EDITORIAL

Parasites and tissue micro-environment

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Human parasitic diseases cause hundreds of thousands of deaths per year, in addition to the significant morbidity and socioeconomic suffering experienced by millions of people worldwide. The development of vaccines and new treatments has been impeded by a lack of basic understanding of the infection and survival mechanisms utilised by parasites. Most parasites have multifaceted life cycles with numerous morphological stages that infect discrete host cell types and tissues. This enormous variety of life cycles and tissue niches result in even greater diversity in the host immune response, targeting not only the different types of parasitic organisms but also the different life cycle stages of the same species within the mammalian host. Parasitic organisms have evolved together with the mammalian immune system over many millennia and hence have become remarkably efficient modulators of host immunity in order to promote their own survival. Indeed, the multiplicity of developmental stages, combined with distinct tissue tropisms, and the ensuing elaborate mechanisms of immune evasion, vastly compound the complexity of host–parasite interactions.

In this special issue of Parasite Immunology, we have brought together a series of reviews on our current knowledge of the intimate interactions between the parasite and the tissue microenvironment. Focusing on several parasitic infections, these reviews highlight the complex interactions between parasites and the host immune response in tissues, both in terms of achieving protection against infection as well as protecting tissue integrity.

Despite recent successes in global control programmes, malaria continues to be a devastating disease worldwide, with hundreds of millions of cases and hundreds of thousands of deaths per year. The life cycle of *Plasmodium* within its mammalian host is extraordinarily complex, with both extracellular and intracellular life stages moving between different tissues. Pre-erythrocytic stage infection occurs though the inoculation of sporozoites into the skin by a mosquito vector; the sporozoites migrate to the liver and infect hepatocytes, where they multiply rapidly into exo-erythrocytic forms. Parasites egress from hepatocytes as merozoites, which infect red blood cells (RBCs) and initiate blood-stage infection. The merozoites then multiply inside RBCs, which rupture to release new merozoites that infect further RBCs in cyclic intervals. All the symptoms of malaria such as fever, anaemia and splenomegaly occur during this stage, as the parasites repeatedly infect RBCs. Two reviews on immune responses to malaria parasites are included in this special issue. **Abuga et al** [1] emphasize early work in animal models with radiation-attenuated sporozoites. which has become the basis of current whole sporozoite strategies (expanding to genetically attenuated parasites, and chemoprophylaxis and sporozoites) and sub-unit vaccines (including RTS,S – the most advanced malaria vaccine candidate to date). The authors summarise current knowledge in rodent models and humans of both innate and adaptive immune responses induced against both the sporozoite and exo-erythrocytic forms, with particular reference to the relevant tissue niches of the skin and the liver. Following RTS,S vaccination, the quality of antibodies and their interactions with cellular mechanisms, correlate better with protection than just titres. It is conceivable that these antibodies act as early as when the parasites are in the skin. In the liver, patrolling resident memory CD8+ T cells offer first line responses and current research are focused in harnessing these cells for improved vaccines. **Yui et al** [2] focus on the malaria erythrocytic stage and discuss how the splenic microvasculature and peripheral blood vessels offer the interface of host-parasite interaction, and how these structures are severely altered during infection. The parasite itself contributes to modulating the host environment by expressing proteins – such as *P. falciparum* erythrocyte membrane protein 1 and rifins – that engage with host receptors, allowing for host evasion, or directly inhibition host responses. Importantly, exploiting the importance of the fine balance between pro-inflammatory and regulatory responses in protecting the host from severe disease will be crucial in developing novel strategies against malaria blood stage infections.

Given the complexity of host-parasite interactions at the tissue level, much basic research have been hampered by the lack of suitable technology and appropriate *in vitro* systems. In

this issue, **Hares et al** [3] consider recent developments in the use of 3D stem cell-derived enteroid models to investigate the interaction between enteric apicomplexan parasites and the intestinal epithelium. Enteroids are 3D tissue culture models generated from small intestinal stem cells cultured in a matrigel and growth factor medium. The resulting 3D structures contain intestinal crypts and villus domains enclosing a central lumen. Importantly, the enteroids contain a representative mixture of the differentiated cell types that make up the intestinal epithelium, including goblet cells, enteroendocrine cells, Paneth cells, tuft cells and enterocytes. The use of such organoid cultures have now resolved the mystery of species specificity of the sexual reproduction of *Toxoplasma gondii*, which only occurs in the feline small intestinal epithelium, and has now been demonstrated to be dependent on linoleic acid, which is present at high levels in the feline intestine. Moreover, the use of enteroids in *Cryptosporidium* research has now enabled researchers to complete the life cycle *in vitro* and gain much-needed new biological insight into the epithelial autonomous host defence system. Clearly, these new tissue model technologies will provide exciting new opportunities for the study of interactions between not only the intestinal epithelium and various pathogens, but also the importance of immune cells in these interactions, as well as the role of the commensal flora. Other recent technological advances include the development of real-time bioluminescence and fluorescence imaging methods, allowing for real-time tracking of parasites in live tissues. **Perez-Masliah et al** [4] discuss the additional benefits of using such technology in research on *Trypanosoma cruzi* (Chagas disease) host-pathogen interactions. The authors underscore the findings from *in vivo* imaging studies that the gastro-intestinal tract appears to be a universal site of continual parasite persistence in the chronically-infected host, where blood parasitemia is typically sub-patent; analysis at single cell resolution level also reveals that smooth muscle cells are the most frequent targets of the parasite in the colon. It is evident that the possibility of integrating these imaging methods with analyses of concomitant immune responses hold considerable promise for advancing our understanding of *T. cruzi*- host interactions.

Helminth infections are amongst the most common infections of humans and are notoriously chronic in nature, with some species of worms surviving within their host for many years and in some cases, even decades. In order to facilitate such long-term survival within an immunocompetent host, these organisms have developed sophisticated survival strategies, including the ability to modulate and manipulate our immune system. In this issue, **Mourão Dias Magalhães. et al** [5] review the immune response generated against intestinal hookworm infection, with a particular focus on the immunomodulatory capacity of such organisms, as well as the prospect of a vaccine. Multiple studies aimed at understanding the immunomodulatory mechanisms of helminths have provided support for the ability of hookworms to modulate inflammation, thus allowing the exploration of the use of live parasitic worms, worm secretions, and worm-derived synthetic molecules to treat various allergic, inflammatory, autoimmune and metabolic diseases. Finally, not only does different genera and phyla of parasites evoke distinct types of localised immune responses, but diverse species of the same genus can also generate substantial disparities in the host response even within similar tissue niche. In this issue, **Llanwarne et al** [6] highlight some of the key differences in the host response to the two major species that cause intestinal schistosomiasis, *Schistosoma japonicum* and *S. mansoni*. The majority of immunoepidemiological and experimental work on intestinal schistosomiasis have historically been conducted using *S. mansoni*, with little attention given to *S. japonicum*, despite the latter being widely regarded as the more pathogenic species. In schistosomiasis, the key pathogenic agent is the egg that gets trapped in tissues, eliciting strong immune activation and granulomatous responses. Not only is the egg production rate substantially higher in *S. japonicum* than in *S. mansoni*, resulting in faster development of pathology, but the composition of the granulomatous response is also remarkably dissimilar, with a more prominent infiltration of neutrophils in the *S. japonicum* granuloma. A closer inspection of the available data show that multiple understated differences in both cytokine and chemokine responses already at the initiation phase of the response subsequently impact downstream effectors, such as cellular recruitment. These

contrasting responses contribute to the different levels of pathology seen between *S. japonicum* and *S. mansoni* infections.

Taken together, these reviews emphasize the complexity, intricacy and oftentimes confusing interactions of parasitic pathogens with the host tissue. Parasites have evolved elegant strategies to survive and replicate within their hosts and we still lack clear understanding of the processes involved in the molecular and immunological crosstalk between parasites and their tissue environment. However, the recent development of new technologies and improvement in model systems ought to greatly enhance our fundamental understanding of these mechanisms in the not very distant future.

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