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The Impact of Dietary Components on Regulatory T Cells and Disease

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The rise in the prevalence of autoimmune diseases in developed societies has been associated with a change in lifestyle patterns. Among other factors, increased consumption of certain dietary components, such as table salt and fatty acids and excessive caloric intake has been associated with defective immunological tolerance. Dietary nutrients have shown to modulate the immune response by a direct effect on the function of immune cells or, indirectly, by acting on the microbiome of the gastrointestinal tract. FOXP3$^+$ regulatory T cells (Tregs) suppress immune responses and are critical for maintaining peripheral tolerance and immune homeostasis, modulating chronic tissue inflammation and autoimmune disease. It is now well-recognized that Tregs show certain degree of plasticity and can gain effector functions to adapt their regulatory function to different physiological situations during an immune response. However, plasticity of Tregs might also result in conversion into effector T cells that may contribute to autoimmune pathogenesis. Yet, which environmental cues regulate Treg plasticity and function is currently poorly understood, but it is of significant importance for therapeutic purposes. Here we review the current understanding on the effect of certain dietary nutrients that characterize Western diets in Treg metabolism, stability, and function. Moreover, we will discuss the role of Tregs linking diet and autoimmunity and the potential of dietary-based interventions to modulate Treg function in disease.

Keywords: diet, microbiome, Treg—regulatory T cell, autoimmunity, environmental factors

INTRODUCTION

An appropriate balance between pro- and anti-inflammatory immune responses is required to protect organisms from invading pathogens and tumor development without incurring in autoimmune and allergic diseases. While different cell populations with anti-inflammatory activity have been identified, CD4$^+$FOXP3$^+$ regulatory T cells (Tregs) are the most well-defined. FOXP3 transcription factor determines Treg cell lineage and is essential for appropriate immune homeostasis. Loss-of-function mutations in *foxp3* lead to fatal immune disorders in humans (IPEX) (1, 2) and mice (Scurfy phenotype) (3).

Tregs suppress innate and adaptive immune responses using a broad array of molecular mechanisms which e.g., involve cell-contact dependent mechanisms (4), the release of soluble factors (5, 6), deprivation of growth factors (7), induction of apoptosis of target cells (8), and ATP hydrolysis and adenosine production (9, 10). Although there is versatility in the Treg response that allows for a specialized response according to the environment, the anatomical location, and the type of the cell to suppress (11, 12), increasing evidence suggests lack of Treg stability as a culprit of autoimmunity (13). Tregs isolated for instance from T1D (14, 15), MS (16–19) and SLE

(20) patients showed acquisition of pro-inflammatory functions and reduced suppressive potency *in vitro*.

Whereas, genetic factors clearly predispose to autoimmune development, the dramatic increase in the incidence of autoimmune diseases in Western countries suggests Western lifestyle patterns as important triggers of disease [reviewed in (21, 22)]. A variety of factors have been proposed to favor autoimmune development such as decrease pathogen exposure, smoke, hormones, stress, pollutants, dietary components and obesity (23–27). Moreover, increasing data highlight the complex interplay between nutrition, metabolic state and the immune response. Caloric restriction ameliorates disease severity and increases the lifespan in experimental animal models of inflammation and autoimmunity (28–30). By contrast, obesity is one of the most consisting factors that predispose for autoimmunity, having being linked with MS (31), T1D (32), psoriasis (33), and Chron's disease (34) (**Figure 1**). In addition, diet alters the gut microbial composition. Gut bacteria and their metabolites regulate pro-inflammatory and regulatory T cell responses in the gut, which could exert systemic effects in the individual (35–37).

Although there are many other cell types and environmental factors involved in triggering autoimmunity, given their crucial role in disease regulation, we will summarize the evidence provided by experimental and epidemiological studies associating nutrition, regulatory T cell function and autoimmunity.

Treg REGULATION AND HETEROGENEITY

We and others have shown before that different cell subsets can be distinguished within the pool of Tregs (9, 38). Recent immune phenotyping by mass cytometry and single cell transcriptomic analysis have further demonstrated the heterogeneity of the FOXP3$^+$ Treg population (39, 40). Therefore, these technologies could potentially aid in the identification of novel markers involved in Treg function, stability and migration and in gaining a better understanding of Treg biology. Tregs are typically categorized according to their origin into two subsets; those that develop in the thymus (tTregs) as a distinct cell lineage, and those induced from CD4$^+$CD25$^-$FOXP3$^-$ naive T cells in peripheral tissues (pTregs). *In vitro*, FOXP3$^+$ Tregs can also be generated from CD4$^+$FOXP3$^-$ T cells by e.g., culturing them in the presence of TGF-β, IL-2, and anti-CD3 stimulation (41, 42) being generally named as iTregs, although their functional activity is not well-defined in humans.

FOXP3 is regulated at transcriptional and post-transcriptional level in response to environmental cues [reviewed in (43)]. Demethylation at specific regions of the *foxp3* locus is pivotal for regulating FOXP3 expression in different Treg subsets (44). Moreover, distinct FOXP3 splicing variants have been described in humans (45–49) and variations in their relative expression are present in autoimmune disease patients (50–54), suggesting a link between FOXP3 post-transcriptional regulation and autoimmune pathogenicity.
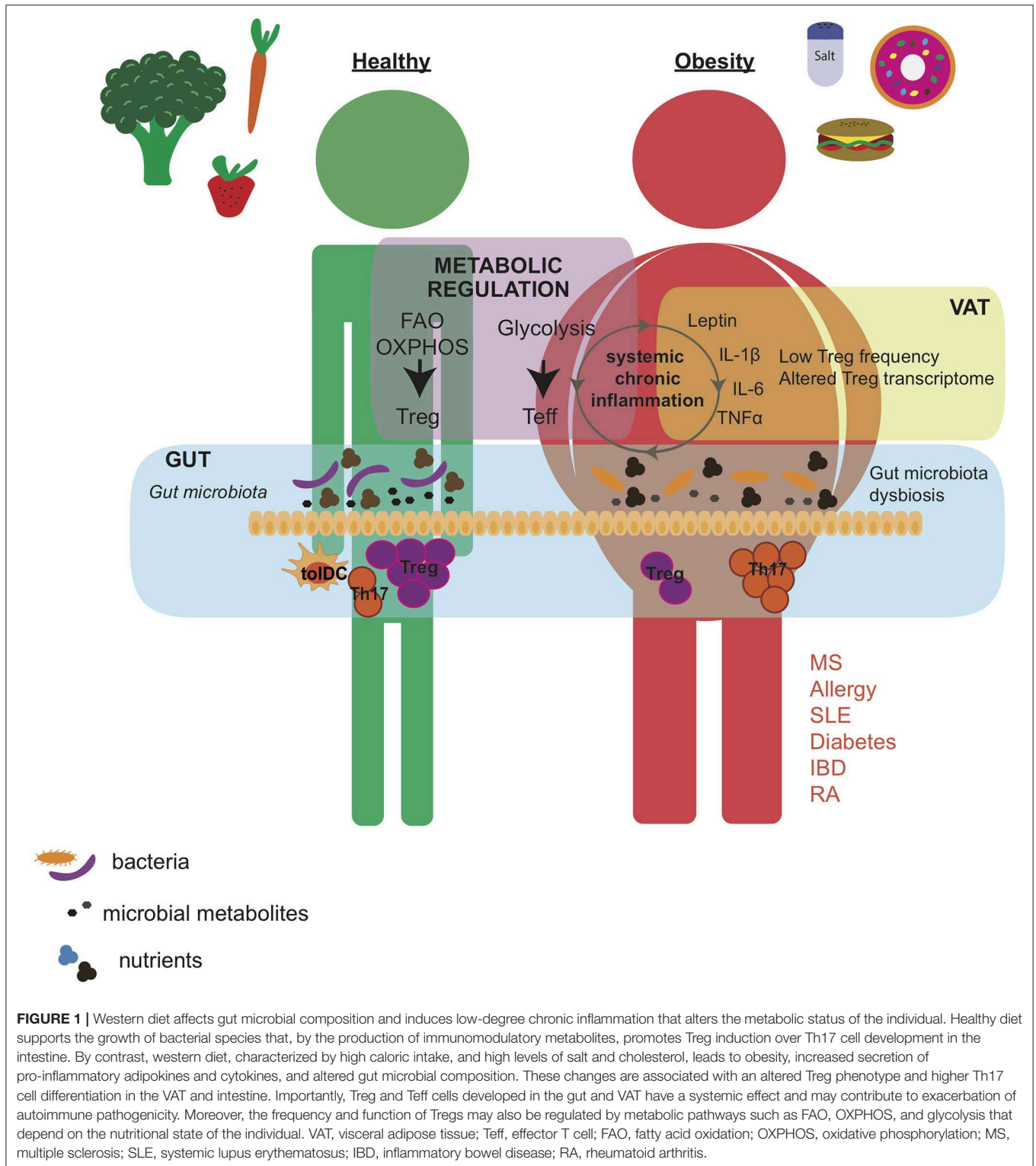
Signals driven by the cytokine milieu (55–59), co-stimulatory molecules (60–62) and the strength of the TCR signaling (63–65) allow Tregs to adapt to the immune environment through e.g., changes in FOXP3 expression. Several studies have shown that, under certain inflammatory conditions, some Tregs secrete pro-inflammatory cytokines and lose their suppressive function (13, 66–72). Interestingly, phenotypically distinct Treg subsets in humans and mice have been described that mirror CD4$^+$ Th cell populations by specific co-expression of chemokine receptors, cytokines, and lineage specifying-transcription factors classically associated with Th cells (18, 73–76). The acquisition of Th-specific markers may allow Tregs to co-localize and regulate particular Th cell subsets *in vivo* (76). However, it might also be an indication of loss of function. Indeed, an increase in IFN-γ-producing Tregs has been associated with e.g., T1D, MS and autoimmune hepatitis (15, 18, 77). Also, the frequency of Tregs expressing IL-17 is increased in e.g., human patients with psoriasis, IBD and RA (62, 78–83). These data suggest that some Th-like Tregs may lose their ability to suppress immune responses and, instead, may contribute to autoimmunity.

Additionally, Tregs show phenotypical differences depending on which tissue they reside in, with the best non-lymphoid-tissue Treg populations described being those residing in visceral adipose tissue (VAT), skeletal muscle, colonic lamina propria and skin [reviewed in (84–86)]. In general, tissue-resident Tregs are characterized by higher frequency, self-antigen TCR repertoire with clonal micro-expansion, and a specific transcriptional profile different from Tregs in lymphoid organs (87–90). Moreover, by the use of single cell transcriptomics it was revealed that Tregs are highly homogenous within each tissue (40). These distinct phenotypes allow for cell accumulation in specific tissues and dedicated function within the microenvironment [reviewed in (84)].

The existence of multiple Treg subsets with specialized function dependent on environmental signals shows the complexity of Treg biology, but it also makes Treg plasticity and function susceptible to pharmaceutical intervention. Whether changes in diet or microbial composition associated with a Western lifestyle can control Treg function is being actively studied.

OBESITY AND VAT Tregs

Excessive calories are stored as fat in adipose tissue, which also acts as an "endocrine organ" releasing pro-inflammatory adipokines and cytokines such as TNF-α, IL-6, IL-1β, and leptin, resulting in systemic low-degree chronic inflammation (91, 92) (**Figure 1**). Multiple immune cell types reside in the adipose tissue and play a role in inflammation and metabolic dysregulation (87, 93–99). In particular, obese mice display a dramatic reduction in Treg numbers specifically in adipose tissue, but not in other fat depots, nor in other non-lymphoid tissues and spleen or lymph nodes (87, 100). Cytokines and adipokines may be involved in controlling Treg fluctuations in obese VAT. Obesity positively correlates with IL-6 and IL-17 expression in mice and humans (101, 102). IL-6 promotes

FIGURE 1 | Western diet affects gut microbial composition and induces low-degree chronic inflammation that alters the metabolic status of the individual. Healthy diet supports the growth of bacterial species that, by the production of immunomodulatory metabolites, promotes Treg induction over Th17 cell development in the intestine. By contrast, western diet, characterized by high caloric intake, and high levels of salt and cholesterol, leads to obesity, increased secretion of pro-inflammatory adipokines and cytokines, and altered gut microbial composition. These changes are associated with an altered Treg phenotype and higher Th17 cell differentiation in the VAT and intestine. Importantly, Treg and Teff cells developed in the gut and VAT have a systemic effect and may contribute to exacerbation of autoimmune pathogenicity. Moreover, the frequency and function of Tregs may also be regulated by metabolic pathways such as FAO, OXPHOS, and glycolysis that depend on the nutritional state of the individual. VAT, visceral adipose tissue; Teff, effector T cell; FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; MS, multiple sclerosis; SLE, systemic lupus erythematosus; IBD, inflammatory bowel disease; RA, rheumatoid arthritis.

Th17 over Treg development (103) and obese-induced Th17 cell expansion was correlated with exacerbated disease symptoms in autoimmune disease models of experimental autoimmune encephalomyelitis (EAE) and colitis (102, 104). Leptin favors Th1 responses (105–109) and Th17 differentiation (110), but inhibits Treg proliferation (111). Moreover, leptin deficient mice showed a decrease in pathogenic inflammation in most of experimental models of IBD (112), RA (113, 114) and MS (108,

109). Similarly, relapsing-remitting MS patients also displayed an inverse correlation between frequency of Tregs and serum leptin levels (115), indicating that leptin may act as a link between obesity, Treg numbers and immunological tolerance.

In addition to differences in frequency, it was demonstrated that VAT-Tregs isolated from genetically promoted (leptin-deficient) or diet-induced (high fat chow) insulin-resistant mouse models of obesity have an altered transcriptional signature compared to lean mice (116). Phenotypical changes driven by obesity highlight the adaptability of VAT-Tregs to metabolic perturbations and suggest that obesity might alter Treg plasticity. Although most of the molecular mechanisms still need to be elucidated, it has been shown that excessive caloric intake leads to a dysregulation of intracellular nutrient-energy-sensing pathways and metabolic overload in immune cells (117, 118).

METABOLIC REGULATION OF Tregs

Cellular metabolism regulates cell development, proliferation and function and is controlled by environmental cues and nutrient availability (119, 120). Tregs have a specific metabolic profile, which is mainly dependent on mitochondrial metabolism through fatty acid oxidation (FAO) or pyruvate dependent oxidative phosphorylation (OXPHOS) (121–125). mTOR, one of the main pathways linking nutritional availability with cellular activity, promotes glycolysis (126, 127) and regulates differentiation of Th1, Th17, and Tregs (128–130). Studies showed that *in vitro* over-activation of mTOR, by culturing in media containing high concentration of nutrients or leptin, impaired Treg proliferation and the induction of FOXP3 expression (131). Treatment with rapamycin or neutralizing anti-leptin mAb reversed this effect and resulted in increased Treg frequencies and lessened EAE severity. However, continuous treatment with rapamycin or genetic mTOR silencing impeded Treg proliferation in the long term *in vivo* (131). Hence, periods of high and low nutrient levels, required for oscillatory changes in mTOR activity, may be necessary for Treg homeostasis and immunotolerance [reviewed in (132)].

Deletion of PTEN, a negative regulator of PI3K, also contributes to Treg regulation by enhancing glycolysis, decreasing FOXP3 expression and inducing the generation of effector T cells (133, 134). Additionally, the metabolic sensor LKB1 acts through AMPK promoting OXPHOS over glycolysis, and its deletion on Tregs led to alterations in cellular metabolism and the development of autoimmune diseases associated with dampened FOXP3 expression (124, 135). On the other hand, AMPK is considered an antagonist of mTOR activity with the ability to promote FAO (136, 137). Berod et al. showed that deletion of ACC1, a key enzyme in fatty acid synthesis, promoted AMPK activity in CD4$^+$ T cells leading to increases in FAO and Treg development, and ACC1 inhibition under EAE conditions improved disease severity by increasing Treg/Th17 ratio (138).

Vitamins and indoles also modulate Treg function (59). For example, retinoic acid (vitamin A metabolite) acts in conjunction with TGF-β promoting the induction of Tregs from naive T cells and stabilizing FOXP3 expression, which prevented their

conversion into Th1/Th17 cells in the presence of IL-1β/IL-6 (139, 140). Calcitriol, a vitamin D metabolite, enhanced the growth of Tregs (141, 142). Vitamin C has been found to increase the generation of FOXP3$^+$ iTregs on alloantigen-specific Treg induction cultures and to cause a pronounced TSDR demethylation, resulting in an elevated FOXP3 stability (143). Interestingly, vitamin C treatment may act in a distinct manner on tTreg and iTreg function. A recent study by Oyarce et al. showed that tTreg cells pretreated with vitamin C before coculturing with effector CD4$^+$ T cells did not enhanced Treg ability to suppress T cell proliferation regardless of their increased FOXP3 expression. By contrast, *in vitro*-induced iTregs generated in presence of vitamin C showed improved suppressive capacities (144).

Metabolites associated with aryl hydrogen receptor (AHR) also control Treg function. Kynurenine is important for the generation, expansion and function of Tregs (145–147) and indole-3-carbanole (I3C) and 3,3′-diindolylmethane (DIM) promoted Treg infiltration to the CNS under EAE conditions, improving disease severity, and progression (147).

These data highlight the potential of targeting Treg metabolism to ameliorate autoimmune disease progression. However, more research regarding the therapeutic level of such modulation still has to be conducted. Besides, the limitations associated with studying Treg metabolism, due to their plasticity, culturing method, and biological source prompt a big challenge in the field.

THE EFFECT OF SALT IN Treg PLASTICITY

Increased intake of salt that is also common in Western diets has been linked with cardiovascular disease (148, 149) and autoimmunity (22, 150–154). Although the specific mechanisms are still being revealed, several studies in murine EAE and colitis models have demonstrated that elevated NaCl intake could exacerbate disease by promoting the induction of pathogenic Th17 cells via the SGK1-FOXO1 pathway (35, 36, 155). Besides, Wu et al. have recently described a direct effect of SGK1-FOXO1 in controlling Treg function, such as SGK1 deficiency in Tregs protected mice from the development of autoimmunity (156).

High-salt also induced secretion of IFN-ɣ and repressed IL-10 expression in Tregs, which resulted in impaired suppressive function *in vitro* and *in vivo* (155, 157, 158). In mice fed with high-salt diet, Tregs secreted more IFN-γ and failed to control colitis and xenogeneic GvHD, which was dependent on SGK1 signaling (157). IFN-γ-secreting FOXP3$^+$ Tregs with reduced IL-10 expression have been found in MS and T1D patients and are thought to contribute to disease (15, 18, 158). Interestingly, the imbalance between IFN-γ- and IL-10-expressing-Tregs in MS patients was also observed when Tregs from healthy donors were exposed to high-salt *in vitro* (158), suggesting that a high-salt environment could skew Tregs toward a dysfunctional state. Moreover, PTGER2 and β-catenin appeared as upstream regulators of the SGK1-FOXO1 axis in response to high-salt concentration, and constitutive expression of active β-catenin in Tregs caused the development of Scurfy-like autoimmunity

(158). Interestingly, stabilized active β-catenin has been also found in MS patients (158), suggesting that similar regulation may exist in humans. Recently, Luo et al. have proposed that, while high-salt alters the function of tTregs, it has no effect on pTregs or iTreg, which maintained unaltered transcriptional signature and stable FOXP3 expression, cytokine profile and suppressive function under high salt conditions (159). However, Wu et al. reported higher FOXP3 expression and regulatory function in iTregs and pTregs that lack SGK1 function (156), indicating that iTregs and pTregs could also be affected by high-salt via SGK1-FOXO1 axis. More studies are therefore required to clarify the role of high salt in Treg subpopulations.

Based on these findings, multiple studies have attempted to study the relation between salt intake and autoimmune disease in humans. In MS patients, Farez et al. have reported a positive correlation between disease activity and increased dietary sodium intake (150). Moreover, higher sodium concentration was observed in acute MS lesions than in chronic lesions (160). However, studies in larger cohorts have shown no significant correlation between salt consumption and the risk of MS development (161) or disease severity (162). Limitations in accurate measurement of NaCl levels and in the identification of the specific effect of salt independently of other dietary components may account for these controversial results [as discussed in (163)]. Since moderate increases in salt intake has proven to affect human immune cells, including T cells *in vivo* (26, 37), more specific analysis are needed to establish the role of NaCl in human autoimmune disease.

THE GUT MICROBIOTA AFFECTS DISEASE-CONTROLLING Tregs

The human gastrointestinal tract is the major reservoir of microorganisms including bacteria, microeukaryotes, archaea, and viruses, all of which collectively constitute the commensal microbiota (164). Extensive research has demonstrated the intimate crosstalk between commensal microbiota and immune balance. Tregs residing in the intestine are critical for maintaining intestinal immune homeostasis (165–167). Increasing evidence shows that Tregs in the colonic lamina propria are mostly peripherally-induced and depend on microbiota-derived signals for proper development and function (90, 168, 169). In fact, germ-free mice or antibiotic-treated mice show a substantial reduction in colonic Treg frequency (168, 170, 171). Interestingly, induction of pTregs in the small intestine appears more dependent on dietary antigens than on microbial signals (172). By investigating germ-free mice fed on an antigen-free diet, Kim et al. elegantly showed reduction in pTreg numbers in small intestinal lamina propria compared to germ-free mice fed on conventional diet. Importantly, pTregs residing in small intestinal lamina propria suppressed immune responses against dietary antigens (172).

Haghikia et al. elegantly demonstrated that dietary fatty acids profoundly impact T cell subset differentiation in the gut, which had a subsequent impact on central nervous system autoimmunity. The authors showed that SCFAs increased Treg proliferation while long-chain fatty acids (LCFAs) supported Th1 and Th17 differentiation in the gut, which had a significant effect in EAE severity (173). The short-chain fatty acid (SCFA) butyrate, derived from fermentation of dietary carbohydrates by gut microbiota, is an important promotor of colonic Treg differentiation through epigenetic modifications in the *foxp3* locus, which induces FOXP3 expression and pTreg conversion (171, 174–176). *Clostridia* are known to produce high levels of butyrate and colonization of germ-free mice with these bacteria increased colonic Treg frequency and protected mice from colitis (177). By contrast, segmented filamentous bacteria (SFB) induced Th17 cell development in the gut promoting systemic autoimmunity (178–180). In a recent study, Luu et al. have shown that the SCFA pentanoate inhibited SFB-promoted Th17 cell induction by metabolic and epigenetically reprogramming CD4$^+$ T cells to suppress IL-17 production and fostering IL-10 production in CD4$^+$ T cells and B cells (181). Furthermore, Häger et al. reported increased Treg numbers in 36 RA patients after receiving high-fiber dietary supplementation for 28 days, which correlated with a higher Th1/Th17 ratio and decreased expression of markers associated with bone erosion (182).

Several studies have shown that administration of probiotic bacteria containing members of the *Lactobacillus*, *Streptococcus*, and *Bifidobacterium* genera primed DCs to induce the development of FOXP3$^+$ Tregs and IL-10-secreting regulatory T cells (183, 184) (**Figure 1**). Poutahidis et al. showed that mice fed with Westernized "fast food"-style chow developed obesity and had increased IL-17 levels. By contrast, the addition of probiotic yogurt containing *Lactobacillus reuteri* into the diet was sufficient to induce weight loss by a Treg dependent mechanism (174). Importantly, diet alters the gut microbiome (185–187) and dysregulation of intestinal microbiota is associated with autoimmunity [reviewed in (188, 189)]. Wilck et al. have shown that increased salt consumption affects intestinal bacterial composition in mice and humans. *Lactobacillus* spp. was suppressed in high salt condition, but its supplementation prevented high salt-induced Th17 differentiation and ameliorated salt-sensitive hypertension and EAE severity (37, 154). Cekanaviciute et al. found that MS patients have a high presence of the *Akkermansia calcoaceticus* and *Akkermansia muciniphila,* and the exposure of healthy donor PBMC to these bacteria impaired Treg conversion while enhancing Th1 differentiation (190). These data connect diet with microbiota composition and autoimmune pathogenesis, raising the potential of microbiota-targeted therapies.

DIET AS A THERAPEUTIC AID TO CONTROL AUTOIMMUNITY

It is becoming clear that nutrition, metabolic state, microbiota, and autoimmunity are deeply interconnected. In addition to genetic factors, the Western diet characterized by high caloric intake in the form of processed food enriched in protein, sugar, fat and salt, is widely believed to contribute to the rise in autoimmune diseases in the last decades (**Figure 1**). However,

one of the major challenges in investigating the effect of diet in human health is the impossibility to address the role of individual nutrients, which maybe the reason why a definite association between dietary interventions and outcomes in human autoimmune disease has not been established yet. Besides, dietary nutrients and microbial metabolites alter the immune response by acting on different immune cell populations, challenging our aim to identify underlying immunological mechanisms targeted during dietary interventions. For instance, we have recently corroborated that high salt diet lead to alterations in T cell populations in murine tumor transplantation models (191). However, inhibition of tumor growth given by high salt diet was largely independent of T cells in these models. Instead, high salt blocked the suppressive function of myeloid derived suppressor cells (MDSCs) *in vitro* and seems to promote thereby more pronounced anti-tumor immunity *in vivo* (191).

Obesity alters the balance between pro-inflammatory and suppressive T cells responses in adipose tissue, with Tregs losing their phenotypic identity and function (116), and resulting in break of self-tolerance (131) (**Figure 1**). Caloric restriction exerts immunoregulatory effects but is not suitable as general therapy for humans. Interestingly, Cignarella et al. have recently reported that intermittent fasting also improves disease outcomes in the EAE model as caloric restriction does (192). This effect was partially mediated by changes in the gut microbiota, since microbiota transplantation from mice under intermittent fasting into normally-fed mice could induce protection from EAE (192). Microbiota is a major determinant in the regulation of pro-inflammatory and regulatory T cell plasticity in the gut (35–37). Importantly, gut-resident T cells have the ability to traffic between different organs and exert a systemic effect in the organism (193, 194). Furthermore, these findings were translated into a small trial studying 16 MS patients that were on intermittent fasting for 15 days. Although no significant changes in gut bacteria composition was observed, a trend toward increased abundance of the Treg-inducer *Clostridia* bacteria was reported (177, 192).

As indicated by these data, dietary interventions and the use of probiotics may aid in the control of Treg stability and function by altering the milieu in which Tregs act *in vivo*, and help to restore immune responses in individuals with autoimmune prone Western lifestyle.

CONCLUDING REMARKS

Although it is clear that Treg function is frequently altered in human autoimmunity, it should be noted that Tregs are a heterogenous population with distinct tissue-specific features, multiple functions and differential degree of plasticity in response to environmental cues. Moreover, autoimmune diseases are highly heterogenous and it is likely that different defects in Treg-mediated regulation are involved in different types of autoimmune disease and even in each individual depending on the specific genetic background (195). Increasing progress in purifying and subdividing Treg subsets and defining the mechanisms that dictate their function and plasticity will likely contribute to a better understanding on the role of Tregs in autoimmunity.

Dietary factors, via direct effects on immune cells or by acting indirectly through modulation of the gut microbiota, may regulate Treg plasticity and function and, therefore, may have the potential to control disease outcome. However, more research and tightly controlled studies are needed to assess the impact of specific dietary nutrients and bacteria or microbial metabolites on Tregs, autoimmunity, and human health.

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