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Review Article

Regulatory T Cells and Parasites

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Human host encounters a wide array of parasites; however, the crucial aspect is the failure of the host immune system to clear these parasites despite antigen recognition. In the recent past, a new immunological concept has emerged, which provides a framework to better understand several aspects of host susceptibility to parasitic infection. It is widely believed that parasites are able to modulate the magnitude of effector responses by inducing regulatory T cell (Tregs) population and several studies have investigated whether this cell population plays a role in balancing protective immunity and pathogenesis during parasite infection. This review discusses the several mechanism of Treg-mediated immunosuppression in the human host and focuses on the functional role of Tregs and regulatory gene polymorphisms in infectious diseases.

1. Immunomodulation by Parasites

In this paper, we specify parasites as eukaryotic pathogens that largely include protozoa and helminths and survive off their host partly or completely for their life cycle. They employ various strategies to evade against an effective host innate immune system. Innate immunity rarely eliminates parasites but can successfully inhibit growth while they recruit antigen-specific T and B cells to differentiate into effector cells that thwart the infection [1]. For an effective parasite survival, evasion of adaptive immunity remains the key [2]. In this scenario, parasites strike a balance with the host immune system to increase their survival rate. This balance is accomplished by complex alteration of the innate and acquired immune response of the host where regulatory T (Tregs) cells play an important role [3].

2. Regulatory T Cells

Understanding the complex cellular and molecular mechanism that regulates the host immune response to parasitic infections still remains a key issue in immunology. The crippling effect of host immunity on onset of an infection is due to the fact that parasites induce Tregs that in turn suppress antiparasite effector cells [4]. The Tregs are a subset of T cells that function to control immune responses. The primary role of Tregs is active suppression of several pathological and physiological immune responses in the host, thereby contributing to the maintenance of immune homeostasis [5–7]. Although Tregs are defined as T cells with suppressive activity on immune responses, it had been documented that regulatory T cell populations remain diverse [8]; a few of them are induced in response to infectious challenge and the others are considered as natural regulators [9]. Parasites can ably manipulate natural Tregs by amending the T cell immune response at the infection site to an extent that could lessen the infection burden, thereby prevailing in the host for a longer time frame [10]. The well-characterized Tregs are $CD4^+CD25^+$ population and represent about 10% of peripheral $CD4^+$ T cells both in mice and humans [11]. Tregs are considered as negative regulators of T cell immune response and these natural Tregs originate during thymic development and appear first in the fetal circulation [12]. The suppressor activity is enriched in naturally occurring Tregs such as $CD4^+CD25^+$ that plays a vital role in the initiation and orchestration of immune responses [13, 14]. The $CD4^+CD25^+$ population reveals a high expression of Foxp3 transcription factor which is vital for differentiation and function of naturally occurring Treg cells [15] and for programming the suppressor T cell function [16, 17]. $Foxp3^+$

Tregs play an essential role in controlling the voracity of the response as they generally strike a balance that limits potentially harmful immune-mediated pathology to the host while still allowing sufficient immune pressure against the pathogen [18].

3. Mechanism of Suppression

T-cell receptors remain the key to trigger suppressive function in both naturally occurring and induced Tregs [19]. The regulation of T cells is either by contact-dependent regulation or by soluble factors such as immunosuppressive cytokines. To date, no precise mechanism has been clearly postulated to explain the suppressor function exhibited by Tregs.

3.1. Contact-Dependent Mechanism. Many different hypotheses have demonstrated how Tregs are regulated based on the contact-dependent suppressive mechanism. However, two specific mechanisms are reviewed here. One mechanism is the interaction of T effector ligand CD80 and CD86 with cytotoxic-T-lymphocyte-associated protein (CTLA-4). This interaction triggers the transmission of immunosuppressive signals on T effector cells thus inhibiting effector T-cell function [20] (Figure 1(a)). CTLA-4 is expressed at high levels on $CD4^+CD25^+$ Tregs, and there is substantial evidence that CTLA-4 expressed by natural Tregs has a key role in Treg-mediated suppression both *in vivo* and *in vitro* [6, 21, 22]. In another model, the costimulatory molecules CD80 and CD86 expressed in antigen-presenting cells (APCs) interact with CTLA-4 leading to consequential signalling and activation of IDO (indoleamine 2,3 dioxygenase) in dendritic cells (DCs), an enzyme responsible for immune tolerance on effector T cells [23] (Figure 1(b)). IDO catalyzes the conversion of tryptophan to kynurenine that provides immunosuppressive effects in the local environment of DCs by cytotoxicity or by *de novo* generation of Tregs [8]. Studies have reported decreased activation of T cells and T cell deletion in association with reduced tryptophan concentration in cultures [23, 24]. Studies have also demonstrated that human adaptive Tregs preferentially expressed granzyme B and are capable of killing allogenic tumour cells in a perforin-dependent manner [25]. In line with these studies, it is demonstrated that both subtypes $CD4^+CD25^+$ Tregs exhibit perforin-dependent cytotoxicity against a variety of autologous target cells including $CD4^+$, $CD8^+$, $CD14^+$ monocytes and dendritic cells [26].

3.2. Immunosuppressive Cytokine Mediated. In contrast to contact dependent suppressive mechanism, reports indicate that cytokines such as IL-10 and transforming growth factor (TGF-ß) are needed for *in vitro* mediating suppression [27, 28]. Several *in vivo* studies have indicated the role of immune suppressive cytokines in suppression. In this model, Treg-dependent inhibition of tumor-specific CD8 T cell-mediated cytotoxicity requires expression of the TGF-ß receptor by CD8 cells thereby demonstrating a specific role of TGF-ß signaling in the inhibition of cytotoxicity independent of cellular proliferation [29] (Figure 1(c)). The IL-10 cytokine hampers the antigen presenting ability by downregulating the MHC class II and costimulatory molecules on DCs thereby preventing the maturation and activation of dendritic cells both in humans and in mice [30]. TGF-ß also downregulates the MHC class II expression and costimulatory molecules on DCs [31].

In addition, in mouse models, a recent study had demonstrated that helminth parasites have evolved a novel mechanism to directly expand $Foxp3^+$ Tregs which may be a key part of the parasite's strategy to survive in the host for a longer time [32]. On infection with intestinal helminth *H. polygyrus,* an expansion of the Foxp3-expressing $CD4^+$ T cells was observed. The *H. polygyrus* excretory-secretory antigen (HES) induced Tregs and was demonstrated to suppress *in vitro* effector cell proliferation. The hypothesis proposed that HES ligated the transforming growth factor TGF-ß receptor and promoted Smad2/3 phosphorylation. The Foxp3 induction by HES was lost in dominant-negative TGF-ßRII cells and was eliminated by the TGF-ß signaling inhibitor [32].

4. Tregs and Tropical Diseases

Tregs can reduce injurious host inflammatory and immune responses through mechanisms of cell-to-cell contact, inhibitory cytokines, and cytokine deprivation. This prevents an overexuberant immune response with bystander tissue damage during the host response to infections [33]. However, Tregs may also blunt Th2 responses such as IL-5-dependent eosinophil activation required to kill parasites. The interplay and balance among host Th1, Th2 and Tregs responses is crucial in the defense against a parasitic infection [34]. Some of the earliest studies emphasized that natural Tregs help control the extent of immune-mediated pathology. During malarial infection increased numbers of $CD4^+CD25^+Foxp3^+$ T cells have been found in both human and murine malaria infection [35, 36]. Evidences of the role of Tregs as suppressors of T-cell responses in malaria was initially demonstrated in murine models, where Tregs are known to be associated with increased or delayed parasite growth [37, 38]. Higher Tregs numbers are associated with increased parasite load and development of human infection caused by *P. falciparum* [39, 40]. Given these associations between severe disease and exacerbated immune pathology, a number of studies have explored the role of $CD4^+CD25^{hi}$ $Foxp3^+CD127^{-/lo}$ Tregs in determining the outcome of malaria infection. In a study conducted among Gambian children with severe, uncomplicated clinical malaria and with healthy (controls), Tregs were unable to control the inflammation during acute and severe *P. falciparum* infections, suggesting that this component may be rapidly overwhelmed by virulent infections [41]. Tregs may be beneficial to the host in the later part of the infection—when parasitemia is being cleared—by downregulating the inflammatory response and thereby preventing immune-mediated pathology [41]. On the other hand, if Tregs mediate their suppressive effects too early, this could hamper the responses required for initial control of parasitemia,

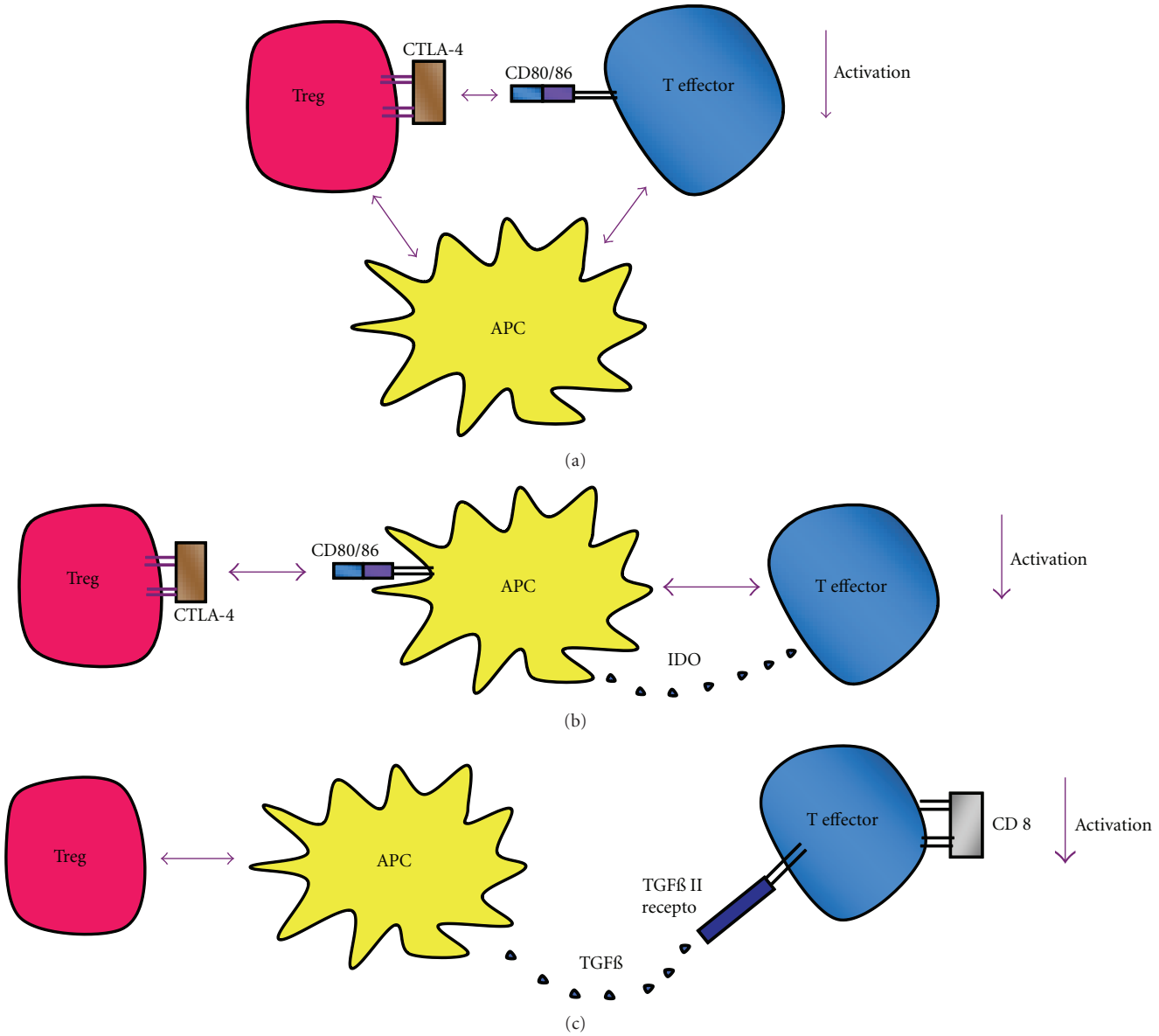

Figure 1: Mechanism(s) of suppression: illustrates various molecular and cellular mechanisms to explain how Tregs can suppress host immune responses. (a) In contact dependent mechanism the costimulatory molecules, namely, CD80/86, interact with CTLA-4 to trigger immunosuppressive signals on T effector cells leading to subtle effector cell function. (b) In contact dependent mechanism, CD80/86 expressed in APC interact with CTLA-4 leading to consequential signalling and activation of IDO leading to immunosuppressive effects. (c) The crosstalk of TGFß expressed in APC to TGFß II receptor leads to immunosuppressive cytokine-mediated suppressor function.

permitting unbridled parasite growth, which may also lead to severe disease. It was also demonstrated that patients with acute *P. vivax* infection presented a significant augmentation of circulating Tregs producing anti-inflammatory (IL-10 and TGF-ß) as well as pro-inflammatory (IFN-γ, IL-17) cytokines, which were further positively correlated with circulating parasites [42]. Malaria-specific induction of Tregs has been observed in a variety of experimental malaria infections in mice [36, 43], but their role in preventing severe malarial pathology is still unclear.

Tregs are widely believed to be involved in silencing the immune response during chronic stages of any filarial infection. Although patients with chronic Onchocerciasis (river blindness) posses higher worms burden, they reveal little/no signs of dermatitis. Studies have argued that Tr1 (a subset of $CD4^+$ T cells) induce a substantial increase in IL-10, IL-5, and IFN-γ levels conferring an immunosuppressive effect [44] in chronic onchocerciasis individuals, whereas in animal models studies had demonstrated that a subtle immune response is mediated by female worms [45, 46] and is dependent on TGF-β and IL-10, two cytokines closely implicated in the activity and induction of Tregs [47–49]. In *Litomosoides sigmodontis* model, the infective L3 stage induces the proliferation of $CD4^+Foxp3^+$ Tregs,

which translates to an increased percentage of $CD4^+$ T cell population at the site of infection expressing $Foxp3^+$ cells within 7 days after infection [49]. The $CD4^+$ regulatory T cell population has also been found significantly higher in several other filarial infections, including *Brugia malayi* [50], the gastrointestinal nematode *Heligmosomoides polygyrus* [51, 52], and the gut/muscle-dwelling nematode *Trichinella spiralis* [53].

Chagas, a tropical disease caused by *Trypanosoma cruzi* is known to cause cardiomyopathy, an inflammatory response in the heart [54]. The occurrence of larger proportion of $Foxp3^+$ population has been demonstrated to control the inflammatory responses in the heart during chagas disease [55]. Therefore, $Foxp3^+$ cells may be involved in a possible mechanism to prevent exacerbation of the inflammatory responses [54, 55]. A similar pattern of Tregs role was established with African trypanosomiasis in a mouse models where naturally occurring $Foxp3^+$ Tregs induce IL-10 production with subtle IFN-gamma response by $CD4^+$ and $CD8^+$ effector T cells. In addition, Tregs also downregulate classical activation of macrophages resulting in decreased activity of TNF-alpha [56]. The Treg activity is believed to decrease the tissue damage in the host cells suggesting a cardinal role for naturally occurring Tregs in the development of a tolerant phenotype during African trypanosomiasis [57].

The immune response against *T. gondii*, an intracellular parasite and the etiological agent of toxoplasmosis, has been largely characterized and demonstrated that cellular immunity plays a vital role in controlling infections [58]. Of which, Tregs were demonstrated to modulate the protective immune response against *T. gondii*, thereby driving a powerful Th1 immune response [59, 60]. Also, it is believed that the absence of Tregs in toxoplasmosis may induce an uncontrolled inflammatory response [60].

Foxp3-expressing Tregs have been implicated in parasite-driven inhibition of host immunity during chronic infection [32]. One of the major effects of chronic helminth infections is induction of T-cell hypo responsiveness [61]. The mechanisms involved have been thought to be multiple and the involvement of natural and inducible Tregs in down regulating effector T cell responses upon chronic infection has been proposed [62]. The cytokines IL-10 and TGF-ß have been associated with down regulation, indicating that regulatory populations are activated during infection. The importance of IL-10 as a crucial mediator of regulation in parasite infections has been well recognized both in humans and murine [63–65]. In human filariasis, heavily infected individuals have high IL-10 levels and IL-10 messenger RNA production which was inversely correlated with T cell proliferation [34, 66]. Similarly infection in experimental *Schistosoma mansoni* was shown to be associated with immunoregulatory mechanisms, including Treg that may help control morbidity and dampen resistance to reinfection. Treg responses control both Th1 and Th2 responses in an IL-10 independent manner [67, 68] and are associated with regulation of granuloma formation in chronic infections [69]. In a study conducted among patients infected with *S. mansoni* in Kenya, it was revealed that few patients had higher proportions of $CD3^+/CD4^+/CD25^{high}$ Tregs that subsequently decreased after treatment with praziquantel. The study concluded that not all *Schistosoma mansoni*-infected individuals develop high percentages of circulating Tregs. The effective treatment decreases the proportion of Tregs and their phenotypes, possibly because of the removal of constant exposure to antigens from intravascular, egg-producing adult worms [70]. In a NOD mice model, treatment with *S. mansoni* egg antigen (SEA) was shown to upregulate TGF-ß on T cells and Th2 cells resulting in the expansion of $Foxp3^+$ that remain crucial in determining the SEA-mediated diabetes outcome [71]. Also, hsp60 peptide (SJMHE1) of *S. japonicum* induces $CD4^+CD25^+Foxp3^+$ Tregs both *in vivo* and *in vitro* resulting in subsequent release of IL-10 and TGF-ß [72].

Nematode infections have been shown to induce regulatory cell expansion in both mice and humans [73]. In a study conducted in Lima, Peru, among human T lymphocyte virus (HTLV-1) patients with or without *Strongyloides* infection, increased proportions of $CD4^+CD25^+Foxp3^+$ Tregs were observed in patients with *S. stercoralis* and HTLV-1 coinfection in comparison to normal controls [33]. Furthermore, those with increased proportions of $CD25^+FoxP3^+$ cells had decreased antigen driven production of IL-5 and lower eosinophil counts. This reduced response is inversely correlated with the proportion of CD4 cells, which are $CD4^+CD25^+FoxP3^+$, suggesting a role for these cells in blunting antigen-driven protective responses.

Visceral Leishmaniasis (VL) represents a parasitic disease that has been shown not to induce expansion of natural Tregs. In a study conducted among patients presenting with symptoms of Kala-azar, frequencies of $Foxp3^+$ cells in patient with VL before and after treatment did not increase, neither were they elevated when compared to endemic controls. It was therefore concluded that active VL is not associated with increased frequencies of peripheral Foxp3 Treg or accumulation at the site of infection [74]. While active VL does not induce expansion of Treg, it has been shown in animal models that Treg is directly responsible for its reactivation [75]. During the primary infection, *L. major* can disseminate to other tissues within the body which may persist after parasite reduction and healing [76, 77]. These persistent parasites are associated with the establishment of strong immunity against reinfection, a state that is referred to as concomitant immunity [75, 78, 79]. Tregs have been found abundantly at these reinfection sites while it reduces at the site of initial infection confirming its importance in reactivation of VL infection. Significant increase in IL-10 production by dermal and LN $CD4^+$ T cells has been shown during the reactivation process confirming a role of IL-10 mediated *Leishmaniasis* both in susceptible and resistant individuals [80, 81]. In macaque (*Macaca mulatta*) model, *L. braziliensis* strain that produces self-healing dermal lesions was used to characterize the systemic and local cell-mediated immune responses that led to controlled growth of granulomas in the infected host. Resolution of infection was observed to be dependent on concomitant recruitment of interleukin- (IL-)-10-producing $CD4^+CD25^+$ regulatory T (Treg) cells that suppress the effector T-cell-mediated inflammatory response [82].

5. Regulatory Gene Polymorphisms

Parasites exert a selection pressure on their hosts and are accountable for driving diversity within gene families and immune gene polymorphisms in a host population. The pathogen driven selection on immune genes can potentially alter the primed sequence and can direct to substantial changes in gene expression [1]. A number of loci were known to be associated to Treg activity. Genes such as *IL-2*, *IL-4*, *IL-10*, *IL-13*, *STAT-4*, *STAT-6*, *GITR*, *TLRs*, and *Foxp3* are established as key players in regulating Tregs [1]. The investigation of human polymorphisms in loci associated with Treg activity may underlie both susceptibility to infection and level of Treg expression. Many of these polymorphisms evolved and are maintained in a human population exposed to infectious diseases. Genotype associations may predict likely susceptibility and allow identification of subjects at the risk of developing the disease and may be subjected to therapeutic treatment.

Investigation of human polymorphisms in immune relevant genes has been used to determine the level of Treg expression and thereby the extent of susceptibility to parasitic infection [10]. The single-nucleotide polymorphisms (SNPs) in the promoter region of the genes such as *STAT6*, *Foxp3*, and *TNFRSF18* were well characterized for their functional role [4, 10, 83]. One gene of interest that plays a key role in the function of Tregs is the *IL-10* gene locus. In populations exposed to *Leishmania braziliensis* in Bahia, Brazil, genetic analysis of the *IL-10*-819C/T SNP polymorphism, located in the *IL-10* promoter, showed that the C allele increased the risk of lesions. The *IL-10*-819 C/C genotype was associated with higher levels of *IL-10* than C/T and T/T genotypes demonstrating a vital role for *IL-10* in skin lesions in humans infected with *L. braziliensis* [84]. Also, *IL-10* promoter polymorphism was recently shown to influence nonspecific total IgE levels, but not schistosomiasis-specific immunity [85]. In chagas disease low *IL-10* expression was associated with cardiac function and it was demonstrated that the polymorphic allele, which correlates with lower expression of *IL-10*, was associated with the development of chagas disease cardiomyopathy. *IL-10* gene polymorphism and *IL-10* expression are important in determining susceptibility to chagasic cardiomyopathy [86]. Also, in malaria infection it was shown that common IL-10 promoter haplotypes condition susceptibility to severe malaria anemia and functional changes in circulating *IL-10*, TNF-alpha, and *IL-12* levels in children with falciparum malaria [87]. In a study among subjects infected with urinary schistosomiasis in Mali, an association was found between *STAT6* (rs324013) gene polymorphism and infection level in subjects under 20 years while the same study did not observe any association with *IL-4* and *IL4R* polymorphism [88]. *IL-13* promoter polymorphism has also been associated with urinary schistosomiasis [89].

6. Conclusion

In summary, the field of infectious disease immunology is at an exciting intersection with new concepts in regulation of immune responsiveness. Despite extensive studies, there is still much that remains unclear about the mechanism and activities of Treg. A more comprehensive understanding of the mechanisms and gene-expression pathways that underlie the Treg activities will be essential if new therapeutic strategies are to be developed. The ability of the Treg cells to control many facets of the immune response makes them an interesting model to study possible immune-modulatory intervention.

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