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Micro-Review

The Yin and Yang of regulatory T cells in infectious diseases and avenues to target them

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Abstract

$CD4^+CD25^+FoxP3^+$ regulatory T cells (Tregs) are key players for maintaining immune tolerance. Tregs are critical for reducing the inflammation-mediated tissue damage following infection. However, Tregs also suppress protective immune responses to pathogens (including virus, bacteria, parasites and fungi) and vaccines, and enhance pathogen persistence by inhibiting the activation and functions of both innate and adaptive immune cells such as dendritic cells, macrophages, T and B lymphocytes, and by promoting immunosuppressive environment. Therefore, equilibrium in the Treg number and function is important to ensure pathogen clearance and protection from infection-associated immunopathologies. Recent advances in understanding of Treg influence on the outcome of infection opened new avenues to target them. Various small molecules, pharmacological inhibitors, monoclonal antibodies that target Tregs provided proof of concept in experimental models. The field also benefits from advances in other subjects; particularly oncology and autoimmunity, where Treg targeted therapies are exploited in the clinic to a greater extent. The future research should aim at translating this pre-clinical success to human application.

1. IMMUNE RESPONSE TO PATHOGENS

As a part of first line of defence, professional antigen presenting cells (APCs) recognize pathogens via pathogen-associated molecular patterns (PAMP) and pattern-recognition receptors (PRR) interaction. PRR-PAMP interaction signals phagocytosis of antigens and their processing in endosomes and lysosomes for the presentation by MHC class II to CD4+ T cells. Endogenous antigens are processed in proteasomes for the presentation by MHC I to

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CD8+ T cells. Signalling by PRR also leads to activation of APCs characterized by enhanced expression of co-stimulatory molecules to enhance T cell activation, chemokines to guide migration of immune cells, and cytokines to mediate CD4+ T cell polarization into effector Th1, Th2, Th17 cells or various T suppressor cells including $CD4^{+}CD25^{+}FoxP3^{+}$ regulatory T cells (Tregs). Suppressor T cells are diverse. In addition to classical Tregs, type 1 regulatory T cells that express LAG3 and CD49b, and secrete IL-10; TGF-β-producing Th3 cells and CD8+ suppressor T cells are also identified. Among them, Tregs are most studied population and are the focus of this review.

Pathogens deploy several mechanisms to evade protective immune responses and enhancement of immune suppressor mechanisms such as Tregs represents one of them. Although Tregs suppress protective immune responses and support persistence infection, they are also critical for reducing the inflammation-mediated tissue damage following infection (Figure 1). Therefore, equilibrium in the Treg number and function is important to ensure pathogen clearance and protection from infection caused immunopathologies.

2. $CD4^{+}CD25^{+}FOXP3^{+}$ REGULATORY T CELLS

Tregs are important for maintaining immune tolerance (Sakaguchi et al., 2008). In addition to thymus-derived Tregs that are mostly self-antigen-specific, Tregs can be induced in the periphery under the influence of cytokines and APCs. Induced Tregs are generally specific for foreign antigens and phenotypically similar to thymus-derived Tregs. However, thymus-derived Tregs are functionally stable. FoxP3 is the master regulator of Treg development and functions. In addition, Tregs constituently express CTLA-4 and are $CD127^{low}$. The other markers described on the Tregs are LAG-3, ICOS, GITR, CCR4 and neuropilin-1.

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Current evidence suggest that Tregs can suppress most immune cells including $CD4^+$ and $CD8^+$ T cells, B cells, NK cells, NKT cells and APCs such as DCs, monocytes and macrophages. Tregs inhibit proliferation and cytokines of effector T cells, promote B cell anergy and impede antibody production, inhibit the expression of co-stimulatory molecules, antigen-presenting molecules and inflammatory cytokines in APCs and reduce their ability to stimulate T cell responses. Tregs enhance tryptophan catabolism via IDO pathway and induce cytotoxic effects on target cells via perforin and granzymes. In addition, by consuming IL-2, Tregs hamper activation of effector T cells and promote apoptosis. Thus, Tregs affect all stages of immune response. Treg-mediated suppression of target cells implicates both soluble factors (TGF-β, IL-10, IL-35, perforins and granzymes) and cell-associated molecules (CTLA-4, LAG-3, CD39 and neuropilin-1) (Sakaguchi et al., 2008). One of the main mechanisms that underlie Treg expansion upon infection is direct modulation of APCs by pathogen or its PAMPs. In addition, direct stimulation of Tregs is also reported for certain PAMPs.

3. Tregs IN BACTERIAL INFECTIONS: INHIBITION OF PROTECTIVE IMMUNE RESPONSES

Tregs are expanded in several chronic bacterial infections such as tuberculosis. Tuberculosis patients have increased Tregs both at the site of infection and in the circulation that compromise protective IFN-γ responses (Guyot-Revol et al., 2006; Hougardy et al., 2007) and interfere with stasis of mycobacterial growth in macrophages (Semple et al., 2013) (Figure 2). Detailed exploration in mice indicated that upon aerosol infection, expansion of Tregs occurs in the draining lymph nodes that defer the influx of effector CD4 and CD8 T

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cells to the lungs during early tuberculosis (Shafiani et al., 2010) and prevent bacilli clearance (Kursar et al., 2007; Scott-Browne et al., 2007).

Tregs also have role in the persistence of other chronic bacterial infections such as *Mycobacterium leprae, Streptococcus pneumonia* and Salmonella (Johanns et al., 2010; Saini et al., 2014; Zhang et al., 2011). In case of *Helicobacter pylori*, adequate Treg response although prevents peptic ulcer (Rad et al., 2006; Robinson et al., 2008), bacterial persistence leads to chronic inflammation and tumor induction. Tregs enhance susceptibility to prenatal pathogens wherein expansion of maternal Tregs predisposes to *Listeria monocytogenes and S.enterica* and was dependent on IL-10 (Rowe et al., 2011).

Tregs also influence clinical outcome of bacterial disease due to altered tissue distribution properties. Human challenge studies with *S. typhi* showed that pathogen-specific upregulation of gut-homing integrin α4β7 on Tregs is important determinator of typhoid disease outcome (McArthur et al., 2015). Importantly, depletion of Tregs enhanced *S. typhi*-specific cytokine production by effector-memory CD8+ T cells *in vitro*.

In addition to expansion of Tregs, bacteria can enhance Treg migration at the site of infection by via chemokine axis such as CCL17/CCL22-CCR4 and CCL20-CCR6 axis (Cook et al., 2014; Wang et al., 2016) and thus increasing the contact between them and target cells.

Bacteria stimulate Treg expansion by several mutually non-exclusive mechanisms. *M. tuberculosis*-mediated Treg expansion in humans implicate PD-1-PD-L1/PD-L2 axis and COX-2-catalyzed PGE2 (Garg et al., 2008; Holla et al., 2016; Periasamy et al., 2011; Singh et al., 2013; Trinath et al., 2012). Blockade of these pathways *in vitro* not only abrogated Treg expansion but also reciprocally enhanced IFN-γ responses (Periasamy et al., 2011; Singh et al., 2013; Stephen-Victor et al., 2015; Stephen-Victor et al., 2016; Trinath et al., 2012). Additional pathways include Treg activation and expansion by bacteria-derived

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superantigens that directly link MHC class II on APCs and TCR on T cells (Taylor and Llewelyn, 2010); and MHC class II and PGE2-dependent Treg expansion by human colonic myofibroblasts (Pinchuk et al., 2011).

4. Tregs IN VIRAL INFECTION: DISTINCT ROLES IN ACUTE VERSUS CHRONIC INFECTION

Initial studies in mice ascribed a role for Tregs in attenuating CD8 T cell response to virus (Dittmer et al., 2004; Suvas et al., 2003). Tregs account for increased virus load by restraining IFN-γ responses from virus-specific CD8 T cells in the mouse model of herpes simplex virus (HSV) (Suvas et al., 2003). Subsequent reports demonstrated a role for Tregs in viral persistence and blunting immune response to other viruses including HIV, HBV and HCV. Various studies reported increased Tregs in lymphoid and mucosal tissues of HIV-patients (Epple et al., 2006; Nilsson et al., 2006). Furthermore, HIV can influence relocation of Tregs by inducing homing receptors CD62L and integrin α4β7 on Tregs (Ji and Cloyd, 2009). Tregs from lymphoid tissues of HIV patients had intact suppressive functions on HIV-specific T cells (Kinter et al., 2007), and *in vitro* depletion of Tregs from peripheral CD4 T cells of HIV-patients augmented anti-HIV responses (Weiss et al., 2004). Memory Tregs frequently express HIV co-receptor CCR5 and hence can accelerate HIV infection (Chachage et al., 2016). Low Treg frequencies are characteristics of elite HIV controllers and long-term non-progressors and reduced Treg numbers following therapy provide pointer towards success of anti-retroviral therapy (Hunt et al., 2011; Montes et al., 2011; Piconi et al., 2010).

Increased frequency of circulating Tregs and diminished antigen-specific immune response is also reported in hepatitis patients (Cabrera et al., 2004; Stoop et al., 2005) (Figure 2). HCV was reported to alter the functions of myeloid DCs to promote IL-10 production and to

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augment Treg expansion. Neutralizing IL-10 or depleting Tregs restored effector immune response (Dolganiuc et al., 2008).

Enhanced Tregs in chronic viral infections might be due to several mechanisms. Interaction of HIV-gp120 with CD4 on CD25+ Tregs favours Treg survival and Treg expansion (Ji and Cloyd, 2009). As in the case of bacteria, superantigen-mediated Treg expansion has been reported in chronic LCMV infection (Punkosdy et al., 2011). Treg expansion could be also due to homology of viral peptide with human protein sequences as reported in HCV (Losikoff et al., 2015). Additionally, viruses can alter the functions of DCs to promote Tregs. Chronic HBV and HCV patients have enhanced IDO expression in the liver (Larrea et al., 2007). Importantly, IDO+ DC differentiated from monocytes of HCV patients are potent inducers of Tregs and blocking IDO function significantly abrogates Treg generation from IDO+ DCs (Higashitani et al., 2013). Similarly, HIV also induces IDO expression in plasmacytoid DCs to promote Treg expansion (Manches et al., 2008).

A role for the co-inhibitory molecules PD-1/PD-L1 in orchestrating Treg expansion and effectuating viral persistence has been suggested (Penaloza-MacMaster et al., 2014). Japanese encephalitis virus induces PD-L1 on monocyte-derived DCs to arbitrate Treg expansion and suppression of Th1 response (Gupta et al., 2014). PD-1 on Tregs also suppressed CD8 T cell responses in murine LCMV model via interaction with PD-L1 expressed on CD8 T cells (Park et al., 2015).

In contrast to chronic infections, Tregs have beneficial role in acute viral infections and it goes beyond controlling excessive inflammation and immunopathology (Stross et al., 2012). Mucosal HSV infection in mice showed that Tregs are vital for the influx of NK cells, DCs and T cells to the site of infection and hence for the early immune response (Lund et al., 2008). Treg-derived TGF-β helps in the maintenance of memory CD8 T cell response to

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West Nile virus (Graham et al., 2014). In the influenza model, Tregs enhance differentiation of virus-specific follicular T helper cells and hence germinal center responses by controlling the availability of IL-2 (Leon et al., 2014).

5. Tregs AND PARASITIC INFECTION: FRIEND OR FOE?

Tregs benefiting persistence of parasite was first described in a mouse model of chronic *Leishmania major* infection. Tregs accumulate at the site of inoculation/infection and suppress protective Th1 response by both IL-10-dependent and -independent mechanisms (Belkaid et al., 2002). Similarly, murine models of *Plasmodium yoelii* and *Trypanosoma congolense* have shown negative effects of Tregs towards T cell response and eradication of parasites (Hisaeda et al., 2004; Okwor et al., 2012) (Figure 2).

In humans, *P. falciparum* induces Tregs possibly by antigen non-specific mechanism (implicating IL-2, IL-10 and TGFβ) that decreases antigen-specific immune response and promotes parasitaemia (Scholzen et al., 2009; Walther et al., 2005). Further, TNFRII+ subset of Tregs with enhanced suppressor functions was proposed to contribute for the severity of malaria (Minigo et al., 2009). Of note, deficit in Tregs as observed in Fulani ethnic group has been attributed to lower susceptibility towards malaria (Torcia et al., 2008). All these studies suggest detrimental role for Tregs in controlling parasitic infections.

Tregs have been implicated in disease reactivation as well. In Leishmania infection model, transfer of Tregs from infected mice into chronically infected mice resulted in the reactivation of disease (Mendez et al., 2004). In agreement with this, depletion of Tregs at the time of secondary challenge prevented disease reactivation (Mendez et al., 2004). Also, the frequencies of Tregs are higher in aged individuals and mice than their younger counterparts

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(Lages et al., 2008). Importantly, Tregs in aged mice spontaneously triggered the reactivation of chronic Leishmania infection (Lages et al., 2008).

As in the case of virus, Tregs do benefit host from parasite-associated inflammation and issue damage. In *Schistosoma mansonii* infection, dysregulated Th1, Th2 and Th17 response towards parasite or eggs is the leading cause of infection-associated liver and colon pathology and Tregs limits those responses (Baumgart et al., 2006; Herbert et al., 2008; Taylor et al., 2006). More recently it was demonstrated that Th17/Treg ratio was higher in *S. haematobium*-infected children with bladder pathology (Mbow et al., 2013). As Th17 and Tregs are reciprocally regulated, the higher Th17 response might have supressed Treg generation leading to uncontrolled inflammation. Inability of Tregs to control sustained Th1-mediated inflammatory responses is also reported in lethal oral infection model of *T. gondii* (Oldenhove et al., 2009).

Low-level of parasite persistence in fact provides life-long immunity to the host following reinfection. For example, mice that failed to completely eradicate the parasite were preimmune to subsequent infection. In contrast, mice that achieved sterile clearance were susceptible. By promoting persistence, Tregs exert beneficial role in the maintenance of recirculating tissue-specific memory T cells that confer concomitant immunity (Belkaid et al., 2002).

6. INTERPLAY BETWEEN Tregs AND FUNGAL INFECTIONS: MORE THAN COMMENSALISM MAINTENANCE

Of the diverse classes of pathogens that cause human diseases, fungal pathogens are the least characterized and often underappreciated. The main reason is that in healthy individuals fungi

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stay as mostly commensal and Treg-mediated immune tolerance ensures fungal survival and commensalism at various parts of the body.

In a mouse model of disseminated candidiasis, Tregs suppress proinflammatory responses and enhance susceptibility to candidiasis. TLR2 can directly control the expansion and function of Tregs (Sutmuller et al., 2006), and the Treg frequencies and IL-10 production are lower in $TLR2^{-/-}$ mice (Netea et al., 2004). Further $TLR2^{-/-}$ mice have enhanced Th1 response and are resistant to candida infections. In fact, neutralizing TLR2 in $TLR2^{-/-}$ mice that receive wild-type Tregs is sufficient to reduce Candida infection (Sutmuller et al., 2006). These results suggest that Tregs employ TLR2 in effectuating immunosuppression during candida infections.

Interestingly, Tregs mediate a protective role during early phase of chronic mucocutaneous candidiasis wherein Th17 response plays a central role in the clearance of infection. By quenching IL-2, Tregs augment Th17 differentiation and the clearance of candida during acute phase of infection (Pandiyan et al., 2011). In contrast, Tregs exert a suppressive effect during later phases of infection (Pandiyan et al., 2011). Thus, depending on the timing of infection Tregs can effectuate differential immune response.

In the context of *Aspergillus fumigatus*, Tregs suppress both inflammatory as well as allergic response. During acute phase of infection, neutrophils are essential for initiating inflammation and resolution of infection. However, excessive ROS and proteases released by neutrophils can contribute to lung pathology and the development of fungal sepsis. A division of labor occurs between distinct subsets of Tregs in controlling immunity and tolerance towards *A. fumgatus*. During early phase of infection, Tregs suppress innate cellular functions of neutrophils by contact-dependent (CTLA-4) and -independent (IL-10) mechanisms acting on IDO. During later phase of infection, Tregs coordinate suppression of allergic Th2

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response via IL-10 and TGF-β (Montagnoli et al., 2006). Studies in human and murine cystic fibrosis support a role for IDO in balancing Th17 and Treg responses to *A. fumigatus* (Iannitti et al., 2013).

Treg-mediated suppression of pathological Th2 response that causes pulmonary injury is also observed in experimental *Pneumocystis carinii* and *Cryptococcus neoformans* infections (McKinley et al., 2006; Schulze et al., 2014). Mechanistically, Tregs used IRF4-dependent CCR5 to colocalize with Th2 cells in the lungs (Wiesner et al., 2016). Conversely, expansion of Tregs by administration of IL-2/anti-IL-2 complex during Cryptococcus infection reduced IgE production and decreased allergic airway inflammation (Schulze et al., 2016).

7. COLONIC Tregs, COMMENSAL MICROBIOTA AND GASTROINTESTINAL INFECTION

Compared to other organs, colon harbors higher proportion of Tregs(Atarashi et al., 2011; Round and Mazmanian, 2010). Approximately 30% of colonic CD4 T cells express FoxP3. As these Tregs are helios$^-$, majority of the studies suggest that colon Tregs are induced in nature (Atarashi et al., 2011). However, a case for thymus-derived Tregs in the colon has also been made (Cebula et al., 2013). As helios can be expressed in induced Tregs, and during activation and proliferation of T cells, the use of helios as a marker to distinguish induced and thymus-derived Tregs is questionable (Szurek et al., 2015). A substantial proportion of Tregs in the colon expresses RORγt, the lineage-specific transcription factor of Th17 cells (Sefik et al., 2015). Transcriptomic analysis of RORγt$^+$FoxP3$^+$ Tregs indicate that these cells display dual signatures of both Th17 and Treg cells(Yang et al., 2016). Importantly, Treg-specific signature markers such as FoxP3, CTLA-4, GITR, Eos, and Helios

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are significantly demethylated in RORγt^{+}FoxP3^{+} Tregs and hence represent stable Treg subset (Yang et al., 2016).

The commensal microbiota in the gut has a major influence in regulating Treg response in the intestine and in maintaining intestinal homeostasis. Although the gut encompasses diverse bacterial species, recent studies have identified specific bacteria that can induce Tregs in the colon. *Clostridium* species of the cluster IV and XIVa as well as *Bacteroides fragilis* were shown to induce IL-10-secreting Tregs in the colon (Atarashi et al., 2011; Round and Mazmanian, 2010). Further, by fermenting dietary fibers into small chain fatty acids like acetate, butyrate and propionate, commensal bacteria regulate Treg induction in the colon (Furusawa et al., 2013; Smith et al., 2013).

The induction of Tregs by microbiota regulates pro-inflammatory responses to gastrointestinal (GI) tract infections and hence suppresses infection-associated immunopathologies (Round and Mazmanian, 2009). However, an important question that needs to be addressed is whether one can harness the potential benefits of gut microbiota in treating GI tract infections by improving Treg number and functions. Some of the approaches include oral administration of prebiotics and probiotics. In addition, fecal microbial transplantation aiming at replenishing GI tract microbiota has shown great promise in treating *Clostridium difficile* infection (Gough et al., 2011).

8. Tregs DAMPEN IMMUNE RESPONSE TO VACCINES

Tregs inhibit intensity and duration of protective immunity to vaccines. Murine models have shown that Tregs suppress vaccine-generated primary and memory T-cell responses against viruses, bacteria, recombinant subunit and DNA vaccines (Moore et al., 2005; Toka et al.,

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2004). Human studies also suggest participation of Tregs in the suppression of immune response to vaccines (Wang et al., 2012).

9. FUTURE DIRECTION: TARGETING Tregs IN INFECTIOUS DISEASES

As discussed earlier, although Tregs suppress protective immune responses, they are also important to control inflammation. Therefore, it may not be ideal to inhibit Tregs in acute infections as generated immune response normally sufficient to confine infection and Treg role in this scenario is more towards reducing the inflammation. On the other hand, chronic infection and vaccination represent ideal situations to block Treg activity to enhance protective immune responses.

9.1 Potential strategies to block Tregs

Elimination of Tregs: Treg-depletion can enhance inflammation and autoimmunity and hence transient depletion is desirable. Oncology field provides several options to deplete Tregs. Metronomic doses of cyclophosphamide transiently decreases Treg frequencies while T cell effector functions are preserved, resulting in improved vaccine immunogenicity in human trials (Le and Jaffee, 2012). Daclizumab, a CD25 MAb has been approved for clinical use (Vincenti et al., 1998) and represents another way to improve immune response in chronic infections. This approach however has limitation as adverse effects (like appearance of autoimmune response) were observed even in the experimental animals following CD25-based Treg depletion. In addition, this approach can eliminate CD25-expressing activated effector T cells and can reduce cytotoxic T cell responses.

Blocking molecules implicated in suppressive functions of Tregs: PD-1-PD-L1/PD-L2 pathway has major role in the Treg biology. Inhibition of this pathway lead to enhanced IFN-

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γ response *in vitro* to *M. tuberculosis* (Periasamy et al., 2011; Singh et al., 2013; Stephen-Victor et al., 2015; Trinath et al., 2012) and increased proliferative capacity of HIV-specific-CD8 T cells *ex vivo* (Peligero et al., 2015). Of note, blocking PD-1 pathway in combination with therapeutic LCMV vaccine synergistically augmented epitope-specific CD8 T cell response and accelerated viral clearance in mice (Ha et al., 2008). In macaques, *in vivo* PD-1 blockade increased SIV-specific CD8 T cells and enhanced the expansion of virus-specific CD4 T cells and memory B cells culminating in better control of the virus and increased survival of SIV-infected macaques (Velu et al., 2009). Perturbing the PD-1-PD-L1 pathway also enhanced effector responses against HIV and other viruses (Trautmann et al., 2006). In view of encouraging results with therapeutic PD-1 MAbs in cancer, this approach could be undertaken along with anti-tuberculosis chemotherapy or anti-HIV therapy. However, it has to be noted that the PD-1 axis has a pivotal role in controlling immunopathology, therefore complete abrogation of this pathway can be detrimental. Inhibitors of CTLA-4 and FoxP3 represent additional ways to suppress Treg function (Ohkura et al., 2011).

Blocking chemokine receptors on Tregs: Human Tregs express CCR4 and promotes contact between Tregs and innate cells such as DCs that secrete CCR4 ligands leading to suppression of immune response. Since activation of DCs at the time of encounter with antigens determines the outcome of immune response, we proposed that reducing the impact of Tregs on DCs at this initial phase of immune response boost the protective immune response to vaccines. To avoid adverse effects of Treg depletion, we targeted migration of Tregs by using small molecule antagonists to CCR4. In line with our hypothesis, CCR4 antagonists significantly enhanced cellular and humoral immune response to diverse vaccine antigens including Mycobacterium, *H. suis*, HBV and Plasmodium (Bayry et al., 2014; Bayry et al., 2008; Bosschem et al., 2015; Davies et al., 2009). Tregs were not altered in these vaccinated animals and signs of autoimmune response were also not observed.

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A humanized CCR4 MAb mogamulizumab developed for the treatment of CCR4-expressing T cell lymphomas has been shown to deplete Tregs (Sugiyama et al., 2013). Experimental model also reported enhanced anti-simian T-cell leukemia virus type 1 immune responses upon CCR4 MAb administration (Sugata et al., 2016). Whether CCR4 MAbs enhance immune response in chronic infections remains to be explored.

Tregs are increased in AIDS patients and CCR5 expressed on Tregs has been implicated in the spread of HIV (Chachage et al., 2016)**.** CCR5 antagonist Maraviroc in chronically HIV-1-infected patients reduced frequency and activation of Tregs (Pozo-Balado et al., 2014). This effect might be due to reduced viral loads and hence reduced signals for Treg activation.

Blocking inducers of Tregs: Tregs are induced in the periphery by several molecules including TGF-β and prostaglandin E2. Therefore, targeting them provides options to inhibit Treg generation (Chen et al., 2015; Ohkura et al., 2011).

In silico determination of Treg epitopes in vaccine antigens: The 'computational vaccinology' aiming at mapping of epitopes, designing antigens devoid of Treg epitopes might helps in reducing Treg response to vaccines and hence improve protective immune response (Moise et al., 2015).

9.2 Potential strategies to boost Tregs

Tregs can be enhanced by numerous methods. Subinfectious exposure of pathogen can lead to Treg expansion as shown in the case of HCV in nonhuman primates (Park et al., 2013). Administration of IL-2/anti-IL-2 complex, rapamycin, TGF-β and sphingosine 1-phosphate receptor agonist are the additional ways to boost Treg response (Ohkura et al., 2011; Schulze et al., 2016).

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10. CONCLUSION

Recent advances in understanding of Treg influence on the outcome of infection opened new avenues to target them. Various small molecules, pharmacological inhibitors, MAbs that target Tregs provided proof of concept in experimental models. The field also benefits from advances in other subjects; particularly oncology and autoimmunity, where Treg targeted therapies are exploited in the clinic to a greater extent. The future research should aim at translating this pre-clinical success to human application.

Acknowledgments

Due to space restrictions, we have included only the key references that in no way undermine the great value of uncited articles.

Conflict of Interests

JB holds patent on small molecule CCR4 antagonists to target regulatory T cells in vaccination.

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Figure Legends

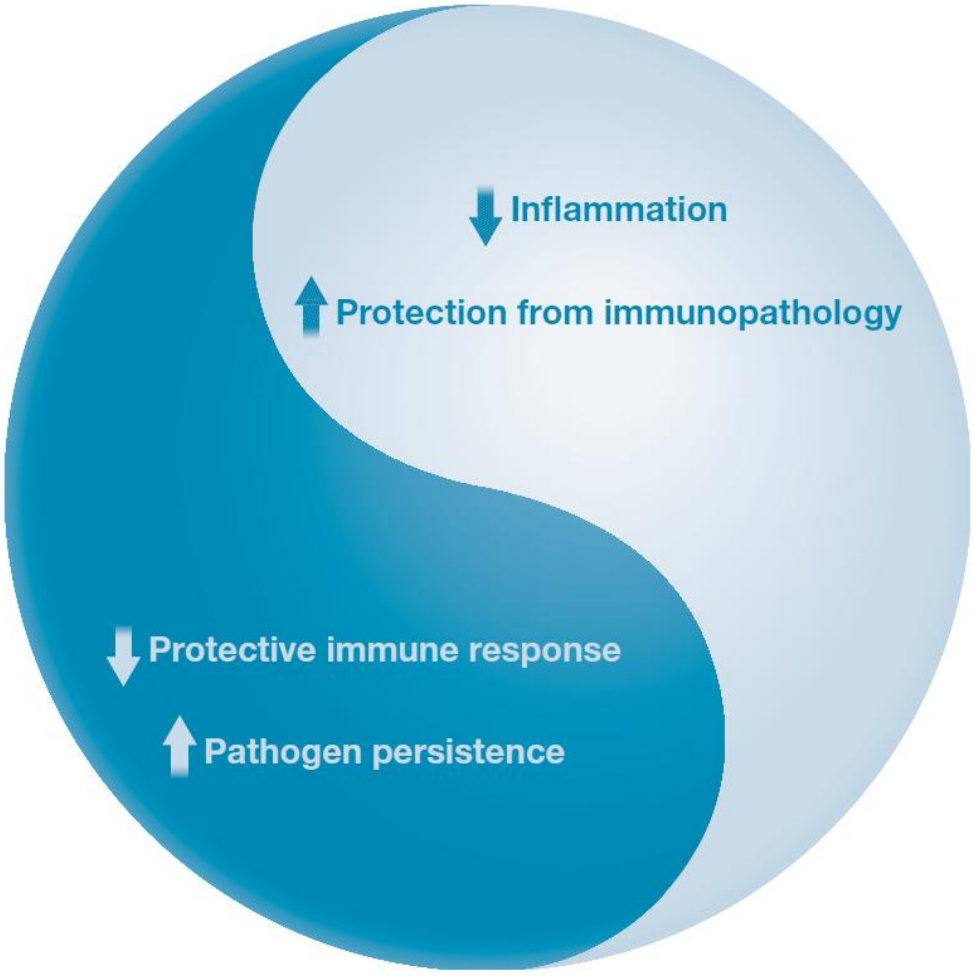


FIGURE 1. The Yin and Yang of regulatory T cells in infectious diseases.

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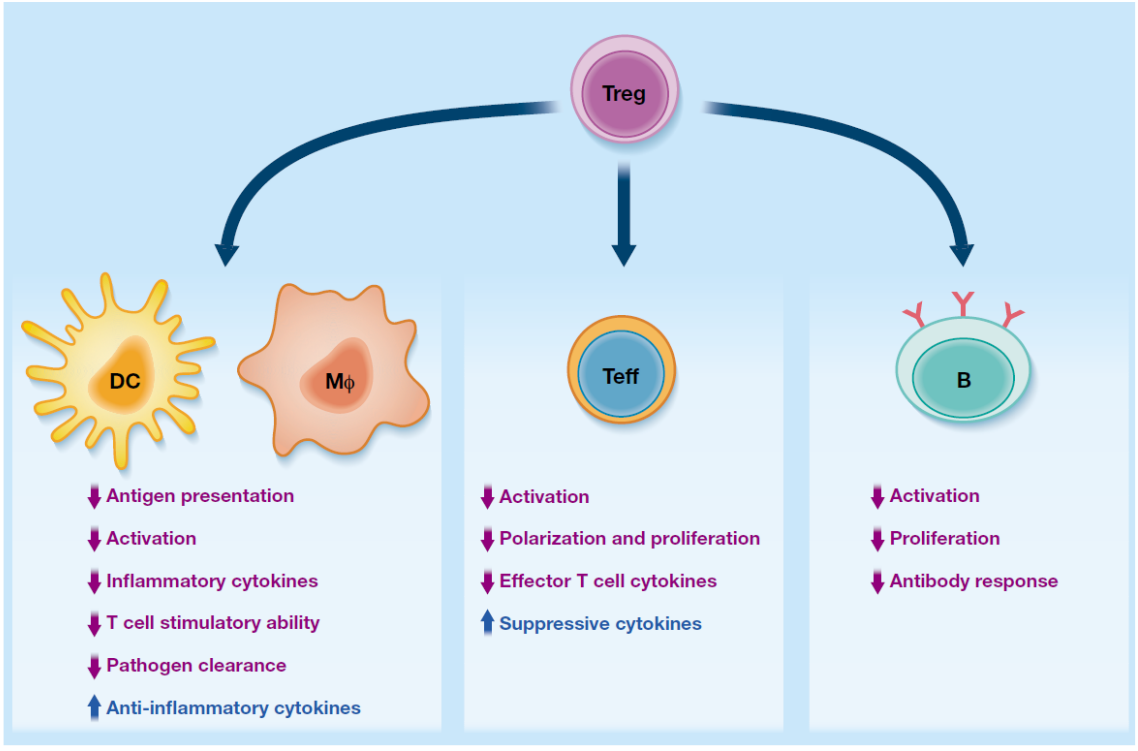


FIGURE 2. Various effects of regulatory T cells (Tregs) on innate and adaptive immune cells to suppress protective immune response to pathogens.

Abbreviations: DC, dendritic cells; MΦ, macrophage; Teff, effector T cells; Treg, regulatory T cell; B, B lymphocytes.

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