Biohelikon: Immunity & Diseases, 2014 2:a8

Editorial

Interplay between T Regulatory and T Helper 17 Lymphocytes in Modulation of Immunity to Blood Stage Malaria Infection

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Abstract

Malaria claims millions of lives worldwide each year. While a pro-inflammatory immune response is required to control parasite replication and promote clearance of infected erythrocytes, considerable disease pathology is caused by an excessive and dysregulated inflammatory reactivity to blood stage infection. Clinical symptoms, including fever and chills, correspond to production by $CD4^+$ T helper (Th) lymphocytes of high levels of pro-inflammatory cytokines including tumour necrosis factor-α, interleukin-12 and interferon-γ in response to parasite components released upon erythrocyte rupture. Differentiation into specific effector Th subsets is directed by polarizing cytokines and expression of master transcription factors. From a perspective of homeostasis, further regulatory Th subsets have been described that secrete specific cytokines to modulate the effector immune response and thus play a pivotal role in protecting the body from direct and indirect pathogenic effects of malaria infection. In particular, T regulatory (Treg) lymphocytes are associated with immune tolerance and play a crucial role in suppressing the host response by inhibiting the function of effector subsets such as Th1 and Th17. This prevents inflammation produced downstream by (non-T) effectors cells. Treg lymphocytes, exemplified by $CD4^+CD25^+Foxp3^+$ cells, gradually increase in number during infection to achieve and maintain the homeostasis of an otherwise imbalanced T cell response. This editorial discusses the production of Treg and Th17 lymphocytes and the interrelated roles played by their signature cytokines during malaria infection and considers the contribution of each to parasite clearance or progression.

Keywords
Malaria, *Plasmodium*, immunity, regulation, Th17, IL-17, Treg, IL-6

Introduction

Malaria is caused by protozoan parasites of the genus *Plasmodium* which complete a complex life cycle in vertebrate and mosquito hosts. Globally, up to three million human deaths per annum are attributed to malaria infection, principally *P. falciparum* [1]. Parasites replicate rapidly within erythrocytes and evade host immune responses, both of which are major drawbacks to design of an effective vaccine [2,3]. In murine models, an association has been demonstrated between T regulatory (Treg) lymphocytes and increased malaria parasite burden and, in some cases, a strong correlation between Treg cells and increased disease severity [4]. While other immune components like $CD4^+$ T helper (Th)1 cells and gd T cells are major sources of interferon (IFN)-γ which promotes parasite clearance during blood stage infection [5], the function of Th17 cells that produce the pro-inflammatory cytokines interleukin (IL)-17 and IL-22 during malaria remains to be established [6,7]. Low levels of IL-17-secreting $CD4^+$ T cells were identified in the spleen of mice infected with *P. chabaudi* AS. Neither outcome of infection nor pathology was affected by a lack of IL-17 [7]. IL-9 is also secreted by Th17 and $CD4^+CD25^+Foxp3^+$ Treg cells[8], but the role of IL-9-producing T cell subsets in malaria infection is yet to be investigated. IFN-γ plays both protective and pathogenic roles in malaria [9], whereas IL-10 is protective during infection of murine models with non-lethal strains *P. berghei* XAT, *P. yoelii* 17XNL and *P. chabaudi* AS [10]. Anti-inflammatory cytokines transforming growth factor (TGF)-β and IL-10, as well as pro-inflammatory IFN-γ and IL-17-producing $Foxp3^+$ T cells, are associated with immune tolerance and may perform important functions during malaria infection [11,12]. The discovery of Forkhead box protein 3 (Foxp3) as a definitive transcription factor for Treg cells has permitted investigators to identify, isolate and study the role of these cells in many immunological systems including infectious diseases [13].

Role of mesenchymal stem cells

The malaria parasite survives and replicates in the human host by modulating immunity through an imbalance of humoral and cellular responses [14]. Levels of immune cells fluctuate with severity of infection. In a murine model, mesenchymal stem cells

(MSC) and Treg cells have been shown to increase in concentration with infection that is non-protective in nature. While pre-primed MSC are able to protect from infection by modulating Treg cell responses [15], multipotent MSC differentiate into adipocytes, osteoblasts, chondroblasts and chondrocytes under suitable conditions [16]. MSC have the capacity to control immune dysfunction in a spectrum of diseases. For example, in lung disorders MSC control inflammation [17] and IL-17-producing MSC have been reported to inhibit the growth *in vitro* of the fungus *Candida albicans* and possess therapeutic effect in *C. albicans*-infected mice [18]. MSC regulate immunity by modulating Treg cell responses and accumulate in sites of infection [15]. Treg cells inhibit host protective responses during malaria [19-21], while Treg function is inhibited by IL-6 secreted by MSC in response to parasite challenge [15] (Figure 1). Generation of Th17 cells from naive $CD4^+$ T cells is induced by IL-6 together with TGF-β and inhibits Treg cell differentiation [22-24].

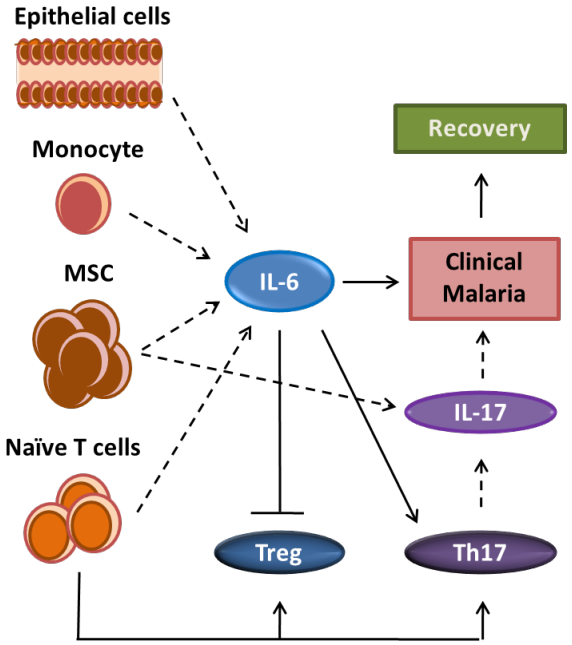

Figure 1 Cytokine interleukin (IL)-6 plays a central role in immune regulation to prevent disease progression during malaria infection. Epithelial cells, monocytes, T lymphocytes and mesenchymal stem cells are sources of IL-6 production. IL-6 inhibits development of Treg cells while also enhancing IL17-producing Th17 cell differentiation.

IL-6 versus Th17 lymphocytes

IL-17-producing Th17 cells represent another subset of pro-inflammatory Th cell that differs from Th1 and Th2 cells in development and functions. Th17 cells secrete IL-17 family cytokines [25]. IL-17 induces synthesis of pro-inflammatory cytokines and chemokines as well as being involved in immunity against bacteria through the recruitment and activation of neutrophils and macrophages [25-27]. Elevated levels of IL-17 cytokines have been detected in serum and tissues of patients suffering with various autoimmune diseases [28,29]. Blockade of IL-17 and regulation of differentiation of Th17 cells provides preventive and effective treatments against development of autoimmune disorders [30-32]. Differentiation of Th17 cells requires the combined effects of IL-6, TGF-β, IL-21 and expression of the transcription factor retinoid-related orphan receptor (ROR)γt. TGF-β singularly is sufficient to induce development of Treg cells [33]. While the functions of IL-17- and IL-22-producing Th17 cells during malaria infection have not been investigated, in a macaque model of AIDS and malaria co-infection they exhibit a protective role via inhibition of the Th1 response [34]. IL-6 is required for Th17 cell differentiation from naive $CD4^+$ T cells (Figure 1), while post-differentiation it does not show any functional property to maintain Th17 cells [35]. Pro-inflammatory cytokines secreted by Th17 cells show functional properties in autoimmune diseases [28,29]. In contrast, during blood stage malaria infection a protective role has yet to be reported. It is tempting to speculate that transfer of agonists of IL-17 and IL-22 in order to prevent disease progression may provide a viable novel approach for the treatment of malaria infection.

IL-6 versus Treg lymphocytes

IL-6 is induced by TNF [36,37] and functions as a pleiotropic cytokine secreted by various cell types [38,39] (Figure 1). It inhibits TGF-β-induced Treg cells [22-24]. $CD4^+CD25^+Foxp3^+$ Treg cells play an important role in disease control and IL-2, retinoic acid and TGF-β serve to maintain Treg functions [40]. For various diseases Treg cells have been reported as an immunosuppressor that maintains homeostasis of the immune system during infection [41,42]. IL-6 alone is able to enhance RORγt expression in Th17 cell whereas the addition of TGF-β further elevates RORγt expression [43,44]. The inhibitory effects of IL-6 on Foxp3 are dependent on signal transducer and activator of transcription 3 (STAT3), a transcription factor that regulates RORγt expression in Th17 cells [40].

Conclusions

Studies from a variety of infectious and autoimmune diseases suggest that Treg cells and Th17 cells are mutually antagonistic in the immune response [45,46]. Clinically, this is manifested as a Treg/Th17 ratio imbalance, which may be linked to disease progression and to continuity of infection [47,48]. Appreciable research has been performed in various murine experimental systems in order to identify a role for IL-17-producing Th17 cells [49]. While IL-17 was originally implicated in the pathogenesis of several autoimmune diseases [30-32], and tumour development [50], induction of Th17 cells has also been described in infections of *Toxoplasma gondii* and *Leishmania donovani* [51,52], suggesting that they may function in protection or immunopathology of parasitic diseases. Moreover, IL-17-producing MSC play a central part in resistance to fungal infection [18]. The mechanism(s) by which IL-17 alters immune responses, and affects the Treg/Th17 balance, in blood stage malaria is still to be explored in a murine model. It may be approached by administering IL17-producing stem cells during organ dysfunctions as well as by direct transfer of *ex vivo*-generated

IL17-producing Th17 cells. The use of Treg cells is regarded as a potentially attractive therapeutic approach for autoimmune diseases but given the less clear picture of immune regulation in parasitic diseases that is emerging, caution here is advised. In this contest, dissection of the interplay between Treg and Th17 cells to the pathogenic stages of *Plasmodium* would be a welcome advance in our understanding of modulation of immunity to this important human pathogen.

Competing Interests

The authors have declared no competing interests.

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