

# Unravelling the Functions of Regulatory T Cells during Infection

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**How to cite this paper:** Rahman, T., Seraj, M.F. and Casellato, A. (2018) Unravelling the Functions of Regulatory T Cells during Infection. *Open Journal of Medical Microbiology*, 8, 118-131.

<https://doi.org/10.4236/ojmm.2018.84011>

**Received:** October 22, 2018

**Accepted:** November 27, 2018

**Published:** December 11, 2018

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## Abstract

Accumulating evidences have suggested that Treg have an active role in the regulation of immunity to infection. Treg suppress not only autoimmune responses but also other immune responses for instance, during acute infections, against commensal microbes in inflammatory diseases or during chronic illness. Treg have been shown to limit exacerbated inflammation to avoid collateral tissue damage. Treg are also suggested to provide early protective responses in some viral infections as the permitting timely entry of effector cells in infected tissue. Furthermore, Treg have been shown to contribute to form memory pool after resolution of infection. In this review, we survey and analysis our current knowledge and relative dynamics of Treg in a wide range of infection settings and elaborate the examples in which these cells are of critical importance in conferring tolerance, suppressing pathogenesis, inducing protection and optimizing immunity to eliminate infection.

## Keywords

Treg Suppression, CD4 T-Cell Response, CD8 T-Cell Response, CD25<sup>+</sup> Treg, RAG-1-Deficient mice, Foxp3<sup>DTR</sup> Mice, DEREK Mice, Colonic Treg

## 1. Introduction

Treg are developmentally and functionally different from conventional T cells. Treg are initially characterized as expressing a CD4<sup>+</sup> CD25<sup>high</sup> phenotype [1] [2]. However, as CD25 is expressed on other activated T cells and there are some Treg in the peripheral tissues which do not express CD25 limiting the use of this

marker for Treg [3] [4] [5] [6]. To date, the most specific marker identified for the classification of Treg is expression of the transcription factor recognized as forkhead box P3 (Foxp3) [7], which has been exhibited to be expressed specifically in CD4<sup>+</sup> T cells. In mice, neither activated CD4<sup>+</sup> T cells nor differentiated Th1/Th2 cells express Foxp3 [8] [9]. Treg constitute 5% to 10% of CD4<sup>+</sup> T cells. In the steady state, they are generated in the thymus and can be induced from naïve CD4<sup>+</sup> T cells in the periphery. Preliminary studies with Treg were based on their role in dominant tolerance and development of autoimmune disease. However, a handful of studies indicate that Treg play roles in the development of allergic diseases (reviewed in [10]), in the suppression of anti-tumour immunity [11], during pathogen infection (reviewed in [12]) and in controlling responses to commensal microbes in inflammatory diseases [13]. Treg are well known for their immunosuppressive role of varying immune cells including non-Treg CD4<sup>+</sup> T cells [14], CD8<sup>+</sup> T cells [15], dendritic cells (DC) [16], B cells [17], Th17 cells [18], natural killer (NK) cells [19], macrophages [20] and mast cells [21] which are activated in response to pathogen.

## 2. Infection

A substantial body of evidence has demonstrated an increased recruitment of Treg following infection and accumulation at the sites of infection. For example, Treg have been found to expand in viral infections *i.e.*, hepatitis C [22], friend retrovirus [23], Herpes Simplex Virus-1 [24], Lymphocytic Choriomeningitis Virus [25], in protozoal infections *i.e.*, *Plasmodium falciparum* [26], *Leishmania infantum* [27], in fungal infection *i.e.* *Paracoccidioides brasiliensis* [28] and bacterial infection *i.e.*, *Mycobacterium tuberculosis* [29] [30], *Helicobacter pylori* [31]. In this work, we have investigated the role that Treg have in order to identify various protective and pathological responses during different infection models. We have demonstrated that Treg do indeed play crucial roles in different infection settings.

### 2.1. *Helicobacter pylori*

It has been reported that Treg suppression was associated with the inability of the host to clear *Helicobacter pylori* infection [32] [33] [34]. In *H. pylori* infected mice, Treg accumulated at the site of infection early after bacterial ingestion. However, depletion of CD25<sup>+</sup> Treg with PC-61 antibody resulted in severe gastritis with a sharp increase in cytokine expression and increased numbers of mucosal T cells, B cells, macrophages and increased titres of *H. pylori*-specific IgG1 and IgG2 antibodies [32]. This increased gastric inflammatory response in CD25-depleted mice was associated with reduced bacterial loads signifying that during *H. pylori* infection, Treg down-modulated gastric immunopathology but at the cost of bacterial eradication. Similar to Rad *et al.*, Lundgren *et al.* demonstrated that the inability of the host to clear the *H. pylori* infection was a consequence of pathogen-specific regulatory T cells that actively suppress T-cell re-

sponses [33]. They showed that *H. pylori*-infected individuals have impaired memory CD4 T-cell responses that are linked to the presence of *H. pylori*-specific Treg that actively suppress the responses. On the contrary, Kaparakis and co-workers demonstrated that depletion of CD25<sup>+</sup> Treg prior to and during infection did not influence bacterial colonization or severity of gastritis in *H. pylori* infection [35]. Depletion of CD25<sup>+</sup> Treg resulted increased *Helicobacter*-specific antibody levels and an altered isotype distribution.

## 2.2. Herpes Simplex Virus

Treg normalize disease intensity associated with virus induced inflammatory lesions. Suvas and co-workers [24] demonstrated that immunity to Herpes simplex virus (HSV) was dependent upon a protective CD8<sup>+</sup> T cell response. In this study, PC-61 mediated depletion of Treg generated an amplified CD8<sup>+</sup> T cell response resulting an efficient viral clearance [24]. In contrast, Lund *et al.* [36] reported opposite effect on depletion of Treg. They found an exacerbated viral burden in mucosa and nervous system following depletion of Treg using Foxp3<sup>DTR</sup> mice. Also, Treg depletion profoundly reduced effector cell migration and secretion of inflammatory cytokines at the site of infection suggesting a protective role of Treg in herpes virus infection [36].

## 2.3. *Mycobacterium tuberculosis*

Treg check efficient clearance of bacteria during *Mycobacterium tuberculosis*. Treg-depleted mice infected with *M. tuberculosis* showed a decreased bacterial burden in the lungs with an elevated pathogen-specific effector T cells [37]. Co-transfer of Treg with Th into RAG-1-deficient mice resulted in suppression of effector CD4<sup>+</sup> T cells responsible for protection against *M. tuberculosis* [29]. In another study, Shafiani and co-workers [38] demonstrated that a small proportion of *M. tuberculosis* specific Treg, were exclusively capable of suppressing protective immunity. Treg recognising *M. tuberculosis* delayed the priming of effector CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the lung which prolonged the bacterial proliferation and explained the augmented bacterial load found in these mice [38].

## 2.4. *Leishmania major*

Treg contribute to pathogen persistence and form a memory pool after resolution of the infection. The latency of *Leishmania major* in the skin was controlled by the prevalence of Treg [39]. During infection, Treg accumulated in the dermis and suppressed the ability of effector cells to clear parasite from the site of infection. Interestingly, this parasite persistence provided the host long-term protection from re-infection.

## 2.5. West Nile Virus

In West Nile virus infection, Treg maintained a resident memory pool of T cells [40]. During infection, Treg numbers increased in lymphoid organs and infected

tissues (CNS) and allowed memory formation through promoting antigen persistence [40]. Using Foxp3<sup>DTR</sup> mice, they found that Treg-deficient mice had increased numbers of short-lived CD8<sup>+</sup> T cells, but the memory CD8<sup>+</sup> T cell response was impaired. This suggests that with prevention of pathogen clearance Treg maintain a pool of pathogen-specific memory cells which prevent subsequent rechallenge.

### 2.6. *Trichuris muris* Infection

The impact of Treg depletion is time and course of infection dependent. Sawant *et al.* explored the functional role of Treg following intestinal parasite *Trichuris muris* infection [41]. Early Treg depletion post-infection led to accelerated worm clearance accompanied with reduced Th1-mediated inflammation. This protective immunity was impaired and worm titre augmented when Treg were depleted following establishment of infection.

### 2.7. *Salmonella typhimurium*

The role of Treg following *Salmonella typhimurium* infection was demonstrated in which Treg influenced the course of infection [42]. During *S. typhimurium* infection, depletion of Treg early after infection when the bacterial burden was gradually increasing, the suppressive potency of Treg was decreased which accelerated bacterial eradication. However, depletion of Treg during later phase of infection, when the bacterial burden was slowly decreasing, there was no significant changes in bacterial clearance [42]. Thus, Treg tune the balance between bacterial multiplication and clearance of pathogen during different phases of infection.

### 2.8. Retroviral Infection

Treg mediated suppression of CD8 T cells is a significant factor in the consistency of retroviral infections. Dietze and co-workers using DEREK mice showed that transient ablation of Treg following a chronic retroviral infection helps CD8 T cells to recover antiviral potency [43]. Furthermore, transient Treg ablation had a long-lasting effect in diminishing chronic virus titre. During Friend virus, a retrovirus infection, depletion of Treg in DEREK mice resulted in a significant increase of FV-specific CD8 T-cell mediated responses [44] [45]. In addition, it significantly diminished FV loads in lymphatic organs however, no evidence of immunopathology to the host was found following depletion.

### 2.9. Hepatitis C Virus

Treg control the mutual host-pathogen interaction during hepatitis C virus infection. Hepatitis C virus was capable of inducing Treg to exert their suppressive potency on effector T cells, and thereby promoted HCV persistence [46]. In support of this hypothesis, several groups found a significantly greater proportion of Treg in chronically infected patients compared with spontaneously re-

covered or normal controls [47] [48]. And the increase in Foxp3 was absolutely correlated with the extent of inflammation and the expression of apoptotic mediators [48]. Depletion of Treg increased HCV-specific CD4, CD8 cell and IFN $\gamma$  activity [47]. However, despite Treg suppress effective immune response against HCV; they protected infected subjects from elevated tissue pathology as demonstrated by lessened histological inflammatory activity in persistent HCV infection. Thus in cases of chronic infection, generation of Treg appear to be advantageous to both the pathogen and the host by promoting persistence of infection and limiting immune-mediated pathology.

In contrast to chronic infections, where excessive number of Tregs leads to pathogen persistence, Tregs in acute infections might aid in limiting immune mediated pathology without delaying viral clearance. For example, in mouse hepatitis virus induced acute encephalitis, Treg play a critical role as their depletion resulted in lethal infection and increased mortality [49]. Also co-transfer of Tregs into infected mice increased survival from 0% to 50%.

### **2.10. Respiratory Syncytial Virus**

There are other acute infection models where Treg have been exhibited to perform a crucial role in limiting immunopathology. For example, in acute pulmonary virus infection by respiratory syncytial virus (RSV), Treg rapidly accumulated in draining LNs and lungs [50] [51]. Fulton and co-workers [50] demonstrated that in vivo depletion of Treg using anti-CD25 mAb before RSV infection resulted in delayed viral clearance along with an early interval in the enrolment of antigen-specific CD8 T cells. Moreover, Treg depletion led to aggravated disease intensity, including enhanced weight loss, airway restriction and morbidity. Lee *et al.* [51] also observed an augmented weight loss with delayed recovery following ablation of Treg. However, this was associated with increased levels of CD4 and CD8 T cells producing IFN- $\gamma$  and TNF- $\alpha$  in the lung and the viral load was unchanged subsequent Treg depletion. Also, the inflammatory reactions were diminished when Treg numbers were boosted using IL-2 immune complexes [52]. Thus Treg function a pivotal role in regulating the immune responses to acute infection that is the key cause of disease pathology and in resolving inflammation resulting pathogen clearance.

### **2.11. *Leishmania panamensis***

There are some evidences of chronic infections in which Treg provide a protective role and help to resolve pathogen clearance. Upon infection with *Leishmania panamensis*, Treg were presented with a dysregulated phenotype [53]. Depletion of Tregs using DERE mice resulted in increased parasite load, enlarged lesions, and enhanced production of IL-17 and IFN- $\gamma$ . Also, adoptive transfer of Tregs from naive mice halted disease progression, lowered parasite burden, and reduced cytokine production (IL-10, IL-13, IL-17 and IFN- $\gamma$ ). Thus, Treg-targeted immunotherapy can be used as a safe and potent component in therapeutic

strategies to treat chronic illness.

We summarize below the data from some of the principal infection systems, with additional details listed in **Table 1**.

## 2.12. Commensal Microbes

There is handful of studies in which Treg cross-react with non-pathogenic commensal microbiota in the small and large intestine. Treg are found to suppress microbe-driven intestinal inflammation and Treg repertoire is influenced by the presence of particular commensals or bacterial compounds. For instance, colonization of germ-free mice with commensal microbe altered Schaedler flora (ASF) species resulting in activation and de novo generation of colonic Treg [54] [55]. In multiple murine studies, Tregs have been shown to be induced by commensal microbes. For instance, butyrate, a by-product from commensal metabolism, potentially induced conversion of T cells in to Treg in the intestine [13]

**Table 1.** Treg mediated potential mechanisms in protection and immunopathology to mucosal infections.

Microorganisms	Effect of Treg on immunopathology or pathogen load	Refs
<i>Helicobacter pylori</i>	Treg expand in mucosa, CD25 depletion reduces bacterial burden but generates pathology and inflammation.	[32] [33]
	Treg depletion does not influence bacterial colonization or immunopathology	[35]
Herpes simplex virus	Treg ablation generates CD8 T cell response with an efficient viral clearance.	[24]
	Treg depletion associates with exacerbated viral burden in mucosa and nervous system.	[36]
<i>Mycobacterium tuberculosis</i>	Treg depleted mice show decreased bacterial burden in the lungs with pathogen specific effector T cells.	[37]
	Co-transfer of Treg with Th into RAG-1-deficient mice results in suppression of effector CD4 T cells, responsible for protection	[29]
	Pathogen-specific Tregs activated	[38]
<i>Leishmania major</i>	Treg accumulate in the dermis, suppress the ability of effector cells to clear parasite and provide long-term protection from re-infection.	[39]
West Nile virus	Treg expand in lymphoid organs and allow memory formation through promoting antigen persistence. Treg-deficient mice have impaired number of memory CD8 T cells	[40]
<i>Trichuris muris</i>	Early Treg depletion accelerates worm clearance with reduced Th1 mediated inflammation. However, the worm titre is augmented when Treg are depleted following infection.	[41]
<i>Salmonella typhimurium</i>	Depletion of Treg early after infection accelerates bacterial eradication. However, depletion during later phase is associated with no significant changes in bacterial clearance.	[42]
Retroviral infection	Transient ablation of Treg following a chronic retroviral infection helps CD8 T cells to recover antiviral potency.	[43]
Friend virus	Depletion of Treg results in a significant increase of FV-specific CD8 T-cell mediated responses which diminishes FV loads in lymphatic organs	[44] [45]
Hepatitis C virus	Hepatitis C virus induces Treg to exert their suppressive potency on effector T cells and promotes HCV persistence	[46]
Respiratory syncytial virus	Treg rapidly accumulates in draining LNs and lungs	[50] [51]
	Depletion of Treg results delayed viral clearance, aggravated disease intensity, including enhanced weight loss, airway restriction and morbidity.	[50]
	Augmented weight loss with delayed recovery following ablation of Treg.	[51]
<i>Leishmania panamensis</i>	Depletion of Tregs results increased parasite load, enlarged lesions, and enhanced production of IL-17 and IFN- $\gamma$ . Adoptive transfer of Tregs halts disease progression, lowers parasite burden, and reduces cytokine production.	[53]

[56], through butyrate-mediated histone H3 acetylation in the Foxp3 promoter [56]. Polysaccharide A (PSA) from *B. fragilis* potentially induced Treg and resolved experimental colitis [57]. The CNRZ327-component from *Lactobacillus delbrueckii* induced Treg in colonic tissue [58].

During early life, administration of *Clostridium* species, a gram positive bacteria, in conventional mice provided resistance to colitis and systemic antibody responses signifying a novel therapeutic approach to autoimmunity. Colonization of mice with *Clostridium* species from clusters IV, XIVa, and XVIII isolated from human faeces stimulated Treg generation and also increased the production of anti-inflammatory cytokine IL-10 [59] [60]. This Treg induction was mediated through TGF $\beta$  and it protected mice from DSS induced colitis in colon and retained intestinal homeostasis. Also the caecal extracts had high concentrations of short chain fatty acid (SCFA) suggesting that production of SCFA by *Clostridia* is a contributing factor for the increase in the Treg numbers. Expression of GPR43, a SCFA receptor on colonic Treg has been suggested to promote Treg induction in response to orally administered SCFA [61]. GPR43 signaling has been demonstrated to confer protection in an experimental model of colitis induced on adoptive T-cell transfer into lymphopenic recipients [55].

Tissue inflammation and autoimmune proliferative response following depletion of Treg were analogous in germ free and conventional mice [62]. However, in GF mice lacking in Treg, the inflammation was more intense and pancreatitis was strikingly elevated compared with Treg depleted conventional mice. This suggests the critical role of Treg in subduing reactivity to gut flora. Hence, microbiota colonization driven Treg response is a central process to induce and sustain host-intestinal and microbial mutualistic interaction and existence.

### 2.13. Treg in Cancer

Treg alter antigen-specific immunity and are believed to be responsible for diminished anticancer immune response. Morse and co-workers [63] investigated the immune responses in individuals with advanced cancer following ablation of Treg with CD25<sup>high</sup> targeting immunotoxin (denileukin diftitox). They found an elevated antigen specific T cell response of cancer vaccines after Treg depletion. However, from experiments with Feline immunodeficiency virus (FIV), it was difficult to predict whether Treg cells play a beneficial or a detrimental role during FIV infection [64] [65]. Treg depletion following anti-feline CD25 mAb in FIV infected cats for 4 weeks did not exacerbate viral replication or FIV-specific immune responses or proinflammatory cytokine production. However, cats receiving CD25 were able to produce a robust humoral response to new mouse monoclonal antibody [64] [65]. Thus transient Treg depletion following chronic HIV-1 infection could offer an insight for therapeutic vaccination.

## 3. Concluding Remarks

Several studies of infection have indicated that, though the presence of Treg does

not participate in disease progression, depletion of Treg results in increased effector responses, supporting pathogen clearance and thus acting as suppressive cell. For example, in *H. pylori* infection, Treg ablation led to decreased bacterial burden, yet increased gastric inflammation [32]. In *M. tuberculosis*, Treg ablation resulted decreased bacterial load in lung and elevated effector T cells [37]. In *Salmonella enterica* infection, Treg depletion boosted clearance and produced memory T cells [42]. In *Strongyloides ratti* infection, Treg depletion reduced worm burden [66] and in cerebral malaria, Treg depletion alleviated disease pathology [67].

However, not all studies have revealed that Treg function to control effector activation. Paradoxically, it has been shown that Treg provide protective responses in some pathogen infections permitting timely entry of effector cells in infected tissue. Although not much appreciated, some of the protective functions of Treg cells are characterized as their depletion resulted in more severe infection. For example, in Mouse Hepatitis Virus induced acute encephalitis, Treg depletion led to lethal infection and resulted increased mortality [49]. In Herpes Simplex Virus infection, Treg ablation resulted in loss of immunity through reduced effectors at site of infection [36]. In Respiratory Syncytial Virus infection, Treg ablation resulted augmented weight loss, delayed viral clearance, delayed recovery in the lung and delayed recruitment of CD8 cells [50] [51]. Augmented tissue damage in RSV infection was also demonstrated by another group [68] in which inflammatory reactions were diminished while numbers of Treg were enhanced with IL-2 immune complexes [52]. Treg-deficient mice developed lethal West Nile fever at a higher rate than controls [69]. In Theiler's virus infection, depletion of Treg in resistant mouse strains made them more susceptible to CNS lesions [70]. Clostridium species, a gram + bacteria, mediates Treg induction through TGF $\beta$  and protects against DSS induced colitis [59].

Depletion or reduction of Treg thus augments effective immune responses against pathogenic microbes in most cases while their diminution sometimes reduces effector cell trafficking to the site of infection and might hamper the development of robust secondary immune response following subsequent rechallenge. Also, depletion of Treg in some acute infection models exacerbates disease pathology along with lack of trafficking of effector cells. Hence, Treg providing either suppressive or protective potency over the effector cells either controls or augments the extent of physiological immune response against pathogens and associated immunopathology.

### Conflicts of Interest

The authors declare no conflict of interest that could be perceived to bias the work.

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## Abbreviations

**ASF** altered Schaedler flora; ***B. fragilis*** *Bacteroides fragilis*; **CD** Cluster of differentiation; **CNS** Central Nervous system; **DC** Dendritic cells; **DEREG** Depletion of Regulatory T cells; **DSS** Dextran sulfate sodium; **FIV** Feline immunodeficiency virus; **Foxp3** Forkhead box P3 protein; **Foxp3<sup>DTR</sup>** Forkhead box P3 protein-Diphtheria toxin receptor; **FV** Friend virus; **GF mice** Germ-free mice; **GPR43** G-Protein Coupled Receptor 43; **HCV** Hepatitis C virus; ***H. pylori*** *Helicobacter pylori*; **HSV** Herpes Simplex virus; **IFN** Interferons; **IL** interleukins; **LCMV** Lymphocytic Choriomeningitis Virus; **LN** Lymph nodes; **mAb** monoclonal antibodies; **Mt** *Mycobacterium tuberculosis*; **NK** Natural killer cells; **PSA** Polysaccharide A; **RAG-1** Recombination activating gene-1; **RSV** Respiratory Syncytial Virus; **SCFA** short chain fatty acid; **TGF $\beta$**  Transforming Growth Factor beta; **Th** T helper cells; **TNF** Tumour Necrosis factor; **Treg** CD4+Foxp3+ Regulatory T cell; **HIV-1** The human immunodeficiency virus-1.