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INTRODUCTION

The gamut of host immune responses and immunopathology in parasitic diseases caused by protozoa and helminths: human perspective and experimental models

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Uni- and multicellular organisms have successfully enjoyed parasitic existence in humans from times immemorial when neither the parasites nor their hosts looked like they do today. Benefitting from millions of years of co-evolution, the most refined parasites, such as the helminths, have learned to evade the host's immune response and to cause only the most indispensable harm in order to assure their host's survival, and ultimately their own. On the other hand, today's pathogenic protozoa, conceivably of shorter co-evolution with humans, in general, still cause more severe morbidity, leading to more pronounced symptomatology, organ pathology, and, in some cases, death.

The following review articles examine mechanisms involved in the immune response and resulting immunopathology caused by selected protozoa and helminths residing in various intra- and extracellular niches of the parasitized host. Some of the most pervasive parasites covered in this series are protozoans belonging to the phyla sarcomastigophora, such as *Leishmania*, *Trypanosoma*, and *Entamoeba*, and apicomplexa, such as *Plasmodium* and *Toxoplasma*; also included are helminths of the phyla nematoda (roundworms), such as geohelminths and filariae, as well as platyhelminthes (flat worms), such as the schistosomes. The importance of these review articles resides in the fact that behind each of these pathogens are major human diseases that to this date still inflict enormous personal suffering and communal hardship in vast areas of the developing world.

As is the case with all pathogens, host immune responses to protozoa and helminths are innate and adaptive as well as cellular and humoral, involving an increasing array of innate immune cells, effector and regulatory lymphocyte subsets, antibodies, cytokines and other mediators, and accessory effector mechanisms such as those afforded by epithelial and muscle cell functions. The scenario is one of a struggle in which either the parasite or the host can gain the upper hand; however, more often than not, there is an impasse that results in long-lasting or permanent disease. Inevitably, the immune response carries with it the risk of associated immunopathology, which is largely responsible for morbidity. In general terms, strong proinflammatory Th1, cytotoxic, and possibly Th17 responses are instrumental in the elimination of protozoa, while Th2 responses are for the most part ineffective. By comparison, canonical Th2 responses in conjunction with alternatively activated macrophages are vital for the control of helminths by mediating expulsion and/or dampening excessive immunopathology; ironically, these anti-inflammatory effects are also beneficial in modulating inflammation induced by third-party antigens such as those associated with allergic and autoimmune diseases. Th1 and Th17 responses, on the other hand, fail to achieve helminth expulsion and can per se induce unwanted inflammation and pathology exacerbation, as is the case in infection with filariae, schistosomes, and *Trichuris*. For obvious reasons, any impairment of immune function, notably in the case of human immunodeficiency virus infection, is detrimental to parasite clearance, and a good nutritional status is essential for optimal immune function.

The reviews in this series encompass selected examples of parasites of great medical importance and illustrate both the clinical and epidemiological aspects of the resulting diseases while also analyzing pertinent experimental models that have contributed to elucidating underlying pathogenic mechanisms. The articles have been written by expert investigators with extensive personal experience in the field; unfortunately, space constraints have precluded coverage

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of additional important parasites or additional research approaches on the listed ones.

Among the papers on protozoa, Soong et al. describe and contrast the various forms of human and experimental disease resulting from infection with different *Leishmania* species; they also discuss the innate and adaptive immune mechanisms involved in protection vs. immunopathology. In their article on Chagas disease, caused by *Trypanosoma cruzi*, Machado et al. examine host innate immune mechanisms emphasizing the dual role of reactive oxygen species in controlling the parasite but also causing long-term myocardial tissue damage. Verkerke et al. place particular emphasis on the role of infant malnutrition in the development of symptomatic amebiasis associated with diminished Th1 and leptin responses together with impaired intestinal epithelial cell and inflammatory leukocyte function. Sinnis and Zavala focus on the important but less explored protective CD8 responses originating in the skin, the port of entry for plasmodia that cause malaria, conceivably the most fearsome of all parasitic diseases. Lastly, Dupont et al. analyze in detail the contribution and importance of various cellular and sub-cellular mechanisms affording protection against infection with *Toxoplasma*, which under normal circumstances is controlled by the immune system.

On the topic of helminths, Klementowicz et al. as well as Reynolds et al. examine and discuss the versatile mechanisms involved in the outcome of host immune responses to *Trichuris muris* and *Heligmosomoides polygyrus*, respectively, which are representative of multiple species of parasitic gastrointestinal helminths that cause widespread disease among vertebrates and in vast segments of the human population. Babu and Nutman explain how parasite-induced Th2, T regulatory cell, and alternatively activated macrophage-promoting strategies by filarial worms avert the development of chronic lymphatic immunopathology and the ominous consequences of lymphatic obstruction. Fairfax et al. and Larkin et al. present two complementary aspects of the immune response to schistosomes, focusing on the immunobiology of Th2 and Th17 cell responses, respectively: Th17 cell responses are tied to the development of severe parasite egg-induced granulomatous inflammation while Th2 cells are basically host protective yet capable of mediating pathology largely by enhancing liver fibrosis during chronic disease. Lastly, Wiria et al. provide a comprehensive analysis of helminthic infections in humans and discuss their beneficial or detrimental impact on concomitant infections, as well as on allergic, autoimmune, and cardiovascular diseases.

We present this issue of Seminars in Immunopathology on Immunoparasitology with the expectation that the research described in each of the chapters will bring us a step closer to better understanding diseases caused by parasites, which no doubt touch more human lives than any other diseases in the world.