



Effects of Leishmania Species on Immune Response against Malaria Parasite in Malaria Leishmania Coinfections

**Mosab Nouraldein Mohammed Hamad^{a†}, Sufian Khalid M. Noor^{b#},
Awadalla H. Kashif^{c‡}, Mohammed Medani Eltayeb^{d‡}, Bader Saud Alotaibi^{e‡},
Elizabeth Popova^{f‡}, Shafie Abdulkadir Hassan^{g¥}, Yassin Bakri Salih^{h€},
Yassin Saad Elhossin^{i¥}, Tarig Mohammed Elfaki^{j£}
and Mohammed Ahmed Ibrahim Ahmed^{a‡}**

^a Department of Microbiology, Faculty of Medicine, Nile Valley University, Atbara, Sudan.

^b Department of Medicine, Faculty of Medicine, Nile Valley University, Atbara, Sudan.

^c Faculty of Medical Laboratory Sciences, University of Khartoum, Khartoum, Sudan.

^d Faculty of Medical Laboratory Sciences, Alneelain University, Khartoum, Sudan.

^e Applied Medical Sciences College, Shaqra University, Saudi Arabia Kingdom.

^f College of Health and Allied Sciences, St. Joseph University In Tanzania, Dar Es Salaam, Tanzania.

^g Faculty of Medical Laboratory Sciences, Jamhuriya University of Science and Technology, Mogadishu, Somalia.

^h Reference Diagnostic Laboratory, Ministry of Health and Population, Atbara, River Nile State, Sudan.

ⁱ Department of Chemical Pathology, Faculty of Health Sciences, Elsheikh Abdallah Elbadri University, Berber, Sudan.

^j Department of Medical Laboratory Sciences, Academy of Health Science, Federal Ministry of Health, Khartoum, Sudan.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i54A33715

Editor(s):

(1) John Yahya I. Elshimali, UCLA School of Medicine & Charles R. Drew University of Medicine and Science, USA,

Reviewers:

(1) Nabil Soliman Dhayhi, King Fahad Central Hospital, Saudi Arabia.

(2) Harpreet Kaur, SGRDIMSAR, India.

Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here:

<https://www.sdiarticle5.com/review-history/78212>

Review Article

Received 02 October 2021

Accepted 07 December 2021

Published 08 December 2021

[†]PhD Student;

[#]Professor;

[‡]Assistant professor;

[¥]Lecturer;

[€]Director;

[£]Head;

*Corresponding author: E-mail: musab.noor13@gmail.com;

ABSTRACT

Both malaria and leishmania are most widespread protozoan parasitic diseases, certainly in tropical countries of the world. Malaria leishmania coinfection is common in leishmaniasis endemic areas which is mostly endemic to malaria too.

Researchers notice that in cases of malaria leishmania coinfection, leishmania species find to some extent the outcome of malaria infection, but also behavior of malaria parasite species play a significant role to figure the consequences of it. While *L. donovani* protect from severe malaria complications by suppression of major histocompatibility class II, so it diminish the clinical severity of malaria but not malaria parasite density due to dysfunction of major histocompatibility class I, which controlled by suppressed one. In another side *L. mexicana* tends to sequester in macrophages and lead to severe clinical outcomes when it coexisted with malaria parasite at same host. Experimental studies required to know more information about coinfection of different malaria and leishmania species to establish clinical research.

Leishmania infection excluded when studies aim to assess the immune response to only malaria parasite, experimental studies required involving different species of malaria and leishmania.

Keywords: *L. donovani*; *P. falciparum*; *L. Mexicana*; *P. yoelii*; malaria leishmania coinfections.

1. INTRODUCTION

Malaria infection has an extremely changeable clinical phenotype, varying from a mild febrile sickness to life-threatening severe anaemia, acidosis and end-organ failure, even between persons with slight or no acquired anti-malarial immunity. In part this clarified by heritable dissimilarities in vulnerability to malaria infection or parasite propagation recognized governed, among others, by red blood cell and haemoglobin polymorphisms.

current data have also started to propose that there variations in virulence amid parasite genotypes which clear as variable in vivo growth rates, with those that raise most rapidly being related with severe disease outcomes. But, it is also noticeable that quantitative and qualitative disparities in the nature of the anti-malarial immune response have deep influences on disease development and last outcome. A number of these discrepancies may turn out also to have a genetic basis, polymorphisms in a number of immune response genes have previously been hesitantly connected to vulnerability to malaria in humans and in rodent models, but it is also the case that environmental influences – linked to the occurrence and density of malaria infection; co-infection with viruses, bacteria and other parasites; dietary condition and so on – may also considerably alter the immune response and thus the clinical outcome of malaria infection [1].

2. CORRELATION BETWEEN LEISHMANIASIS AND MALARIA

Leishmaniasis and malaria are between the most significant six diseases on the World Health Organization (WHO). There are 700.000 to one million fresh cases of Leishmaniasis diagnosed annually [2]. While for malaria, 229 million people become infected and 409,000 mortalities in 2019 [3].

Cutaneous Leishmaniasis and Malaria (CL) are co-endemic in wide regions in tropical areas and co-infection may influence evolution of host-parasite interactions. Study done by Pinna Raquel A et al showed that ; In Malaria-Cutaneous Leishmaniasis Co-infection, reduced concentrations of IFN- γ , TNF, IL-6, and IL-10 noticed in the serum of co-infected groups, signifying modulation of Malaria immune response by *Leishmania* co-infections, noticed a strong thymic atrophy in Py single-infected and co-infected groups, which improved earlier in co-infected animals. The CD4 and CD8 T cell profiles in thymus, spleens and lymph nodes did not differ between Py single and co-infected groups, except for a diminish in CD4⁺CD8⁺ T cells which also augmented quicker in co-infected mice. Malaria ending distorted in proportion to the *Leishmania* specie concerned. Malaria infection reduced the harshness or postponed the onset of leishmanial lesions. These changes in Malaria and CL development seem intimately linked with alterations in the immune response as demonstrated by change in

serum cytokine concentrations and thymus/spleens T cell phenotypes dynamics throughout infection [4].

In regions where malaria is co-endemic with visceral leishmaniasis (VL), co-infections with both diseases are frequent [5].

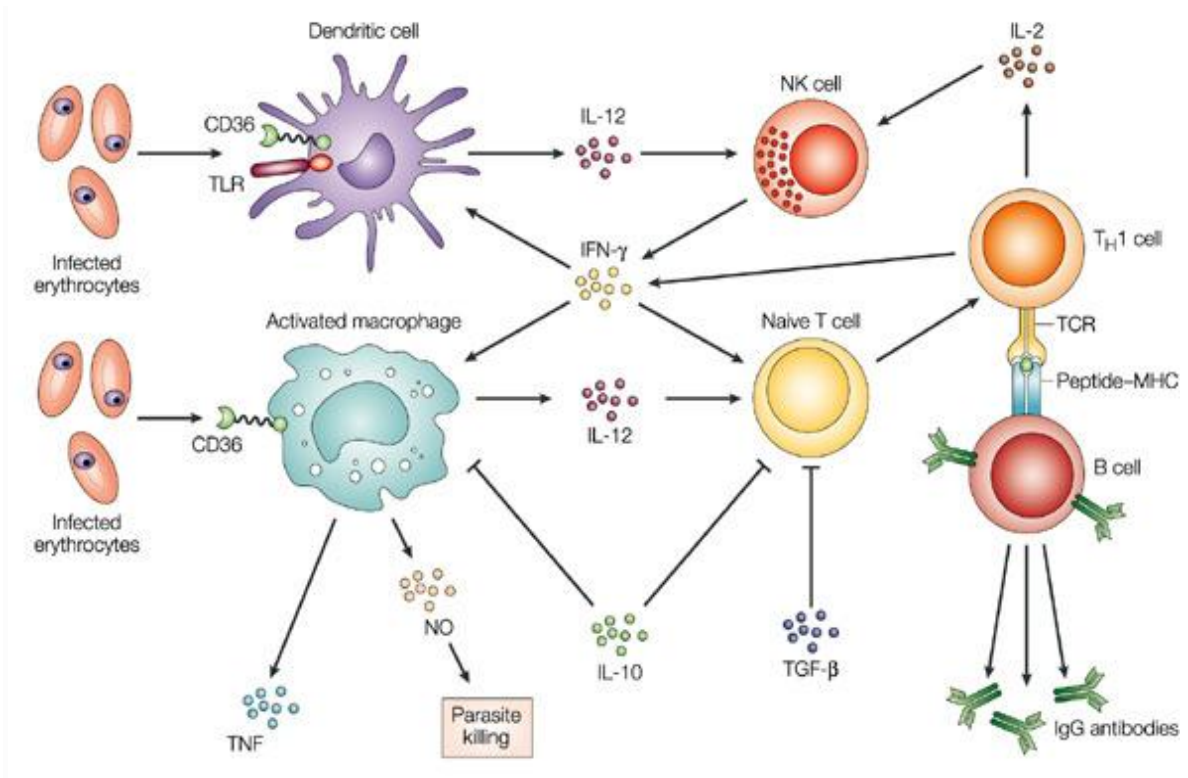


Fig. 1. Shows immunity to malaria parasite

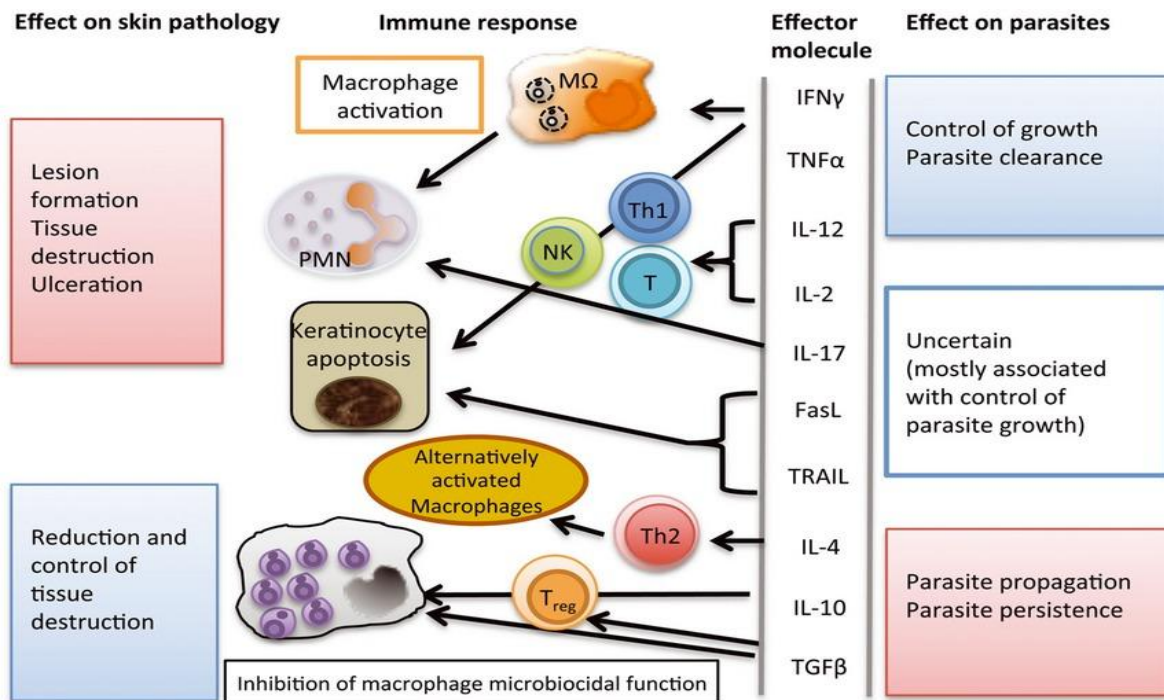


Fig. 2. Immunity to cutaneous leishmaniasis parasite

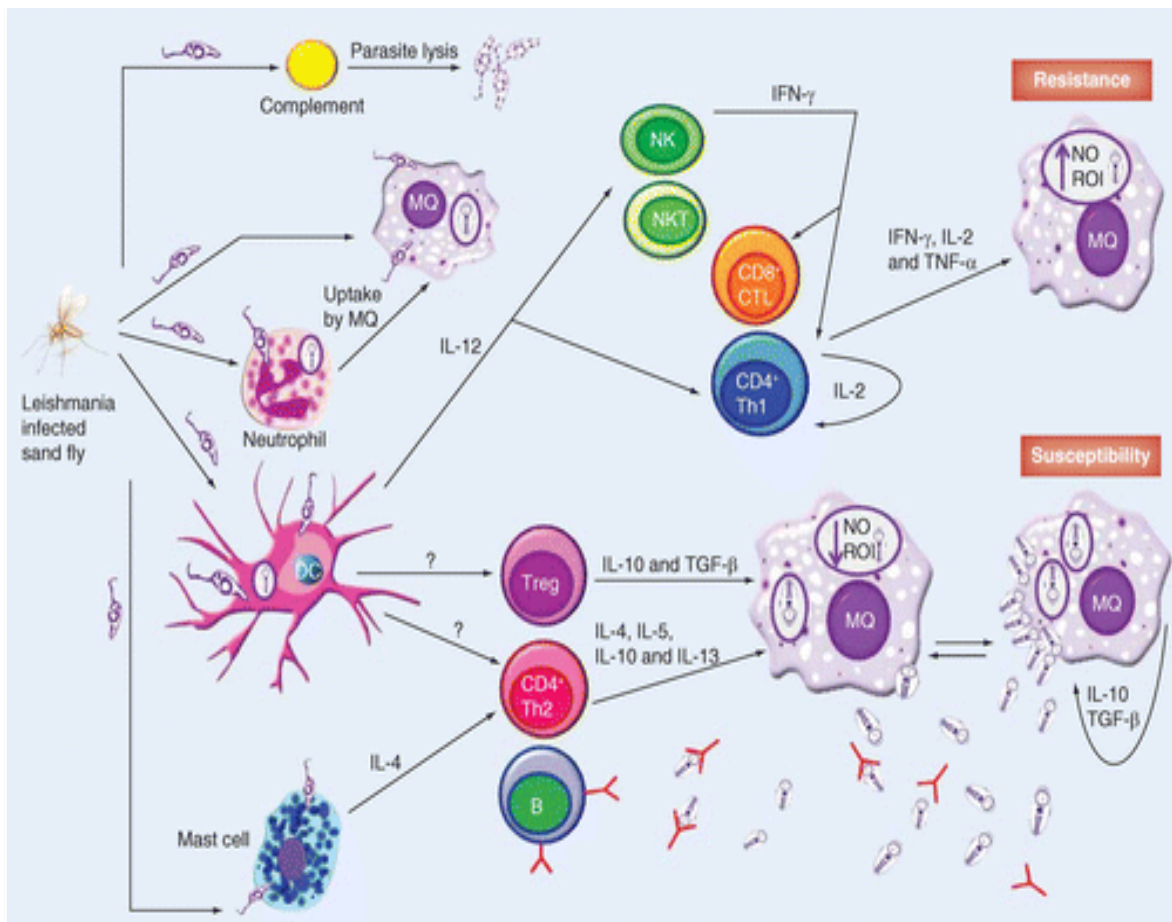


Fig. 3. Shows immunity to visceral leishmaniasis

3. EMPIRICAL REVIEW

Study done by van den Bogaart, E. Et al established that; The capacity of *L. donovani* and *P. falciparum* to jointly interrelate at the immunological point. Progressive polarization towards type-1 and pro-inflammatory cytokine models characterized the co-infected patients, whose response partially echoed the influence elicit by VL (IFN- γ , TNF) and malaria (IL-2, IL-13), and moderately resulted from a synergistic interface of the two diseases upon each other (IL-17A). Considerably decreased levels of *P. falciparum* parasitaemia were identified in the co-infected group as opposite to the malaria-only patients, suggestive of either a defensive or a non-detrimental effect of the co-infection against *P. falciparum* infection [6], signifying suppression of MCH class II expression by *L. donovani* [7]. Study done by Tania Gourley showed that; Class II transactivator (CIITA) recognized as a co-activator for MHC class II gene expression in antigen-presenting cells. Unexpectedly, when *CIITA*^{-/-} CD4 T cells were activated in existence

of IL-12, they formed not only IFN γ but also high levels of IL-4. The IL-4 generation is owing to the buildup of IL-4 gene transcripts in Th1 cells. This transcriptional regulation is noticed in T cells differentiating to the Th1 but not Th2 lineage, reliable with induction of expression of the *CIITA* gene in T cells by IFN γ . Thus, as well as its role in transactivation of genes concerned in antigen presentation, *CIITA* has a significant task through the T cell differentiation by negatively regulating the IL-4 gene transcription [8]. Study done by Elhusein AB showed that; increase of serum IL-4 in Sudanese children suffering from Plasmodium falciparum malaria linked with severity of malaria hyperparasitaemia and not with severity of the disease [9], IFN-gamma up-controls MHC class I expression and antigen processing and presentation on cells [10]. Owing to Class I MHC molecules span the membrane of about all cells (including erythrocytes) in an organism, while class II molecules limited to cells of the immune system named macrophages and lymphocytes [11]. Consistent with the above mentioned details we can suggest the

mechanism offered by *L. donovani* to give to induce protective action against severe falciparum malaria, also we suggest that tendency of *L. donovani* to sequester insides internal organs decrease sequestration of *P. falciparum* schizonts in capillaries of that vital internal organs.

Study done by Russell E. Coleman et al showed that; interfaces between *Leishmania mexicana* and *Plasmodium yoelii* tested in BALB/c mice. Percentage of erythrocytes infected with *P. yoelii* and width of footpad lesions reasoned by *L. mexicana* were the criterion accustomed to assess for disease severity. *L. mexicana* and *P. yoelii* infections were each considerably enhanced in dually infected mice when contrasted to mice infected with either parasite only. Death rates because of the normally nonlethal *P. yoelii* raised during concurrent infections [12], suggested owing to sequestration of leishmania amastigote antigens from presentation [7].

While *L. donovani* offers relative protection against falciparum malaria in human, *L. mexicana* increase death by benign *P. yoelii*, we suggest that residing behaviour of parasite affect the outcome of coinfection with other parasite.

4. CONCLUSION

Malaria and leishmaniasis co-infection is frequent, especially in leishmaniasis endemic area, and in case of research on evaluation of immune response against malaria parasite or studies aim to check the immunobiology of malaria among inhabitants of that areas, recommended to exclude leishmania parasite to get precise results, because of influence of leishmania species on host immunity response, which is variable depends on species. More experimental research required to know more details about the impact of leishmania species other than *L. donovani* and *L. mexicana*, in immunity toward plasmodium species and to enable researchers to conduct clinical studies on its basis.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Riley EM, Wahl S, Perkins DJ, Schofield L. Regulating immunity to malaria. *Parasite Immunology*. 2006;28:35-49. Available: <https://doi.org/10.1111/j.1365-3024.2006.00775.x>
2. Available: <https://www.who.int/news-room/fact-sheets/detail/leishmaniasis>
3. Available: <https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2020>
4. Pinna Raquel A, Silva-dos-Santos Danielle, Perce-da-Silva Daiana S, Oliveira-Ferreira Joseli, Villa-Verde Dea MS, De Luca Paula M, Banic Dalma M. Malaria-Cutaneous Leishmaniasis Co-infection: Influence on Disease Outcomes and Immune Response, *Journal=Frontiers in Microbiology*. 2016;7:982. Available: <https://www.frontiersin.org/article/10.3389/fmicb.2016.00982> DOI: 10.3389/fmicb.2016.00982
5. van den Bogaart E, Berkhout MM, Nour AB, et al. Concomitant malaria among visceral leishmaniasis in-patients from Gedarif and Sennar States, Sudan: a retrospective case-control study. *BMC Public Health*. 2013;13:332. Available: <https://doi.org/10.1186/1471-2458-13-332>
6. van den Bogaart E, Talha ABA, Straetemans M, et al. Cytokine profiles amongst Sudanese patients with visceral leishmaniasis and malaria co-infections. *BMC Immunol*. 2014;15:16. Available: <https://doi.org/10.1186/1471-2172-15-16>
7. Bogdan C, Rölinghoff M. The immune response to Leishmania: Mechanisms of parasite control and evasion. *Int J Parasitol*. 1998;28(1):121-34. DOI: 10.1016/s0020-7519(97)00169-0 PMID: 9504340.
8. Tania Gourley, Stacey Roys, Nicholas W Lukacs, Steven L Kunkel, Richard A Flavell, Cheong-Hee Chang. A Novel role for the major histocompatibility complex class II Transactivator CIITA in the Repression of IL-4 Production, *Immunity*. 1999;10(3):377-386. ISSN 1074-7613.

- Available:[https://doi.org/10.1016/S1074-7613\(00\)80037-0](https://doi.org/10.1016/S1074-7613(00)80037-0)
9. Elhussein AB, Huneif MA, Naeem A, Fadlseed OE, Babiker WG, Rahma NE, et al. Correlation of interleukin-4 levels with Plasmodium falciparum malaria parasitaemia in Sudanese children. Acta Clin Belg. 2015;70(6):414-8. DOI: 10.1179/2295333715Y.0000000042 Epub 2015 Jul 2. PMID: 26138543.
 10. Zhou F. Molecular mechanisms of IFN-gamma to up-regulate MHC class I antigen processing and presentation. Int Rev Immunol. 2009;28(3-4):239-60. DOI: 10.1080/08830180902978120 PMID: 19811323.
 11. Britannica, The Editors of Encyclopaedia. Major histocompatibility complex. Encyclopedia Britannica; 2018. Available:<https://www.britannica.com/science/major-histocompatibility-complex> Accessed 21 November 2021.
 12. Russell E Coleman, John D Edman, Lloyd H Semprevivo, *Leishmania mexicana*: Effect of concomitant malaria on cutaneous leishmaniasis. Development of lesions in a Leishmania-susceptible (BALB/c) strain of mouse, Experimental Parasitology. 1988;65(2):269-276. ISSN 0014-4894. Available:[https://doi.org/10.1016/0014-4894\(88\)90131-2](https://doi.org/10.1016/0014-4894(88)90131-2)

© 2021 Hamad et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

The peer review history for this paper can be accessed here:
<https://www.sdiarticle5.com/review-history/78212>