Journal of Research Administration
Society of Research Administrators International

MINI REVIEW;CHARACTERIZATION OF T CELL ACTIVATION AND REGULATION IN CHILDREN IN SOME PARASITIC DISEASES

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Abstract

In children with asymptomatic infections, levels of Tregs and activated T cells were comparable to those in healthy controls but significantly lower than those in symptomatic children. After iRBC stimulation, levels of Tregs remained lower for asymptomatic versus symptomatic children. In contrast, levels of activated T cells were higher for asymptomatic children. Parasitic infection in human alimentary tract causes a significant change in immune system through its continuous antigens secretion. The aim of this study was to estimate the change in natural regulatory T cell population in peripheral bloodof patients infected with different types of alimentary tract parasites. Regulatory T cells (CD4+CD25+Foxp3+) were detected in eighty patients infected with intestinal parasites and forty healthy volunteers using flow cytometry technique. Statistical analysis showed a significant increase in regulatory T cell percentage in infected patients compared to healthy group ($P< 0.001$). Patients infested with Giardia showed significantly higher CD4+CD25+Foxp3+ cell percentages than those infested with other parasites ($P< 0.001$). Also, mixed infestation showed significantly higher CD4+CD25+Foxp3+ cell percentages than single infestation.In conclusion, natural regulatory T cell frequencies(CD4+CD25+Foxp3+) increase significantly in patients with parasitic diseases compared to healthy controls.The higher levels were associated with mixed infection compared to single infection, and in older than younger patients.

Key words: Regulatory T cell, CD4+CD25+FOXp3+, parasitic diseases, Giardia.

Introduction

Regulatory T cells are known to play a key role to counter balance the protective immune response and immune mediated pathology. However, the role of naturally occurring regulatory cells CD4+CD25+Foxp3+ in malaria infection during the disease pathogenesis is

controversial. Beside this, ICOS molecule has been shown to be involved in the development and function of regulatory T cell enhance IL-10 production. Therefore, possible involvement of the ICOS dependent regulatory CD4+ICOS+Foxp3+ T cells in resistance/susceptibility during malaria parasite is explored in this stud. There is a continual exposure to large number of food-borne pathogens within alimentary tract, which represent a major challenge to the immune system to differentiate between harmful and innocuous antigens; which can be achieved by suppressor Tcells and regulatory T (Treg) cells.[1,2,3] Regulatory T cells refer tosubset of immune cells which suppress immune reactivity via suppressive cytokines and signal.[4]Treg cells can be divided into two types: natural Treg (nTreg) and inducible Treg (iTreg) cells.[5]Natural regulatory T cells develop as a result of contact with self-antigens in the thymus and go to periphery to enforce self tolerance before pathogen exposure. Natural regulatory Tcells include CD4, CD25+, and FOXp3+.[6]Inducible regulatory T cells develop in the periphery from conventional CD4+ Tcells after exposure to signals as regulatory cytokines, immunosuppressive drugs, or antigen presenting cells conditioned by microbial products.[7]NaturalTreg cells participate in immune response to many, if not, all infectious agents. Usually they serve to restrain exuberant immune reactivity which in many chronic infections benefits the host by limiting tissue damage.[8]However, the nTreg response may handcap the efficiency of protective immunity.[9,10,11]Parasites are still, even in the 21st Century, remarkably prevalent across the world.[12]Parasites have evolved in many different ways to avoid detection by their host and to manipulate their host's immune system in order to gain an advantage and survive.[13]The induction and/or manipulation of Tregs by parasites may be one such method to aid their survival.[14]

The aim of this study was to estimate the change in natural regulatory T cell population in patients infected with different types of alimentary tract parasites.

Discussion

Parasitic challenges to the host are met by a wealth of humoral and cellular responses which may ends by tissue damage. So, to avoid this tissue damage, induction of T-cell hyporesponsiveness and bystander suppression is mandatory.[20] Immune modulation by parasitic infection is believed to be mediated by natural and inducible Treg cells. Treg cells mediate their actions via induction of cell cycle arrest, apoptosis and inhibition of pro-inflammatory cytokines.[21]This may be beneficial to host in chronic infections as preventing immune mediated pathology. Too early functioning of Tregs may ends in uncontrolled parasite growth and severe disease.[22]

Also, parasitic infestation status is risk factor for higher CD4+CD25+ Tregs induced by parasites cripples host immunity and suppress antiparasitic effector cells.[14] The expanded profile of Tregs in parasitic infections was reported by Maizels and Smith (2011) [23] which may be attributed to activation of pre-existing (natural or thymic) Tregs or the de novo induction of Tregs from naive peripheral Th0 precursors. Parasitic nematode infections have been shown to induce regulatory cell expansion in both mice and humans.[24]

Also Montes and his colleagues (2009)[25] reported increased proportions of CD4+CD25+Foxp3+ Tregs in patients with Strongyloidesstercoralis and human T lymphocyte virus -1 coinfection in comparison to normal controls which leads to decreased antigen driven production of IL-5 and lower eosinophil counts. Those results suggest a role for these cells in blunting antigen-driven protective responses.E.histolytica triggers development of Treg populations during chronic phases of disease that repress the development of responder T cells.[21]

In the some study, patient infested with Giardia show significantly higher CD4+CD25+Foxp+% than those infested with other parasites ($p<0.001$). The relatively higher CD4+CD25+Foxp+% in Giardia lamblia in relation to other parasites can be attributed to the fact that G. lamblia causes little or no inflammation in humans.[26]Giardia actively down regulates the inflammatory response[27] which may be mediated via T regulatory cells. As evidenced by IL-8 was not induced, in contrast to what is typically seen in intestinal infections that cause inflammation. Its low level during Giardia infection partly explains the low levels of inflammation. Also, by analyzing the gene expression of several different cytokines in human intestinal epithelial cell lines 5 h after G. lamblia infection in vitro did not reveal any cytokines that were induced at a high level.[28,29]

On the other hand, patient infested with Schistosomiasis show significantly lower CD4+CD25+Foxp+% than those infested with other parasites ($p<0.001$) (Figure 1). This lower CD4+CD25+Foxp+% observed in schistosomal infection in comparable to other parasites can be attributed to earlier stage of infection or previous treatment. Watanabe et al. (2007)[30] stated that not all Schistosomamansoni-infected individuals develop high percentages of circulating Tregs. The effective treatment decreases the proportion of Tregs and their phenotypes, possibly because of the removal of constant exposure to antigens from intravascular, egg-producing adult worms. Also, Singh and his colleagues2005[31] found that schistosomal granulomatous livers at 8 and 16 weeks after infection showed 10 and 30fold increases in Foxp3 expression compared with normal liver. Also, the percentage of Treg cells in granuloma rose from 12% at 8 weeks to 88% at 16 weeks after infection.

Also, Mixed infestation showed significantly higher CD4+CD25+Foxp+% than single infestation ($p=0.028$) and heavy infestation showed significantly higher CD4+CD25+Foxp+% than mild infestation ($p=0.003$).This also reported by Minigo et al., 2009[32]; Todryk et al., 2008[33] who stated that higher Tregs numbers are associated with increased parasite load and development of human infection caused by P. falciparum.

In **conclusion**, natural regulatory cells CD4+CD25+Foxp+% increase significantly in late parasitic diseases compared to healthy control, also they significantly increase with mixed infection compared with single infection, and significantly increase with age.

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