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Cytokines in the immunity and immunopathogenesis in leishmaniases

Bhaskar Saha[a,b,c,*], Ricardo Silvestre[d,e,*]

[a] National Centre for Cell Science, Ganeshkhind, Pune 411007, Maharashtra, India
[b] Trident Academy of Creative Technology, Bhubaneshwar 751024, Odisha, India
[c] BLDE University, Vijayapur, Karnataka, India
[d] Microbiology and Infection Research Domain (MIRD), Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, 4710-057 Braga, Portugal
[e] ICVS/3B's–PT Government Associate Laboratory, Braga/Guimarães, Portugal

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ABSTRACT

Cytokines are key mediators of immune responses to autoantigens, tumor antigens and foreign antigens including pathogens and transplant antigens. The cytokines are produced by a variety of immune and non-immune cells and are dynamically regulated. Remarkably, during toxic and septic shock syndromes, anaphylactic shock and in certain viral infections supra-physiologic levels of cytokine storms are produced culminating in multi-organ failure and death. However, *Leishmania* infection is a chronic parasitic infection with alternate outcomes-healing or non-healing. *Leishmania* invades macrophages and inflicts the complex of diseases called Leishmaniases. Depending on the species of *Leishmania* and the organs affected, the diseases are categorized into Cutaneous Leishmaniasis (CL), Muco-cutaneous Leishmaniasis (MCL) and Visceral Leishmaniasis (VL). After successful chemotherapy of VL, a dermal manifestation- termed post-kalazar dermal leishmaniasis (PKDL)- of the same infection occurs in some patients. The operational frameworks for different cytokines have been laid to discuss how these immune mediators control each of these forms of leishmaniases. One of these frameworks is the regulation of monocytopoiesis including the role of macrophages subsets and thrombopoiesis in leishmaniases. Macrophage metabolism is linked to different cytokines and is thereby associated with the manifestation of the resistance or susceptibility to *Leishmania* infection and of drug resistance. The chemokine-regulated immune cell movements present the landscape of infection and pathogenesis. T cells subsets- the IFN-γ-secreting Ly6C + T cells and the regulatory T cell subsets- provide the initial skewing of Th cell subset and regulation of effector Th subsets, respectively, eventually deciding the outcome of infection.

Leishmaniases are a spectrum of diseases caused by the kinetoplastid protozoan parasites *Leishmania* spp. These are the third most-important vector-borne communicable diseases after malaria and sleeping sickness. Leishmaniases are among the six major diseases targeted for research and control by World Health Organization (WHO). Being associated with malnutrition, immune dysfunction, poor housing and lack of financial resources, these diseases mainly affect the impoverished populations in Africa, Asia and Latin America. Environmental changes such as deforestation, building of dams, irrigation schemes, and urbanization have also considerably contributed to the rise of these cases. Leishmaniases show four major clinical presentations: cutaneous (CL), visceral (VL), post-kala-azar dermal (PDKL), and mucocutaneous leishmaniasis (MCL). CL is characterized by a single or multiple localized lesions on exposed areas of the body, face, neck, arms and legs that typically ulcerate or persist as nodules or plaques. The initial lesion, a seldom small and red papule appears in the site of inoculation, showing localized cell infiltration. This disease will spontaneously heal, but the time lapse to resolve the lesion depends both on the species and on the immune status of the individuals. On the other hand, spleen, liver and bone marrow are infected with the parasite in VL- characterized by fever, cachexia, hepatosplenomegaly, polyclonal hyper-gammaglobulinaemia and immunosuppression. Consequently, VL can be fatal without a treatment. Patients who recovered from VL usually have lifelong immunity to reinfection but the disease relapses occasionally in some cases. The reactivation can be spontaneous, but is often provoked by immunosuppressive conditions under corticosteroids, cytotoxic therapies, or advanced HIV disease. A secondary reminiscent complication of VL is the clinically defined PKDL, which may develop in 2–15% of patients several months after treatment. These patients develop nodules over the face and limbs surface and are considered as a major source of parasites for new infections because of the large number of organisms in their skin

* Corresponding authors. National Centre for Cell Science, Ganeshkhind, Pune 411007, Maharashtra, India (B. Saha). Microbiology and Infection Research Domain (MIRD), Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, 4710-057 Braga, Portugal (R. Silvestre).

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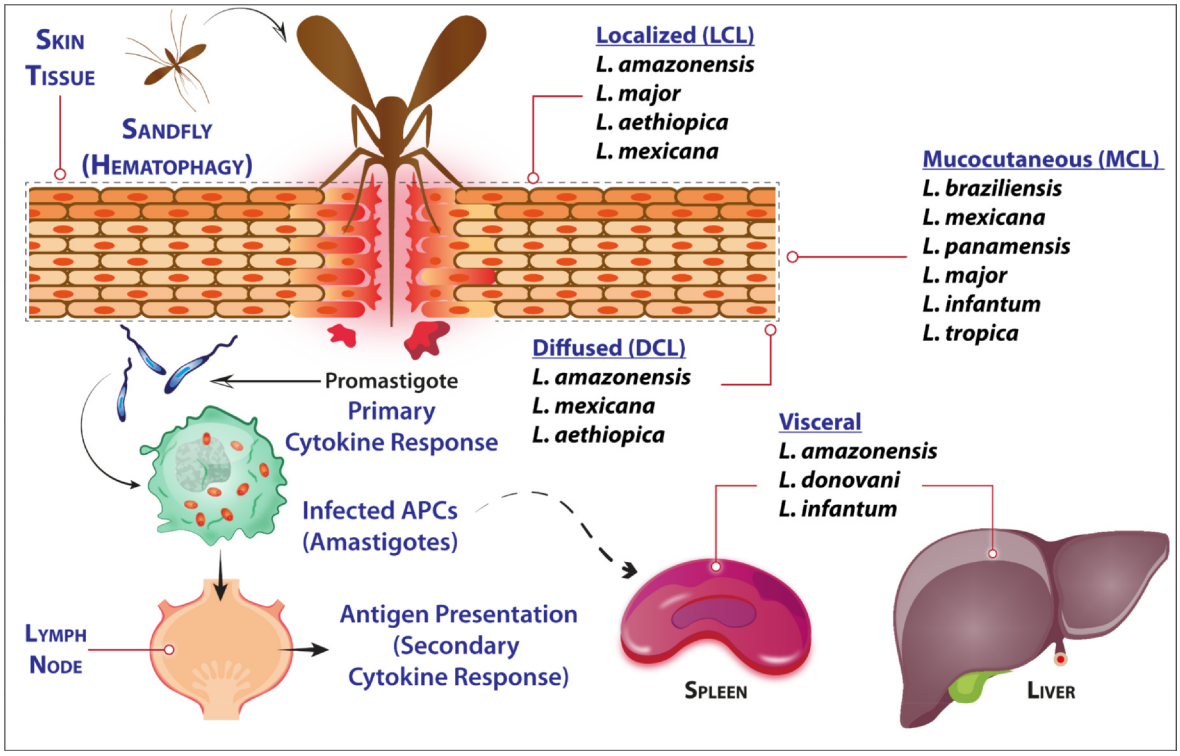

Fig. 1. The figure highlights the Leishmania species specific tissue tropism for development of different forms of Leishmaniasis disease.

accessible to the vector. Being a non-life-threatening disease, it does not affect the daily life, but promotes a poor treatment-seeking behavior. However, it is believed that PKDL patients may serve as a reservoir of *Leishmania* parasites that are ready to be transmitted. Finally, MCL or espundia is usually caused by *Leishmania* species found in Central and South America. A self-healing skin lesion occurs at the initial site of infection. The infection spreads to the mucosal system of the nasal and buccal cavities, where metastatic lesions develop leading to partial or total destruction of those membranes. MCL may arise after inadequate treatment that can lead to severe disfiguration or even death, usually due to secondary bacterial infections or malnutrition. However, secondary infections are common leading to permanent disfiguration. The Leishmania sp and the tissue tropism causing each particular form of Leishmaniasis is shown in Fig. 1.

Leishmaniasis continues to spread, with a total of 97 endemic countries or territories, of which 4 were added in 2017–2018 [1]. As of January 2020, the WHO Global Leishmaniasis programme for 2018 declared 56 VL-endemic countries (73%) and 59CL-endemic countries (66%) [2]. More than 85 percent of cutaneous cases occur in Afghanistan, Algeria, Bolivia, Brazil, Colombia, Islamic Republic of Iran, Iraq, Pakistan, Peru, the Syrian Arab Republic and Tunisia, while more than 90 percent of visceral cases occur in Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan. In addition, almost 90% of MCL cases occur in Bolivia, Brazil and Peru. Overall, an estimated yearly incidence of upto 1 million people although the number of new cases change over time and are often undervalued.

In the absence of a prophylactic vaccine, anti-leishmanial chemotherapy remains the sole means of control for leishmaniases. The anti-leishmanial medicines include the pentavalent antimonials (meglumine antimoniate and sodium stibogluconate), amphotericin B deoxycholate, lipid formulations of amphotericin B, paromomycin, pentamidine isethionate and miltefosine. Despite this therapeutic arsenal, some concerns have arisen regarding leishmaniasis treatment. Existing drugs have serious drawbacks in terms of safety, stability, side effects, and resistance. The current anti-leishmanial arsenal has also a narrow therapeutic index, i.e., the therapeutic efficacy of a drug as compared with that obtained without the drug, low tolerability and prolonged treatment when used individually. A further concern is the fact that most of the available medicines must be administered via intramuscular or intravenous routes, which requires adequate public health services mostly absent from leishmaniasis endemic regions. Resistance to antileishmanial drugs is emerging as a major threat to the global control of leishmaniases. For example, the pentavalent antimony was the standard treatment for almost 100 years. However, in the last 25 years its efficacy was compromised due to the widespread resistance [3], mainly in India, with failure rates higher than 60%. Resistance has been observed also against miltefosine, the only orally bioavailable drug, amphotericin B and paromomycin, calling for urgent actions to develop anti-leishmanial strategies.

Long-term strategies to attain the ultimate goal of eliminating leishmaniasis include not only the vector control but also immunotherapy, immunoprophylaxis and widening of chemotherapeutic repertoire. In the past, immunotherapeutic interventions by vaccination or passive antibody administration proved particularly effective in the prevention or treatment of several infectious diseases. Improved understanding of the pathogenesis of leishmaniasis and mechanisms of protective immunity should provide a strong rationale for designing immunotherapeutic, immunoprophylactic and improved chemotherapeutic interventions. Cytokine-based immunotherapy is one promising strategy for the treatment of leishmaniasis, as cytokines are able to restore the host resistance and immune effector functions eventuating in parasite elimination.

The first proposition of a humoral factor, which is not a gammaglobulin but offers resistance to infection, appeared as early as 1932 [4]. It was followed by the discovery of Interferons that interfered with viral growth [5]. In the meanwhile, the role of not only phagocytes-macrophages and neutrophils- but also lymphocytes in both cell-mediated immunity and humoral immunity were being described. As the functions for Thymus and the Bursa of Fabricius in developing two different types of lymphocytes [6,7] and the role of colony stimulating factors in hematopoiesis were attributed [8], it was appreciated that both cell-mediated and humoral immunity worked for host protection

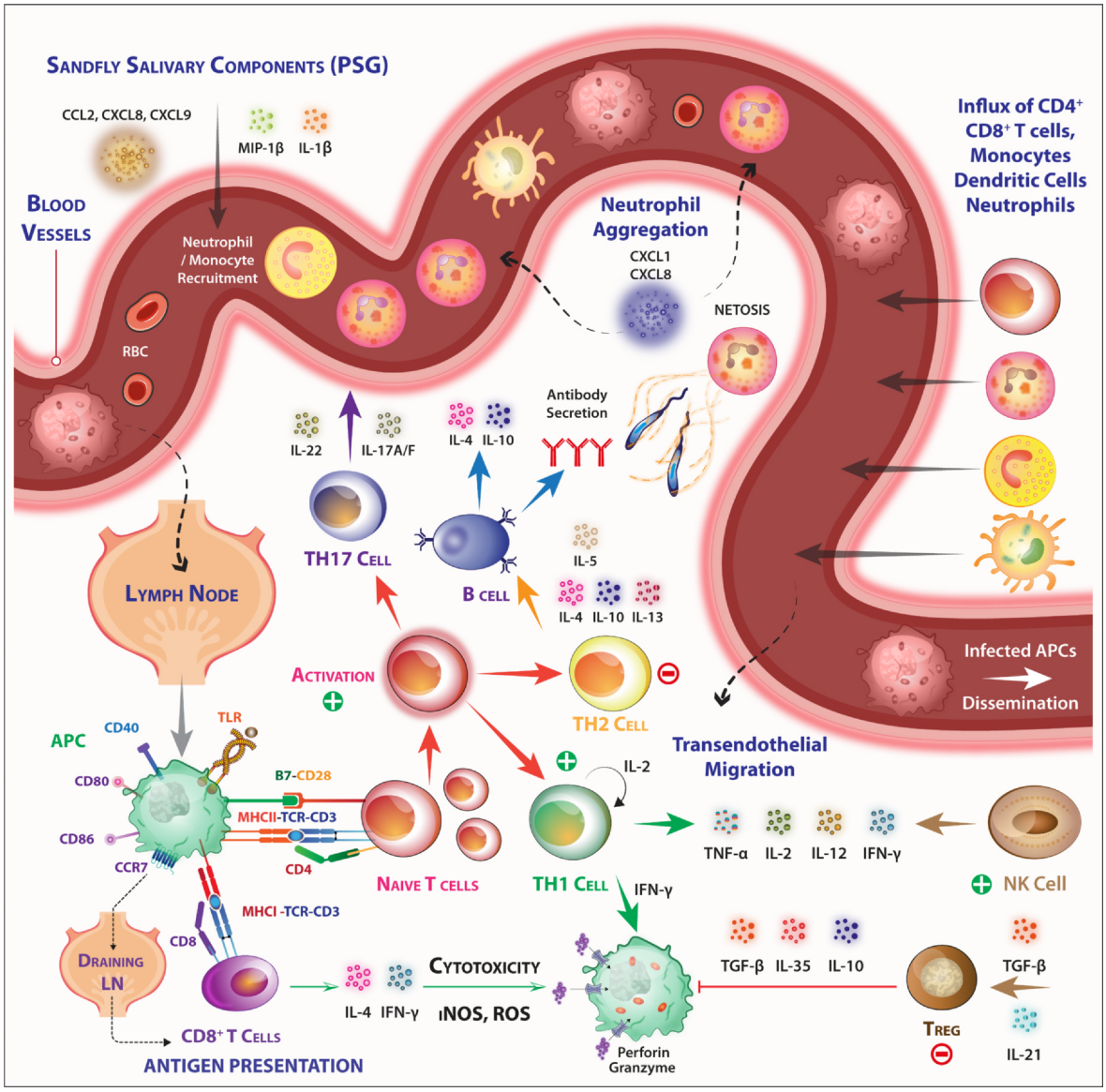

Fig. 2. The other Illustration shows the cytokines and factors involved in producing pro- versus anti- leishmanial effects consequently affecting the Leishmaniasis pathogenesis.

against infections. 1975 onwards, the rate of discovery of these humoral factors- named "Cytokines" by Yoshida et al [9] and "Interleukin" by Aarden [10]- has been accelerated resulting in a huge number of cytokines produced by many immune and non-immune cells.

Because this is a Special Issue dealing with Cytokine in Leishmaniases, a complex of diseases caused by the apicomplexan, dimorphic, protozoan parasite named *Leishmania*, we decided to include a "Cytokine Primer" that would provide a short chronological account of the discovery of cytokines, a glimpse of the complexities in cytokine families and their functional characteristics for the parasitologists and non-specialists [11]. We assembled a few thought-provoking articles covering the chronology of implicating the cytokines in Leishmaniases [12], paradoxes of cytokine functions in Leishmaniases [13] and some cytokine-related outstanding questions [14] in the "Opinion" section.

The subsequent "Reviews" section includes fifteen articles on different aspects of the human and experimental leishmaniases. Bhor et al describes the differential involvement of cytokines in the progression of the disease in Visceral Leishmaniasis patients [15], while Kihel et al describes the cytokines in Cutaneous Leishmaniasis [16]. Post-kalazar dermal leishmaniasis (PKDL) that remains an immunological and parasitological mystery till today is described by Jafarzadeh et al [17]. The cytokines in Leishmaniasis in non-human primates are described by Andre et al [18]. As visceral leishmaniasis involves chronic infection of spleen, an important secondary lymphoid organ that also functions as a scavenging organ, de Oca et al discusses the role of cytokines in the splenic remodeling in *L. donovani* infection [19]. As Leishmania also affects the host cell metabolism [20–23], Bodhale et al reviews the InLeish Consortium effort to decipher the bidirectional influences of cytokines and the parasite in the alternate outcomes- healing or progression- of this parasitic infection [24]. Goncalves et al reflected upon the role of humoral immunity in Leishmaniasis and debated on its conflicting roles in prevention and promotion of the infection [25]. While optimal activation of T cells depends on two signals– TCR-driven first signal and the costimulatory molecule-driven second signal [26,27]- the cytokines do play important roles in the generation and functions of T cell subsets. One important subset of T cells is regulatory T cells. Their generation and functions in Leishmaniasis have been reviewed by Ghosh et al [28]. As mounting of an immune response is dependent on chemokines-guided cellular migration between the primary and secondary lymphoid organs and the site of infection, this

important aspect has been reviewed by deAraujo et al [29]. How cytokines play a significant role in manifesting host genetics-driven cure or non-cure phenotypes in Leishmania infection has been summarized by Krayem and Lipoldova [30]. Finally, a very important issue in T cell bias has been discussed by Seyed and Rafati, as they propose that Th1 concomitant immunity includes Th1 memory cells plus Ly6C$^+$ T_{EFF} and T_{RM} cells [31]. The various functions of cytokines in *Leishmania* infection are shown in Fig. 2.

This special issue also includes a few "Original Research Articles" by the groups of Tasew and Chaneylew describing cytokines in Ethiopian Leishmaniasis [32,33]. Saha et al revisited the host immuno-suppression as a contributory factor to the observed delayed or less clearance of the parasite as a mechanism of partial drug-resistance [34] while Mahapatra et al showed how eugenol oleate alter cytokine abundance to curatively reduce the parasite burden in a susceptible mouse strain [35].

We recognize that this special issue may not comprehensively cover the immunity to Leishmaniases. Nonetheless, these articles provide some very important critical insights on the current status of this public health threat. While we attempted to invite the contributing authors and get their articles reviewed within a limited time-frame, submission of several articles was delayed due to COVID-19, in particular, when the authors themselves were involved in managing the crisis. We hope to bring out another special issue in near future on the aspects not covered in this edition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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