

Role of T Regulatory Cells on Symptomatic and Asymptomatic Individuals Infected with *Plasmodium falciparum* in the Peruvian Amazon

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Ms. Torres has worked in the Malaria Research Working Group at the IMTA vH since 2004 having several tasks in research projects on humoral immunology, organizing and training health workers in a Program of Control Malaria in border areas from the Andean Community. Afterwards, she was in charge of coordinating a Project that involved mainly field work. Currently, she is a PhD candidate at University Cayetano Heredia supported by the NHI-Fogarty Training Grant and has started to work on innate immune responses of asymptomatic and symptomatic individuals during malaria infection.

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Summary

Several studies have demonstrated that regulatory T cells (Tregs) play a critical role balancing protective immune responses and the immune mediated pathology during malaria infection. These cells suppress cellular immune responses through direct contact with immune effectors cells and by producing regulatory cytokines, including TGF- β and IL-10, on experimental models and human *P. falciparum* infection suggesting that Tregs may contribute to the onset of the infection. The objective this study was to find out the association between Tregs and outcome of the disease in individuals infected with *P. falciparum* living in a hypoendemic malaria region (Peruvian Amazon Region).

Treg cells were identified by flow cytometry as CD4⁺ T cells expressing Foxp3, CD25 and low levels of CD127 and are reported as a percentage of total CD4⁺ T cells in three groups: symptomatic (S), asymptomatic (AS) and control (C) individuals. PBMCs from each individual were cultured using the recombinant C-terminal repeat region GLURP (R2) antigen from *P. falciparum*, as stimuli. The concentration of IL-10, TNF- α and IFN- γ from the culture supernatant was measured each day during 6 days.

This study showed that symptomatic (S), asymptomatic (AS) and control (C) groups presented similar Tregs percentage, 3.89%, 3.47% and 3.51% respectively in peripheral blood. Furthermore, there is no a positive correlation between parasitemia and Tregs percentage (P-Value= 0.47).

TNF- α levels were the highest in PBMCs cultures in S group (>1440.24 pg/ml), IL-10 stayed low (~200 pg/ml) over the first four days of culture, having a peak during the 6th day (759.28 pg/ml). IFN- γ levels were low (347.6 pg/ml) in the same group.

About the AS group, TNF- α had a discreet high level at the 1st day (697.6 pg/ml) and going down (~130 pg/ml) during the next 5 days. IL-10 showed a peak of secretion the 1st day (363.55 pg/ml) staying state during the all days. It was also observed a very low secretion of IFN- γ against the stimuli during the first six days.

There was no difference among S, AS and C individuals on Tregs percentage and no correlation between parasitemia levels and Tregs percentage in the different groups. These results suggested that Tregs may are not implicated in the control and/or exacerbation of parasite multiplication, instead, it could imply a control by Th1 and Th2 response during malaria infection in this population.

References

- Riley E, Whal S, Perkins D, Schofield L. 2006. Regulating immunity to malaria. *Parasite Immunology* 28: 35–49.
- Hisaeda H, et. al. 2008. Malaria parasites require TLR9 signaling for immune evasion by activating regulatory T cells. *The Journal of Immunology* 180: 2496–2503.
- Walter M, et al., 2005. Upregulation of TGF- β , FOXP3, and CD4⁺CD25⁺ regulatory T cells correlates with more rapid parasite growth in human malaria infection. *Immunity* 23:287–296.
- Hisaeda H, Maekawa Y, Iwakawa D, Okada H, Himeno K, Kishijara K, Tsukumo S, Yasutomo K. 2004. Escape of malaria parasites from host immunity requires CD4⁺CD25⁺ regulatory T cells. *Nature Medicine* 10: 29–30.
- Hansen D, and Schofield L. 2010. Natural regulatory T cells in malaria: Host or parasite allies? *Plos Pathogen* 6 (4): e1000771.
- Scholzen A, Minigo G and Plebanski M.. 2010. Heroes or villains? T regulatory cells in malaria infection. *Trends in Pathology* 26 (1): 16–25.
- Couper K, Blount D, Wilson M, Hafalla J, Belkaid Y, Kamanaka M, Flavell R, de Souza J, Riley. 2008. IL-10 from CD4⁺CD25⁺Foxp3⁺CD127⁺ adaptive regulatory T cells modulates parasite clearance and pathology during malaria infection. *PloS Pathog* 4:e1000004.
- Minigo G. et al. 2009. Parasite/dependent expansion of TNF receptor II-positive regulatory T cells with enhanced suppressive activity in adults with severe malaria. *PLoS Pathogens* 5 (4): e1000402.