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Trend of Regulatory T-Cells in the Pathogenesis of Leishmania Infection

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Abstract

Leishmaniasis is a global health issue, every year killing thousands of people around the world, majorly from tropical and subtropical countries. It is prevalent mostly in the poorest population suffering from malnutrition and immune dysfunction. Though macrophages have enrolled in the first-line of defence, Leishmania parasite evades macrophage antimicrobial machinery to establish the infection. Before the infection become chronic, T-cell (Th1 subset) plays a crucial role in the complete elimination of the parasite by means of inflammatory response, with appropriate chemotherapy. If it fails, infection become chronic and persists for several years; this situation lead by initially Th2 cells followed by and T-regulatory cells (T-regs). During control of excessive inflammation, T-regs may divert the host immune response in favour of the parasite persistence in lymphoid tissues. In this report, I have presented the trend of regulatory T-cells in the establishment of chronic infection that develops symptomatic disease.

Abbreviations: VL: Visceral Leishmaniasis; PKDL: Post-Kala-Azar Dermal Leishmaniasis; MCL: Mucocutaneous Leishmaniasis; T-reg: Regulatory T-Cells; CL: Cutaneous Leishmaniasis; DCs: Dendritic Cells

Introduction

Leishmania infection in humans is usually sub-clinical, where the parasite persists for the life-time of host. Low grade infection is typically controlled by the cell-mediated immune response (self-cure) or by successful chemotherapy [1]. If the person is immuno-compromised, the infection leads to the development of symptomatic clinical disease; including the reactivation of kala-azar/visceral leishmaniasis (VL) as found in HIV patients [2], development of post-kala-azar dermal leishmaniasis (PKDL) after apparent cure of VL [3], reactivation of localized dormant skin lesions, and the development of destructive mucocutaneous leishmaniasis (MCL) several months after healing of localized skin lesions in normal healthy individuals [4,5]. Generally, immunological homeostasis of a host is maintained by specialized subsets of T-lymphocytes called regulatory T-cells (T-reg). Till date, various types of T-regs have been described in human and mice [6-10].

The naturally occurring T-regs (CD4+CD25+Foxp3+) resides in the thymus and peripheral blood [11-16], which constitutes around 5-10% of peripheral CD4+ T-cells and have crucial role in the control of autoimmunity [17,18] and maintenance of self-tolerance. This statement was validated for the first time by the observation of developing fatal autoimmune disorders in mice with neonatal thymectomy; however, transfer of CD4+CD25+ T-cells purified from normal mice prevented these outcomes [17,19,20]. The transcription factor Foxp3 encodes for a forkhead/winged-helix transcription repressor named Scurfin, whose expression is mainly restricted to CD25+CD4+ T-reg cells and regulates their development and function [21,22]. FOXP3 mutations in humans cause immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome, together called as IPEX, which is characterized by high incidence of autoimmune diseases including type-1 diabetes, thyroiditis, inflammatory bowel disease, and allergic disease such as atopic dermatitis and food allergy [23-28].

T-regs in Chronic Leishmania Infection

T-regs may be a part of misdirected immune responses [29-31] and play a significant role in the reactivation of dormant infection, studied in pathogenesis of Leishmania infection [32-35]. Persistence of Leishmania in the experimental skin model found to be controlled by CD4+CD25+ T-reg cells [36]. Moreover, in intra-dermal low dose of L. major cutaneous infection model, T-reg cells are essential for maintenance and development of persistent skin lesions. T-reg cells rapidly accumulate at the site of L. major infection, suppressing the ability of the immune response which involve in the complete elimination of the parasite. Establishment of chronic infection and the maintenance of a constant number of parasites at

the site of infection depend on a tight equilibrium between effector lymphocytes and T-reg cells. More over depletion of CD25+ cells at the time of secondary challenge prevented disease reactivation at the primary site, while strengthening the expression of immunity in the challenged site [37,38]. Finally, the transfer of T-reg cells purified from chronically infected mice into non-symptomatic infected mice was sufficient to trigger the disease reactivation and prevent the expression of effector memory response.

The equilibrium between T-regs and effector lymphocytes, which could be distributed in the case of super-infection, controlled the efficiency of recall immune response and disease reactivation [38]. However, in the case of human VL no evidence has been found to support a role for CD4+CD25+ cell-mediated immune suppression [39]. In humans, a subset of T-cells that produce both IFN-γ and IL-10- was found to be significantly higher in Leishmania antigen activated PBMC cultures derived from individuals with a past history of VL [40]. IL-10 was produced by innate cells as well as CD4+CD25+Foxp3+ and CD4+CD25−Foxp3− T-cells in the chronic lesion of cutaneous leishmaniasis (CL). Nonetheless, only IL-10 production by antigen-specific CD4+CD25−Foxp3− T-cells, the majority of which also produced IFN-γ, was necessary for suppression of acquired immunity in Rag−/−reconstituted mice [41]. In experimental models, absence or inhibition of T-regs or IL-10 promotes complete clearance of parasite, whereas depletion of effector cells or cytokines (e.g. IFN-γ, IL-12) promotes reactivation [1,42,43].

During the chronic phase of the infection a high number of both IFN-γ producing effector lymphocytes (CD4+CD25− T-cells) and IL-10 producing T-reg cells (CD4+CD25+ T-cells) accumulate at the site of infection. In human VL, elevated level of IFN-γ mRNA in lymphoid organs is correlated by the high expression of IL-10 [44-46], where the predominant source of IL-10 is Foxp3–CD25–CD3+ cells [39]. In accordance to this, a subset of regulatory dendritic cells (DCs) in the L. donovani infected spleen produce IL-10 that induce the expansion of IL-10-producing regulatory T-cells and inhibit the antimicrobial potential (reactive oxygen and nitrogen intermediates production) of macrophages and other phagocytic cells. IL-27 producing regulatory DCs or macrophages and IL-21 producing T-cells together drives the differentiation of Th1 cells into T-regs and also inhibits the development Th17 phenotype. IL-10 produced by T-regs suppresses antigen presentation, mediates T-cell dysfunction, and inhibits IFN-γ producing CD4+ T-cells [47]. Finally, the role T-regs was elucidated in modulating both Th1 and Th2 activity during murine L. major infection [32,35,36].

Conclusion

In conclusion, acquiring better knowledge about Leishmania species-specific T-reg cell phenotypes, function, and their network of interaction and regulation with other subset of T-cells could help in finding a novel immunological target for the cure of leishmaniasis.

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