to SPF control mice (3). These facts indicate that other environmental factors that are enriched in the small intestine may play a more dominant role in the induction of pTreg in this region. In this context, a recent study revealed that dietary antigens play a role in Treg induction in the small intestine. Depletion of macromolecules from the diet precludes the development of pTregs in the small intestine (19), while colonic pTregs are maintained. Additionally, these small intestine peripheral Tregs are not affected in GF mice (19), which suggests this population is dependent on dietary factors. Dietary macromolecules are additionally required for maintenance of pTregs. This implies that a large proportion of Tregs are induced by dietary antigens in the small intestine, distinct from the colon.

Other dietary factors are also reported to contribute to the regulation of Tregs. Retinoic acid is a vitamin A metabolite found in high concentrations in the small intestine. It has been shown that RA induces the differentiation of Foxp3⁺ Tregs from naïve T cells as a cofactor for TGFβ conversion of naïve T cells (20). Retinoic acid acts upon Treg differentiation by enhancing the expression of gut homing receptors on T cells (21, 22). RA additionally can suppress cytokines produced by effector T cells such as IL-4 and IL-6, to indirectly activate the *Foxp3* gene (23).

1,25-dihydroxyvitamin D3 has been shown to induce FoxP3⁺ expression in T cells through binding to target DNA sequences VDREs which are present in the *Foxp3* gene (24). Vitamin B9 (folic acid) has also been shown to positively affect colonic Treg cells. Vitamin B9 receptor is expressed on Treg cells and contributes to Treg survival in the colon by inducing anti-apoptotic factor Bcl-2 (25).

Thus, certain dietary factors modulate Treg development in the intestine in a microbiota independent manner (Figure 1). Although the microbiota-independent control of Tregs likely occurs predominantly in the small intestine, certain dietary factors may contribute to the induction/maintenance of Tregs in the large intestine as well.

Regulation of IL-10 producing macrophages

In addition to Tregs, various regulatory-type immune cell subsets are present in the GI tract. Immune cells producing an anti-inflammatory cytokine IL-10 are known to play a crucial role in dampening excessive immune reactions to resident antigens and hence control GI homeostasis. Indeed, mice lacking IL-10 fail to control immune responses against their commensal microbes and thereby lead to the development of spontaneous bacteria-driven IBD (26–28). In the intestine, IL-10 is produced by several immune cell subsets including Foxp3⁺ Treg, Foxp3[−] CD4⁺ T cells, B cells, and mononuclear phagocytes such as macrophages. Resident macrophages play a central role in the homeostatic maintenance of the intestine (29–32). As is typical of most tissue macrophages, resident macrophages perform phagocytic functions with bacteria that has invaded to intestinal lamina propria (33).

Unlike peripheral blood monocytes or other tissue macrophages, intestinal resident macrophages display unique anergic/tolerogenic phenotypes. Intestinal resident

macrophages lack expression of microbial sensors (TLRs) on their cell surface thereby making them resistant to TLR stimulation. Exposure of intestinal macrophages to microbial stimuli does not produce pro-inflammatory cytokines such as IL-1, IL-6, TNF α , due to lack of innate response receptors (30, 34, 35).

Alternatively, intestinal resident macrophages produce constitutively large amounts of anti-inflammatory IL-10 (30, 34). This contributes to the immune modulatory behavior of intestinal macrophages. IL-10 production by macrophages enhances the maintenance of antigen-specific Foxp3⁺ Tregs in the intestine (36) as seen in decreased numbers of Foxp3⁺ Tregs in chemokine (C-X3-C motif) receptor 1 (CX3CR1) depleted mice (36, 37).

The regulation of intestinal macrophages has been less studied than Tregs. However, it is known that the gut microbiota plays a key role in the regulation of intestinal macrophages in the colon. In colon of GF mice, the lack of microbiota fails to induce IL-10 producing intestinal macrophages (38, 39). Colonic macrophages further have been shown to be constantly replenished by Ly6C^{hi} blood monocytes, requiring microbiota in order to facilitate the replenishment of macrophages (38). Additionally, it has been shown that IL-10 production from colonic macrophages is decreased in GF mice (32, 40, 41). Furthermore, microbial metabolites, such as butyrate and niacin (vitamin B3), have been shown to induce IL-10 production by colonic CD11c⁺ macrophages and dendritic cells via GPR109a receptor, and therefore show improved ability to induce differentiation of naïve T cells to Tregs (42) (Figure 1).

Alternatively, the gut microbiota is not necessary to induce IL-10 producing intestinal macrophages in the small intestine (39), similarly to pTregs in the small intestine. Interestingly, IL-10 producing macrophages are diminished in mice that lack enteral nutrition (39), implying the necessity of enteral dietary factor(s) for the regulation of small intestine macrophages.

Conclusion

Tregs and IL-10-producing macrophages are critical immune regulatory cells contributing to the homeostasis of the intestine. Their functional regulation has been described as both dependent and independent of gut microbiota (Figure 1). This differentiation can be seen when comparing cell populations in different regions of the intestine. It has been increasingly more apparent that, in the small intestine, Tregs and IL-10 producing macrophages are predominantly regulated by dietary antigens, in a microbiota-independent manner. This implies that the predominant resident antigens in the small intestine, i.e., dietary antigens, contribute to the regulation of these immune cell types. This contrasts with the microbiota-dependent regulation of IL-10 producing macrophages and Tregs in the colon.

Further studies will be needed to elucidate the mechanisms of how dietary factors stimulate Tregs and macrophages. The regional differences in regulation will help direct our understanding of the development of pathology and potential therapies. For example, different therapies involving the alteration of dietary antigens may affect the treatment of

inflammatory bowel disease. These factors may provide the basis and mechanism of therapies such as exclusive enteral nutrition in the achievement of remission of new onset Crohn's in pediatric patients.

Currently, there is abundant research in the use of probiotics and intestinal inflammation such as inflammatory bowel disease. These undoubtedly have effects on the entire gastrointestinal tract. However, we should be aware that its effects on the small intestine and colon will differ. More research into this will help us understand how to best guide our use of these therapies.

Acknowledgments

This work was supported by NIH T32 DK094775 (T.L.M.), DK108901 and DK108901 (N.K).

References

Recently published papers of particular interest have been highlighted as:

+ Of importance

++ Of major importance

1. Sakaguchi S, Miyara M, Costantino CM, et al. FOXP3+ regulatory T cells in the human immune system. *Nat Rev Immunol*. 2010; 10:490–500. [PubMed: 20559327]
2. Chen W, Jin W, Hardegen N, et al. Conversion of peripheral CD4+CD25– naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. *J Exp Med*. 2003; 198:1875–1886. [PubMed: 14676299]
3. Atarashi K, Tanoue T, Shima T, et al. Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science*. 2011; 331:337–341. [PubMed: 21205640]
4. Geuking MB, Cahenzli J, Lawson MA, et al. Intestinal bacterial colonization induces mutualistic regulatory T cell responses. *Immunity*. 2011; 34:794–806. [PubMed: 21596591]
5. Tanoue T, Atarashi K, Honda K. Development and maintenance of intestinal regulatory T cells. *Nat Rev Immunol*. 2016; 16:295–309. [PubMed: 27087661]
6. Ohnmacht C, Park JH, Cording S, et al. MUCOSAL IMMUNOLOGY. The microbiota regulates type 2 immunity through RORgammat(+) T cells. *Science*. 2015; 349:989–993. [PubMed: 26160380]
7. Atarashi K, Tanoue T, Oshima K, et al. T induction by a rationally selected mixture of *Clostridia* strains from the human microbiota. *Nature*. 2013
8. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science*. 2013; 341:569–573. [PubMed: 23828891]
9. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013; 504:446–450. [PubMed: 24226770]
10. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*. 2013; 504:451–455. [PubMed: 24226773]
11. Park J, Kim M, Kang SG, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. *Mucosal Immunol*. 2015; 8:80–93. [PubMed: 24917457]
12. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc Natl Acad Sci U S A*. 2010; 107:12204–12209. [PubMed: 20566854]
13. Round JL, Lee SM, Li J, et al. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. *Science*. 2011; 332:974–977. [PubMed: 21512004]

14. Di Giacinto C, Marinaro M, Sanchez M, et al. Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF-beta-bearing regulatory cells. *J Immunol.* 2005; 174:3237–3246. [PubMed: 15749854]
15. Tang C, Kamiya T, Liu Y, et al. Inhibition of Dectin-1 Signaling Ameliorates Colitis by Inducing Lactobacillus-Mediated Regulatory T Cell Expansion in the Intestine. *Cell Host Microbe.* 2015; 18:183–197. [PubMed: 26269954]
- 16+. Mortha A, Chudnovskiy A, Hashimoto D, et al. Microbiota-dependent crosstalk between macrophages and ILC3 promotes intestinal homeostasis. *Science.* 2014; 343:1249288. This study describes microbiota-dependent regulatory control of colonic Tregs by macrophages and dendritic cells by way of cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by ROR γ t+ type 3 innate lymphoid cells. [PubMed: 24625929]
17. Mowat AM, Agace WW. Regional specialization within the intestinal immune system. *Nat Rev Immunol.* 2014; 14:667–685. [PubMed: 25234148]
18. Cummings JH, Pomare EW, Branch WJ, et al. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut.* 1987; 28:1221–1227. [PubMed: 3678950]
- 19++. Kim KS, Hong SW, Han D, et al. Dietary antigens limit mucosal immunity by inducing regulatory T cells in the small intestine. *Science.* 2016; 351:858–863. This study demonstrated microbiota-independent dietary antigens are required for the induction of peripheral Tregs in the small intestine. [PubMed: 26822607]
20. Coombes JL, Siddiqui KR, Arancibia-Carcamo CV, et al. A functionally specialized population of mucosal CD103+ DCs induces Foxp3+ regulatory T cells via a TGF-beta and retinoic acid-dependent mechanism. *J Exp Med.* 2007; 204:1757–1764. [PubMed: 17620361]
21. Iwata M, Hirakiyama A, Eshima Y, et al. Retinoic acid imprints gut-homing specificity on T cells. *Immunity.* 2004; 21:527–538. [PubMed: 15485630]
22. Sun CM, Hall JA, Blank RB, et al. Small intestine lamina propria dendritic cells promote de novo generation of Foxp3 T reg cells via retinoic acid. *J Exp Med.* 2007; 204:1775–1785. [PubMed: 17620362]
23. Hill JA, Hall JA, Sun CM, et al. Retinoic acid enhances Foxp3 induction indirectly by relieving inhibition from CD4+CD44hi Cells. *Immunity.* 2008; 29:758–770. [PubMed: 19006694]
24. Kang SW, Kim SH, Lee N, et al. 1,25-Dihydroxyvitamin D3 promotes FOXP3 expression via binding to vitamin D response elements in its conserved noncoding sequence region. *J Immunol.* 2012; 188:5276–5282. [PubMed: 22529297]
25. Kinoshita M, Kayama H, Kusu T, et al. Dietary folic acid promotes survival of Foxp3+ regulatory T cells in the colon. *J Immunol.* 2012; 189:2869–2878. [PubMed: 22869901]
26. Kuhn R, Lohler J, Rennick D, et al. Interleukin-10-deficient mice develop chronic enterocolitis. *Cell.* 1993; 75:263–274. [PubMed: 8402911]
27. Sellon RK, Tonkonogy S, Schultz M, et al. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. *Infect Immun.* 1998; 66:5224–5231. [PubMed: 9784526]
28. Kim SC, Tonkonogy SL, Albright CA, et al. Variable phenotypes of enterocolitis in interleukin 10-deficient mice monoassociated with two different commensal bacteria. *Gastroenterology.* 2005; 128:891–906. [PubMed: 15825073]
29. Cerovic V, Bain CC, Mowat AM, et al. Intestinal macrophages and dendritic cells: what's the difference? *Trends Immunol.* 2014; 35:270–277. [PubMed: 24794393]
30. Denning TL, Wang YC, Patel SR, et al. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. *Nat Immunol.* 2007; 8:1086–1094. [PubMed: 17873879]
31. Denning TL, Norris BA, Medina-Contreras O, et al. Functional specializations of intestinal dendritic cell and macrophage subsets that control Th17 and regulatory T cell responses are dependent on the T cell/APC ratio, source of mouse strain, and regional localization. *J Immunol.* 2011; 187:733–747. [PubMed: 21666057]
32. Rivollier A, He J, Kole A, et al. Inflammation switches the differentiation program of Ly6Chi monocytes from antiinflammatory macrophages to inflammatory dendritic cells in the colon. *J Exp Med.* 2012; 209:139–155. [PubMed: 22231304]

33. Smythies LE, Sellers M, Clements RH, et al. Human intestinal macrophages display profound inflammatory anergy despite avid phagocytic and bacteriocidal activity. *J Clin Invest*. 2005; 115:66–75. [PubMed: 15630445]
34. Kamada N, Hisamatsu T, Okamoto S, et al. Abnormally differentiated subsets of intestinal macrophage play a key role in Th1-dominant chronic colitis through excess production of IL-12 and IL-23 in response to bacteria. *J Immunol*. 2005; 175:6900–6908. [PubMed: 16272349]
35. Franchi L, Kamada N, Nakamura Y, et al. NLRC4-driven production of IL-1 β discriminates between pathogenic and commensal bacteria and promotes host intestinal defense. *Nat Immunol*. 2012; 13:449–456. [PubMed: 22484733]
36. Murai M, Turovskaya O, Kim G, et al. Interleukin 10 acts on regulatory T cells to maintain expression of the transcription factor Foxp3 and suppressive function in mice with colitis. *Nat Immunol*. 2009; 10:1178–1184. [PubMed: 19783988]
37. Hadis U, Wahl B, Schulz O, et al. Intestinal tolerance requires gut homing and expansion of FoxP3⁺ regulatory T cells in the lamina propria. *Immunity*. 2011; 34:237–246. [PubMed: 21333554]
- 38++. Bain CC, Bravo-Blas A, Scott CL, et al. Constant replenishment from circulating monocytes maintains the macrophage pool in the intestine of adult mice. *Nat Immunol*. 2014; 15:929–937. This study describes the constant replenishment of macrophages in the colon to be reliant on circulating monocytes and microbiota. [PubMed: 25151491]
- 39+. Ochi T, Feng Y, Kitamoto S, et al. Diet-dependent, microbiota-independent regulation of IL-10-producing lamina propria macrophages in the small intestine. *Scientific reports*. 2016; 6:27634. This study shows that microbiota is not necessary to induce small intestine IL-10 macrophages. [PubMed: 27302484]
40. Ueda Y, Kayama H, Jeon SG, et al. Commensal microbiota induce LPS hyporesponsiveness in colonic macrophages via the production of IL-10. *Int Immunol*. 2010; 22:953–962. [PubMed: 21051439]
41. Hayashi A, Sato T, Kamada N, et al. A single strain of *Clostridium butyricum* induces intestinal IL-10-producing macrophages to suppress acute experimental colitis in mice. *Cell Host Microbe*. 2013; 13:711–722. [PubMed: 23768495]
- 42++. Singh N, Gurav A, Sivaprakasam S, et al. Activation of gpr109a, receptor for niacin and the commensal metabolite butyrate, suppresses colonic inflammation and carcinogenesis. *Immunity*. 2014; 40:128–139. This study showed the relationship between microbial metabolites butyrate and niacin and their receptor GPR109A on colonic macrophages and dendritic cells to promote differentiation of Treg cells and IL-10 producing cells. [PubMed: 24412617]

Figure 1. Microbiota-dependent and independent regulation of regulatory immune cells in the intestine

The gut microbiota and its metabolites regulate differentiation and function of regulatory immune cells (e.g., Foxp3⁺ regulatory T cells, IL-10-producing macrophages/dendritic cells). Whereas, dietary factors can regulate the development and function of these cells independent from the microbiota. Abbreviations: pTreg, peripheral T regs; DC, dendritic cells, Mφ, macrophages; RA, retinoid acid; PSA, polysaccharide; SCFA, short-chain fatty acid.