IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Biological Sciences

2011; 7(9):1216-1219

Editorial

Innate and Cellular Immunology in Parasitic Diseases

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Published: 2011.11.09

The infections caused by parasitic pathogens both, protozoan and helminths, are still a major global health problem affecting a quarter or more of the world population. These infections can become chronic and result in significant morbidity and mortality. Many of them may compromise quality of life and life expectancy. While there are not still vaccines available for parasitic diseases, over the last decade has been a period of major advances in our understanding of the development of both innate and adaptive immune response and how it is related to parasitic diseases. Thus, a more complex picture of the role of innate immunity as well as cellular immune responses to control or favor parasitic diseases has begun to emerge. These responses are now known to act both as rapid initiators during a particular infection as well as regulators of ongoing responses against parasitic infections. This in turn has led to the development and refinement of new strategies to combat these diseases.

The study of parasites is unconceivable without the participation of the immune system. However, every year it is more difficult to find audience in immunology meetings for researchers working with parasitic infections; conversely, it is also difficult find place for the immunologists during parasitology meetings. That is one of the reasons for this special issue, put together leading researchers in the field of immunoparasitology, an area that needs to be fueled to accelerate the development of new vaccines as well as new drugs or even for development of immunotherapy in parasitic diseases. In this current special issue, we provide updates on several parasitic diseases through review papers as well as several original research papers. This issue can be divided into four sections: update on malaria innate immunity and its effect on severe anemia, recognition and pathogenecity of *Trypanosoma cruzi* infections and new strategies for control it, costimulation and new factors associated with resistance to leishmaniasis and amebiasis, and finally, antigens, innate immunity and immune-modulation in helminth infections.

Malaria is by far the most deadly parasitic infection in the world, and Africa is the continent more affected for this parasitic disease. Here the group of Mary M. Stevenson [1] addresses the recent advances in understanding the roles of Dendritic Cells (DCs) and natural regulatory T cells (Tregs) in regulating adaptive immunity to blood-stage malaria. They point out the importance of DCs from infected mice to increase the frequency of $DX5^{+}IFN\text{-}\gamma^{+}$(NK cells), but interestingly they also show how DCs are able of produce IFN-γ. This review link lethal malaria infections in mice with functional impairment of DC and indicate that soluble mediators, especially IL-12, are required to induce optimal IFN-γ secretion by NK cells during blood-stage malaria. They also conclude that DC-NK cell interaction is dependent on cell-cell contact. Regarding the role of Tregs in malaria the authors detail studies in individuals with malaria and

in mice infected with various rodent *Plasmodium* species which revealed an important expansion of $CD4^+CD25^+Foxp3^+$ T cells during this infection, seems that expansion of Tregs correlates with high parasitemia levels and low pro-inflammatory responses, findings that suggest a possible link between natural regulatory T cells and the clinical outcome of malaria. Following with malaria, the group of Douglas J. Perkins [2] reviewed the state of the art on Severe Malarial Anemia (SMA), an area where they have been working in the last 10 years with successful results in controlling malaria spread in Kenya. They focus their work on the dysregulation in the innate immune response as an important cause of impaired erythroid responses in children with SMA, thus depending on the magnitude and timing of inflammatory mediator release, the immune response to malaria can result in either successful control of the parasitemia or alternatively, an inappropriate balance in the inflammatory milieu that can induce damage to the host, including suppression of the erythropoietic response. We have also in this section an original contribution by Legorreta et al [3] where demonstrate that nitric oxide (NO) serum levels are not associated with elimination of blood stages of *Plasmodium chabaudi.* To finalize this first group of papers focus on malaria, Ruiz-Rosado and Rodriguez-Sosa [4] offer us a very complete review of the role of Macrophage Migration Inhibitory Factor (MIF) on protozoan infections, where they give a detailed description of a series of articles with contrasting results on the role of MIF during malaria, is MIF deleterious or have a beneficial role during malaria infection? That is the question.

Another very important parasitic disease, affecting now mainly to the Americas, is *Trypanosoma cruzi* infection or Chagas' disease. This disease is endemic in South America, but given the global warming now some cases are detected in USA. Here we present a series of works on *T. cruzi* infection, since the receptor these parasites use to survive in host' cells, until biological control by affecting their vectors, passing by innate immunity and vaccine development. Thus, in an original contribution Fabio Cerbán group [5] describes how *T. cruzi* can manipulate the up-regulation of an innate receptor such as mannose receptor (MR), increasing their expression in parasitized macrophages, moreover, they show how this interaction with MR increase also the arginase activity of such macrophages and the survival of *T. cruzi* in these cells. Interestingly, the blockade between MR and the parasite, by competing sugars, increase the parasiticidal activity of macrophages. In another original contribution on innate immunity in *T. cruzi*, Terrazas et al [6], demonstrate how important is the early secretion of MIF by DCs, they show how MIF-/- mice succumbed faster to *T. cruzi* infection and seems that such effect is because MIF-/- DCs cannot mature and secrete pro-inflammatory cytokines on early times following infection. Another interesting paper is by Espinoza et al [7] which describes the infection of the intestinal tract by Mexican strains of *T. cruzi* and the mucosal immune response they elicited. Next, we have a paper on vaccine development for *T. cruzi* infection by Arce-Fonseca et al [8], where they developed a DNA vaccine with promising results, a clear relationship between high levels of IFN-γ and a protection lasting until one year was observed. Finally, the group of Ravi Durvasula [9] presents a very interesting review regarding biological control of vectors transmitting *T. cruzi* infection, and proposes to avoid chemical pesticides and focus on paratransgenic strategy for transmission control. This strategy involves induction of symbiotic or commensal microbes transformed to express gene products that interfere with pathogen transmission into the transmission vector. They resume their successful experience clearing until 65% of *T. cruzi* in vectors with genetically modified symbiont, whereas in the resting 35% of vectors had substantial reduction on the viability of *T. cruzi*, thus, this strategy is a promising control of *T. cruzi* spread.

Our third block of papers includes *Leishmania* and *Entamoeba* infections, as well as a review on Tregs and protozoan infections. Elizondo et al [10] show a new role for the aryl hydrocarbon receptor (AhR) in resolution of *L. major* infection. AhR has been largely associated with toxicity of environmental pollutants; however, in the last few years a new role for AhR was detected on the immune system. Here this group found that the absence of AhR decrease up to 30% the Treg cell population during *L. major* infection whereas increasing TNF-α levels, this results in a better resolution of the infection. A review by Abhay R. Satoskar and his collegues gives us an overview of the role of important co-stimulatory pathways in Leishmaniasis [11]. Again, the review on MIF and protozoan infections (4) discuss how MIF is important on *L. major* infection. Regarding amebiasis there is an original research by Meneses-Ruiz et al [12] who developed an experimental vaccine based on glycans which is delivered using baculovirus expression on the mucosa of hamsters, they induced protective cellular and humoral immune responses following oral immunization close to 70% of protection. To finalize this section, the group of Edda Sciutto [13] wrote a very complete up-date on the role of Tregs in parasitic diseases, mainly focused on protozoan infections.

The last block of papers is focused on helminth infections, mainly cysticercosis which is an important public health problem in the Americas, Africa, India, China and Taiwan. First we have a contribution of Esquivel-Velazquez et al [14] on antigen diversity found on *Taenia solium* cysticerci which come from the same host. This unexpected large diversity among the proteins and antigens contained in the vesicular fluid of cysticerci may account significantly in the source of diversity in *T. solium´s* infectiveness and pathogenicity. Also studying antigens of cestodes, but now from *Taenia crassiceps;* the teams of Lorena Gómez-García and Luis I. Terrazas [15] report for the first time that glycoproteins of high molecular weight released by cysticerci of *T. crassiceps* induce a "tolerogenic" phenotype in human DCs. These "tolerogenic" DCs are immature and respond poorly to Toll-like receptor (TLRs) agonists. Indeed, a low pro-inflammatory profile is consistently observed in human DCs exposed to these glycoproteins. This could be a new mechanism of immune-modulation on cysticercosis. Following with innate immunity and cysticercosis, Reyes et al [16] show that mice lacking TLR2, otherwise resistant to *T. crassiceps*, become highly susceptible to this infection despite generating a stronger Th2-type biased response compared with their wild type (C57BL/6) counterpart mice. Thus, early antigen recognition by TLR2 in experimental cysticercosis appears to trigger a protective response; this is the first report where resistance to a helminth infection is associated with TLRs.

It is increasingly becoming recognized that helminths modulate the immune response of their hosts, and according to the hygiene hypothesis this could be beneficial in some inflammatory or autoimmune diseases. Here, López-Navarrete et al [17] make an interesting observation that a helminth infection significantly attenuates the inflammatory response in experimental cirrhosis but at the same time exacerbates liver fibrosis. This important finding must be considered when using a helminth to "treat" autoimmune diseases. In taeniosis the group of Morales-Montor [18] that show an important role for progesterone inducing innate mucosal protection against *T. solium* infection. These data show that progesterone induces higher expression of IFN-γ in the duodenum of hamsters. This paper opens new possibilities to treat gastrointestinal helminth infections using the immunoendocrinological network. Finally, a comprehensive review by Becerra-Díaz et al [19] provides insights into the role of the family of Signal Transducers and Activators of Transcription (STATs) factors in helminth infections. STATs have a critical role on modulating the immune response, and surprisingly, besides the expected role for STAT6 in these infections, STAT1 and STAT4 play an important role in the resolution of different helminth diseases.

We believe that this collection of articles will serve as a valuable update for both, those who are actively involved in the immunoparasitology field, and those who are initializing their research in this challenge area. We hope these papers together trigger a productive discussion about the immunology, pathology and therapy of parasitic diseases.

Acknowledgements

The authors sincerely thanks to Consejo Mexiquense de Ciencia y Tecnología and Instituto de Ciencia y Tecnología del Distrito Federal for their support in the organization of the IV Mexican Immunoparasitology Meeting hold in November 2010, which was the base of this special issue.

Conflict of Interests

The authors have declared that no conflict of interest exists.

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