Biomedicine & Pharmacotherapy 117 (2019) 109098

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Functional aspects of T cell diversity in visceral leishmaniasis

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ARTICLE INFO

Keywords:
T cell subsets
Visceral leishmaniasis
Transcription factor
Cytokines

ABSTRACT

Co-ordination between innate and adaptive immunity is a foremost crucial immunological interactions. The interaction is beneficial for the survival of the host against infectious agent and also detrimental for the pathogen during their future encounter. Major cellular components to bridge the gap of innate and adaptive immune system include B cells, varieties of T cell subsets and their interaction with antigen presenting cells. T cells are the components of immune system which recognise antigen that are specifically presented with the different class of MHC molecules like MHCI and MHCII marking the diversity of exogenous and endogenous nature of antigen. T cells further differentiate in varieties of morphological and immunological forms like CD4+, CD8+ T cells, Th-17, Treg and γδ-T cells based on the nature of antigen, interaction and polarizing factors. Therefore the evolutionary selections of these diversities have a different functional aspect which is not only dependent upon their percentage presence but more promisingly dependent upon their physiological state and local environment. Thus this review is highlighting the major contributions of T cells subsets using an infectious disease model of visceral leishmaniasis and also helpful in explaining the reason for the non-responsiveness of the T cells subsets during the onset and progression of infection.

1. Introduction

Visceral leishmaniasis (VL), commonly known as kala-azar affecting mainly the visceral organ of the infected host. The co-occurrence of HIV and VL infection is emerging as a serious threat for the mankind where the main hallmark of the infection is severe immune deficiency [1]. T cells are the important cells of the immune system which is capable of differentiation into various functional forms like Th-1, Th-2, Th-17, Treg and γδ-T cells etc. These various form of T cell subsets are generated once the initial signal are transmitted from the different antigen presenting cells like macrophage and dendritic cells (DC). It has been found that *Leishmania donovani* parasite the causative agent of VL generally recognises antigen presenting cells (APC) and multiply within the hostile environment of these cells [1,2]. During the progression of the infection the parasite modulate the host macrophage or DC for their survival and thereby as a result the specific factors secreted by the reprogrammed APC help in the differentiation of specific T cells subsets.

The components of the immune system play vital role in the removal and executions of these parasite which include antigen presenting cells, soluble mediator like cytokines, chemokines, and the co-ordination of T cells [3,4]. T cells are characterized by the presence of specific markers on their surface like CD3, CD4 and CD8, expression of transcription factors like GATA-3, Tbet, RORγt and Foxp3 etc. and the interaction with specific class of MHC for antigen recognition like MHCI and MHCII for the execution of endogenous and exogenous nature of the antigen [5,6]. Some T cells like Th-17 cells secretes cytokine IL-17, IL-6 etc. which help to achieve pro-inflammatory state and provide protective immunity against parasite infection [7]. The occurrence of such diversity in the T cells subsets helps us to explore the functional aspects of these cells and to categorise the specific group of cells under selective role they play. T cells recognises MHC bound antigens along with that it also helps in the proliferations of other T cells, activation of B cells, regulation of intense immune response and to connect innate and adaptive immune system to induce memory response [8]. These T cells have important role in the inflammatory diseases and also play vital role to prevent our body from hyperimmune activation, autoimmunity, immunodeficiency and the complete execution of infectious agents which can result into the onset of these conditions [9]. During VL it has been found that successful establishment of infection increases the population of Th-2 and Treg cells which secretes increase level of serum IL-10 and TGFβ cytokines which develop severe immune suppressive condition. On the other hand elevated population of Th-17 and Th-1 cells secretes various pro-inflammatory cytokines which resist the onset of infection. Therefore, in this review we have summarise the role

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https://doi.org/10.1016/j.biopha.2019.109098
Received 10 December 2018; Received in revised form 4 June 2019; Accepted 4 June 2019

of different subsets of T cells, their functional aspects and the physiological response with the help of a single infectious disease model of visceral leishmaniasis.

2. T cell and its different subsets in visceral leishmaniasis

2.1. CD4+ T cells

The majority of the T lymphocytes consist of the CD4+ T cells. The membrane glycoprotein molecules CD4 that are expressed by the T cells recognize antigens only bound to MHC class II molecule. CD4+ T cells mainly function as T helper cells. When the naïve CD4+ T cells are activated after interacting with the MHC-class II – antigen complex, they are differentiated into the classical Th-1 and Th-2 type depending on the microenvironment [4]. Since 1986, when it was believed that activated CD4+ T cells can differentiate into Th-1 and Th-2 cells which differ in their mechanism of action and cytokine production, till today's date this view has completely expanded [10,11]. Now it is show that CD4+ T cell exist in distinct subset like Th-1, Th-2, Th-17 and Treg [10]. In visceral leishmaniasis CD4+ T cell found to secrete pro-inflammatory cytokines like IL-12 and TNFα which is associated with major host protective role [12] although the case is not same in all condition. In case of progressive visceral leishmaniasis of experimental hamster model it has been found that the splenic CD4+ T cells showed mixed expression of Th-1 and Th-2 cytokines [13]. It was found that splenic CD4+ T cells from infected hamster shows increased expression of inhibitory receptor PD-1 for the ligand like PD-L2. Blockage of this receptor causes decrease in the expression of arginase-1 as a result of which the organ parasite burden was decreased [13]. In another study using mice model of VL caused by *L. donovani* parasite it was reported that the infection induced increase in the population of IFNγ producing CD4+ T cell is responsible for irreversible loss of bone marrow function [14]. These reports clearly indicates that the presence of CD4+ T cells in large number is just not sufficient for the protection from the infection, the physiological state and polarization towards pro-inflammatory response play a promising role in the defence against the disease.

2.2. CD8+ T cells

CD8+ T cells mainly function as cytotoxic T cells and are restricted to recognize antigens that are bound MHC- class I. This cell expresses dimeric membrane glycoprotein CD8. When the naïve CD8+ T cells become activated, they have 3 major defence mechanisms against the infection. The first is the secretion of cytokines- IFN-γ and TNF-α, the second is the release of cytotoxic granules like perforin and granzyme, and the third is destruction of the infected cells via the Fas/Fasl interactions [15]. In case of VL caused by *L. donovani*, it has been reported that the presence of CD8+ T cells confer protection against the onset and the progression of the disease through the secretion of IFNγ, perforin and granzyme molecules. Whereas the vaccine induced elevation of CD8+ T cells are promising in decreasing organ parasite burden in mice model which is dependent on chemokine CXCL-10 [16]. It was reported that in healed VL individuals the elevated level of CD8+ T cell confer resistance to *L. donovani* infection through the secretion of granzyme B [17]. Although in human VL, the progression of infection drives the CD8+ T cells towards anergy/exhaustion state which restricts the ability of CD8+ T cells to provide protection [18]. Therefore these studies clearly state that the functional aspects of CD8+ T cell response is dependent on the nature of stimulus and the physiological state of the cell.

2.3. Th-17

In addition to the classical Th-1 and Th-2 cells, Th-17 cells are the different lineage of CD4+ T cell that is mainly characterized by the production of IL-17 cytokine [19]. It produces varieties of cytokines which include IL-17A, IL-17F, IL-21, IL-22, TNF-α, IL-6, IL-26 [20]. Th-17 cells are highly responsive to certain chemokines and cytokine receptors like CCR4, CCR6, IL-23R which they express on their cell surface [21]. The cytokines produced by Th-17 have both pathogenic and beneficial effects. RORγt is the specific transcription factor for the differentiation of Th-17. The cytokines produced by Th-17 cells help in the elimination of pathogenic microbes whereas sustained release of IL-17 leads to chronic inflammation autoimmune diseases [22]. The differentiation of Th-17 cells is debatable and the issue still remain unresolved. Previously it was though that activation of T cells in the presence of IL-1β, IL-6 and / IL-23 was sufficient to induce the differentiation of Th-17 cells and that this process was inhibited by TGF-β1 [19,23]. However later reports have shown the importance of TGF- β1 in the development of human IL-17 producing cells. It has been found that in visceral leishmaniasis Th-17 cells is associated with host protective immune response which is through the secretion of IL-17 cytokines and the recruitment of neutrophil to the site of action [24]. Even during human infection, it was found that those individuals displaying high serum level of IL-17 cytokine shows resistance and fast recovery response from *L. donovani* infection [25]. Studies from our lab reported that *Leishmania* antigen and peptidoglycan stimulated dendritic cells based vaccination induces host protective response in VL which is through IL-17 secretion [1]. However, in another study it was reported that IL-17A promotes susceptibility to *L. donovani* infection which is through restricted secretion of IFNγ and less accumulation of neutrophil [26]. Thereby proving that the mere presence of IL-17 is just not enough for the detrimental effect to the pathogen, the regulation of other cytokines due to hyper-responsiveness of IL-17A can reverse the effect.

2.4. Treg cells

Treg cells falls under a category of CD4+ T cells and comprise 5–10% of the total CD4+ T cells. The main functions include suppression of allergy, prevention of autoimmune diseases and the maintenance of self tolerance. Like others, Treg cells also have specific markers for identification. The most widely used markers for Treg cells include CD25, CTLA-4, CD127 and a specific transcription factor known as Foxp3 [27]. Treg cells are a subset of CD4+ T cells constitutively expressing CD25 and are enriched in suppressor activity due to the synthesis of IL-10 and TGFβ cytokines [27,28]. Treg cells is widely explored in case of both human and experimental VL model and it has been found that it is associated with higher susceptibility of infection due to elevated secretions of IL-10 and TGFβ cytokines [29]. IL-10 secreted by Treg cells also induces IL-10 producing CD4+ T cells which confer more immune-suppression in the infected host [30]. The balance and conversion between Th-17 and Treg cells also depends upon the serum level of IL-2, which helps in higher Th-17 generation and decreased Treg population [31]. Another studies reported that CD4+ Foxp3+ Treg cells but not CD8+ Foxp3+ Treg cells are important for the increased susceptibility to *Leishmania* infection and heightened IL-10 production [25]. Therefore the studies have confirmed the specific type of Foxp3+ Treg cells is important to promote tolerance or susceptibility during *L. donovani* infection and the presence of other cytokines can affect the population of Th-17 and Treg cells.

2.5. Natural killer T cells

These are unusual subset of the immune system that does not display the typical membrane molecules and T cell receptors that distinguish the T cell lineages. They are usually characterized by the presence of the markers such as NK 1.1, NK 1.2, CD16, CD56 etc. [32]. These subsets of T cells can work in absence of antibodies or MHC and even work as cytotoxic lymphocytes the CD8+ T cells and can produce abundant amount of cytokines when they are activated upon encountering an antigen [32]. The rearranged T cell receptor of the NKT

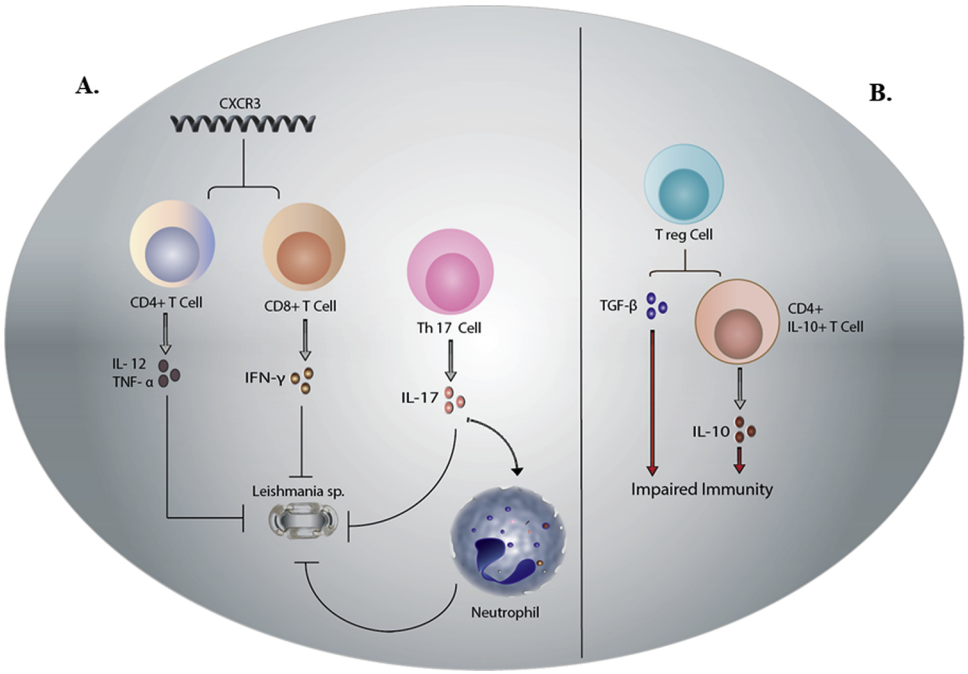

Fig. 1. Differential role of T cell subsets during visceral leishmaniasis. (A) After stimulation the CD4+ T cells secretes IL-12 and TNFα, CD8+ T cell secretes IFNγ and Th-17 cells secrets IL-17 cytokines which together helps in the killing of parasite and provide protective immune response. IL-17 also helps in the activation of neutrophil which again become detrimental for the survival of the parasite. (B) Infection induced differentiation of Treg cells and Th-2 cells (CD4+ IL-10+ T cells) increased the expression of IL-10 and TGFβ which ultimately impair host protective immune response and helps in the progression of infection.

cell recognizes lipid antigens presented on CD1d which are itself not MHC but MHC like molecules [33]. These cells have the ability to bridge the adaptive and the innate immune system by rapidly producing a wide variety of signature cytokines [34]. After activation the NKT cells secretes various type 1 and type 2 immune regulatory cytokines which helps in the clearance of parasite and recovery of host immunity. In context of leishmaniasis it has been found that NKT cells after activation secretes IFNγ, TNFα, IL-23 along with increased generation of IL-17 cytokines which restores host immune response and ultimately helps in the effective clearance of parasite. The uniqueness of the IL-17 generation by NKT is found to be independent of IL-6 cytokines [31]. In another study it was revealed that different subsets of NKT cells namely CD4+ CD56+ NKT cells and CD8+ CD56+ NKT cells are differentially regulated during *L. donovani* infection, where infectious induced CD4+ CD56+ NKT cells was found to be the major source of TGFβ making the host more immune suppressive and restoration of CD8+ CD56+ NKT cells helps in the recovery of the disease [35].

2.6. γδ-T cells

The γδ-T cells are the subsets of T cells which unlike other T cells express γ and δ chain as surface glycoprotein receptors than commonly found α and β receptors. These T cells although found in very less percentage in the total T cell pull of the human body but in gut mucosa these T cells are the most abundant among others. [36]. γδ-T cells develop in the thymus gland and express high levels of TNFα, IFN-γ and granzymes. The TCR of these cells consist of γ and δ subunits. Phospho antigens have been described as ligands for γδ-TCR and traditional antigen presentation is generally not required for its activation. They offer distinct functions like cytolysis, IgE induction, production of growth factors and antigen presentation [37]. They are the subset of the "unconventional" T lymphocytes as they can recognize diverse range of antigens without possessing MHC molecules [38].The functional responses of the γδ-T cells are brought about by the recognition of the stress antigen, which results in the production of cytokine, clearance of pathogen, inflammation and tissue homeostasis [39]. *L. donovani* parasite exploit γδ-T cells pathway by increasing their populations. This increase in population is associated with decrease cellular expression of HLA-DR on T cell blast making the host more immune-suppressive [36]. Another study reported similar finding in VL patients where infection induced γδ-T cells population were observed. This elevated γδ-T cells causes increase secretion of B-cell growth factor and B-cell differentiation factor which are the major cause of humoral immune system abnormality and hypergammaglobulinemia associated with the disease suggesting the pathological and immune-suppressive response of these subsets of T cells [40].

3. Discussion

Infection induced differentiation of T cells are the outcome of reprogrammed antigen presenting cells. Once the parasite entered into the hostile environment of the macrophages it induces the secretion of specific cytokines. These cytokines helps in the polarization of the naive T cells and the induction if specific transcription factors which dictate the fate of T cell differentiation. In context of leishmaniasis it was found that different T cell subsets function differently during infection. Some T cells provide protective immune response while other are associated with suppressive immunity and pathological outcome to the host. IL-12+ CD4+ T cells, CD8+ T cells, Th-17 and NKT cells are categorised under such immune-protective T cell subsets whereas IL-10+ CD4+ T cells, Treg cells, CD4+ TGFβ+ NKT cells and γδ-T cells are associated with progression of the infection. Infected macrophages secretes IL-10, IL-4 and other cytokines and helps in the induction of Foxp3 and GATA3 transcription factors in the naive T cells and thereby help in the generation of Treg and Th-2 cells respectively. On the other hand when the cells are pre-stimulated with antigen or immune-therapeutic molecules it induces the secretion of cytokines like IL-2, IL-6, TGFβ IL-23, TNFα and IL-12. These cytokines helps in the expression of transcription factors like RORγt and t-bet and thereby the differentiation of Th-17 and Th-1 cells take place. Treg and Th-17 cells play important role in the maintenance of inflammatory homeostasis. The decision between these two cell type differentiation is very crucial and somewhat depends upon the expression of IL-6 and TGFβ [1]. Higher serum levels of IL-6 and lower TGFβ induce Th-17 differentiation whereas higher TGFβ and other regulatory cytokines in absence of IL-6 play important role in the induction of Treg cells and Th-2 cell types. As the severe immune response against the pathogen can also harm the host by providing intense pro-inflammatory environment, therefore it is necessary to control these events by maintenance of homeostasis where Th-17 and

Treg cells play major role. Although it has been found that mere presence of the different T cell are just not enough for the protection from the invading pathogens, their nature of stimulus, physiological state, presence and absence of other cytokines are important to induce the different transcription factors and thus it dictate their function. Taken together this review highlighted the functional aspects of T cells diversities with respect to their population and physiological state and the co-ordination between different components of the immune cells focusing on the main aim of disease resolution (Fig. 1). A greater knowledge in T cells biology is required for the predicting the possible involvement of the immune arms in different disease model ranging from infectious disease, autoimmunity, immune deficiency to cancer and is promising in finding the therapeutic targets to restore host defence mechanism.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

We are very thankful to the director Bose institute [Kolkata] for providing us the working environment and all the necessary facilities to support the research work.

References

[1] J.J. Jawed, S. Majumder, S. Bandyopadhyay, S. Biswas, S. Parveen, S. Majumdar, SLA-PGN-primed dendritic cell-based vaccination induces Th17-mediated protective immunity against experimental visceral leishmaniasis: a crucial role of PKCβ, Pathog. Dis. 74 (2016) pii: ftw041.
[2] S. Azzouz, P. Lawton, In vitro effects of purine and pyrimidine analogues on Leishmania donovani and Leishmania infantum promastigotes and intracellular amastigotes, Acta Parasitol. 62 (2017) 582–588.
[3] M.C. Liu, H.Q. Xiao, L.M. Breslin, B.S. Bochner, J.T. Schroeder, Enhanced antigen presenting and T cell functions during late-phase allergic responses in the lung, Clin. Exp. Allergy 48 (2018) 334–342.
[4] R.V. Luckheeram, R. Zhou, A.D. Verma, B. Xia, $CD4^+$T cells: differentiation and functions, Clin. Dev. Immunol. 2012 (2012) 925135.
[5] C. João, B.M. Ogle, S. Geyer, Immunoglobulin promotes the diversity and the function of T cells, Eur. J. Immunol. 36 (2006) 1718–1728.
[6] M.C. Mingari, L. Moretta, Surface markers of human T lymphocytes, Ric. Clin. Lab. 12 (1982) 439–448.
[7] A. Brinkhoff, A. Siebericchs, H. Engler, S. Dolff, S. Benson, J. Korth, M. Schedlowski, Pro-inflammatory Th1 and Th17 cells are suppressed during human experimental endotoxemia whereas anti-inflammatory IL-10 producing T-cells are unaffected, Front. Immunol. 9 (2018) 1133.
[8] H. Rabb, The T cell as a bridge between innate and adaptive immune systems: implications for the kidney, Kidney Int. 61 (2002) 1935–1946.
[9] K. Dornmair, N. Goebels, H.U. Weltzien, H. Wekerle, R. Hohlfeld, T-cell-mediated autoimmunity: novel techniques to characterize autoreactive T-cell receptors, Am. J. Pathol. 163 (2003) 1215–1226.
[10] J. Zhu, W.E. Paul, CD4 T cells: fates, functions, and faults, Blood 112 (2008) 1557–1569.
[11] T.R. Mosmann, H. Cherwinski, M.W. Bond, M.A. Giedlin, R.L. Coffman, Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins, J. Immunol. 175 (2005) 5–14.
[12] J.J. Jawed, S. Banerjee, S. Bandyopadhyay, S. Parveen, B.P. Chowdhury, P. Saini, S. Majumdar, Immunomodulatory effect of Arabinosylated lipoarabinomannan restrict the progression of visceral leishmaniasis through NOD2 inflammatory pathway: functional regulation of T cell subsets, Biomed. Pharmacother. 106 (2018) 724–732.
[13] A.A. Medina-Colorado, E.Y. Osorio, O.A. Saldarriaga, B.L. Travi, F. Kong, H. Spratt, L. Soong, Splenic CD4+ T cells in progressive visceral leishmaniasis show a mixed effector-regulatory phenotype and impair macrophage effector function through inhibitory receptor expression, PLoS One 12 (2017) e0169496.
[14] A.I. Pinto, N. Brown, O. Preham, J.S.P. Doehl, H. Ashwin, P.M. Kaye, TNF signalling drives expansion of bone marrow CD4+ T cells responsible for HSC exhaustion in experimental visceral leishmaniasis, PLoS Pathog. 13 (2017) e1006465.
[15] E.J. Wherry, V. Teichgräber, T.C. Becker, D. Masopust, S.M. Kaech, R. Antia, U.H. von Andrian, Lineage relationship and protective immunity of memory CD8 T cell subsets, Nat. Immunol. 4 (2003) 225–234.
[16] S. Majumder, S. Bhattacharjee, B. PaulChowdhury, S. Majumdar, CXCL10 is critical for the generation of protective CD8 T cell response induced by antigen pulsed CpG-ODN activated dendritic cells, PLoS One 7 (2012) e48727.
[17] H. Kaushal, R. Bras-Gonçalves, N.S. Negi, J.L. Lemesre, G. Papierok, P. Salotra, Role of CD8(+) T cells in protection against Leishmania donovani infection in healed visceral leishmaniasis individuals, BMC Infect. Dis. 14 (2014) 653.
[18] S. Gautam, R. Kumar, N. Singh, A.K. Singh, M. Rai, D. Sacks, S. Sundar, S. Nylén, CD8 T cell exhaustion in human visceral leishmaniasis, J. Infect. Dis. 209 (2014) 290–299.
[19] S.Q. Crome, A.Y. Wang, M.K. Levings, Translational mini-review series on Th17 cells: function and regulation of human T helper 17 cells in health and disease, Clin. Exp. Immunol. 159 (2010) 109–119.
[20] L.E. Harrington, R.D. Hatton, P.R. Mangan, H. Turner, T.L. Murphy, K.M. Murphy, C.T. Weaver, Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages, Nat. Immunol. 6 (2005) 1123–1132.
[21] W. Sato, T. Aranami, T. Yamamura, Cutting edge: human Th17 cells are identified as bearing CCR2+CCR5- phenotype, J. Immunol. 178 (2007) 7525–7529.
[22] W. Ouyang, J.K. Kolls, Y. Zheng, The biological functions of T helper 17 cell effector cytokines in inflammation, Immunity 28 (2008) 454–467.
[23] E.V. Acosta-Rodriguez, G. Napolitani, A. Lanzavecchia, F. Sallusto, Interleukins 1beta and 6 but not transforming growth factor-beta are essential for the differentiation of interleukin 17-producing human T helper cells, Nat. Immunol. 8 (2007) 942–949.
[24] S.D.C. Gonçalves-de-Albuquerque, R. Pessoa-E-Silva, L.A.M. Trajano-Silva, T.C. de Goes, R.C.S. de Morais, C.N. da C Oliveira, V.M.B. de Lorena, M. de Paiva-Cavalcanti, The equivocal role of Th17 cells and neutrophils on immunopathogenesis of leishmaniasis, Front. Immunol. 8 (2017) 1437.
[25] S. Tiwananthagorn, K. Iwabuchi, M. Ato, T. Sakurai, H. Kato, K. Katakura, Involvement of $CD4^+$ $Foxp3^+$ regulatory T cells in persistence of Leishmania donovani in the liver of alymphoplastic aly/aly mice, PLoS Negl. Trop. Dis. 6 (2012) e1798.
[26] C. Terrazas, S. Varikuti, J. Kimble, E. Moretti, P.N. Boyaka, A.R. Satoskar, IL-17A promotes susceptibility during experimental visceral leishmaniasis caused by Leishmania donovani, FASEB J. 30 (2016) 1135–1143.
[27] H. Allos, B.S. Al Dulaijan, J. Choi, J. Azzi, Regulatory T cells for more targeted immunosuppressive therapies, Clin. Lab. Med. 39 (2019) 1–13.
[28] Y. Togashi, K. Shitara, H. Nishikawa, Regulatory T cells in cancer immunosuppression - implications for anticancer therapy, Nat. Rev. Clin. Oncol. 16 (6) (2019) 356–371.
[29] A.K. Rai, C.P. Thakur, A. Singh, T. Seth, S.K. Srivastava, P. Singh, D.K. Mitra, Regulatory T cells suppress T cell activation at the pathologic site of human visceral leishmaniasis, PLoS One 7 (2012) e31551.
[30] L. Leveque, F. Deknuydt, G. Bioley, L.J. Old, J. Matsuzaki, K. Odunsi, M. Ayyoub, D. Valmori, Interleukin 2-mediated conversion of ovarian cancer-associated CD4+ regulatory T cells into proinflammatory interleukin 17-producing helper T cells, J. Immunother. 32 (2009) 101–108.
[31] S. Karmakar, S.K. Bhaumik, J. Paul, T. De, TLR4 and NKT cell synergy in immunotherapy against visceral leishmaniasis, PLoS Pathog. 8 (2012) e1002646.
[32] L. Wu, L. Van Kaer, Natural killer T cells and autoimmune disease, Curr. Mol. Med. 9 (2009) 4–14.
[33] A. Bendelac, P.B. Savage, L. Teyton, The biology of NKT cells, Annu. Rev. Immunol. 25 (2007) 297–336.
[34] F.C. Robertson, J.A. Berzofsky, M. Terabe, NKT cell networks in the regulation of tumor immunity, Front. Immunol. 5 (2014) 543.
[35] S. Kumari, P. Shivam, S. Kumar, F. Jamal, M.K. Singh, S. Bimal, S. Narayan, K. Pandey, V.N.R. Das, P. Das, S.K. Singh, Leishmania donovani mediated higher expression of CCL4 induces differential accumulation of CD4(+)CD56(+)NKT and CD8(+)CD56(+)NKT cells at infection site, Cytokine 110 (2018) 306–315.
[36] A. Saha, G. Chakrabarti, S. Sen, S. Bandyopadhyay, Leishmania donovani parasites interact with gamma/delta+ human peripheral blood T cells and induce susceptibility to NK cell-mediated lysis, Scand. J. Immunol. 50 (1999) 588–595.
[37] P. Vantourout, A. Hayday, Six-of-the-best: unique contributions of γδ T cells to immunology, Nat. Rev. Immunol. 13 (2013) 88–100.
[38] M. Lawand, J. Déchanet-Merville, M.C. Dieu-Nosjean, Key features of gamma-delta T-cell subsets in human diseases and their immunotherapeutic implications, Front. Immunol. 8 (2017) 761.
[39] M. Bonneville, R.L. O'Brien, W.K. Born, Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity, Nat. Rev. Immunol. 10 (2010) 467–478.
[40] S. Raziuddin, A.W. Telmasani, M. el-Hag el-Awad, O. al-Amari, M. al-Janadi, Gamma delta T cells and the immune response in visceral leishmaniasis, Eur. J. Immunol. 22 (1992) 1143–1148.