Macrophages and parasites: Mortal enemies or partners in crime?

The mammalian immune system has evolved to protect our body from a wide variety of dangers. Fending off pathogens is a major function, and under most circumstances, it does so efficiently and effectively. However, parasitic pathogens have developed effective means to dampen and abuse the immune system in order to establish themselves within a host. Macrophages, the all-rounder cell of the immune system, are involved in virtually any biological process: immune defence, embryonic development, wound healing and maintenance of tissue integrity as well as whole body metabolism and thermo-regulation. However, macrophages are also drivers of severe pathology (eg cancer, atherosclerosis, fibrosis) and provide "safe havens" for several pathogens (eg Mycobacterium tuberculosis; Salmonella enterica) rendering the host susceptible to infection and disease. Thus, appropriate responses of macrophages are a key determinant of successful immune resistance, and the interaction of macrophages with parasitic pathogens is no exception. However, the question is: what is an "appropriate response?" Scientists have uncovered a myriad of ways in which macrophages contribute to resistance/susceptibility to parasitic infections. Nonetheless, we remain remarkably ignorant as to why some patients are resistant to infection, others get infected but stay asymptomatic and some develop active disease. In this special issue of Parasite Immunology, a series of reviews have collected our current knowledge on the role of macrophages in several parasitic infections. They highlight the intricate mechanisms, such as phagolysosomal degradation of ingested Toxoplasma. However, Toxoplasma avoids this grisly demise through inhibiting the fusion of the parasite vacuole with the lysosome. In turn, activation by interferon-γ can overcome this inhibition, but this only works in previously uninfected macrophages, as Toxoplasma alters STAT-1 signalling. Lastly, Toxoplasma infection or rather the immune response triggered by Toxoplasma gondii leads to systemic effects, altering monocytes and monocyte activation even before they leave the bone marrow. Thus, Toxoplasma and macrophages are caught in an ever escalating dance for survival. Importantly, macrophages are also important initiators of the immune response, triggering recruitment and activation of T lymphocytes and other immune cells. On the other hand, macrophages are essential in avoiding excessive inflammation or aberrant responses to pathobionts. Infection with Toxoplasma gondii therefore prototypically highlights the balance struck by macrophages trying to compromise between pathogen elimination and host health, while the parasite abuses this balance to ensure its own survival.

Coakley and Harris concentrate on the interaction of macrophages with helminth parasites. Helminths were previously considered too large to be phagocytosed, and therefore, macrophages were thought not to be relevant for the immune response. However, it is becoming increasingly evident that macrophages are crucial for immunity and survival of the host. Coakley and Harris therefore sub-divide the functional role of macrophages into three sub-categories: "react," "repair" and "resolve."

In the "react" phase, macrophages produce a variety of effector molecules which either have direct anti-helminth activity or recruit other immune cells such as eosinophils. Overall, it seems that one of the major functions of macrophages may be to trap helminth larvae in tissues to make them accessible to immune cells, prevent further tissue damage and/or allow killing within a controlled environment.

In the "repair" phase, macrophages are known mediators in wound healing. During helminth infection, due to the damage caused by migration of the worms, rapid repair of tissue damage is often essential, to prevent excessive haemorrhaging or translocation of microbiota. Thus, several of the mechanisms that trap helminth parasites also help to close the breach they may have caused. At this stage, it is unclear which of the two is the primary objective for macrophages.

Finally, in the "resolve" phase, somewhat counterintuitively, helminth-activated macrophages demonstrate substantial anti-inflammatory, immune-dampening activity. Although this inhibits...
resistance to the infection, it reduces inflammation. Therefore, the primary role of macrophages in helminth infection may be to prevent exaggerated immune activation and associated pathology rather than to contribute to resistance.

Of note, many of the findings described above were discovered in rodent models. Translation of these observations to humans is tricky as human macrophages do not express many of the factors attributed to their function in mice. However, several molecules, albeit not direct orthologs (eg YKL40 and Ym1), seem to fulfill similar functions. Furthermore, effector molecules attributed to macrophages in mice are expressed by other immune cells in humans (eg Arg1 in neutrophils), so that the overall aim of the immune response remains similar. In this regard, Coakley et al demonstrate in a separate research article included in this special issue similar trapping activity of human macrophages as described for their murine counterparts. Although it remains to be seen whether such trapping occurs in humans and is an integral part of their immune response, the parallels to the mouse studies are intriguing.

Finlay and Allen give an extensive review of a particular mouse model of filarial nematode infection, Litomosoides sigmodontis. This model has been instrumental in a series of fundamental discoveries in basic macrophage biology, such as interleukin-4 (IL-4)-mediated expansion of resident cells as main macrophage recruitment mechanism. L sigmodontis also remains one of the only nematode infection models allowing study of the whole lifecycle in mice. Importantly, different common mouse strains differ in their resistance to the infection. This highlights that some of the variability seen in humans is likely due to genetic differences. Importantly, these differences go hand in hand with differences in macrophage activation, subset recruitment and differentiation. While they seem to promote parasite survival and dampen immune responses in susceptible BALB/c mice, macrophages in resistant C57BL/6 mice are strongly activated and are thought to contribute to worm killing. Interestingly, macrophages likely play different roles at different stages of the infection and altering macrophage responses early has a profound effect on the long-term outcome of the infection, independent of later macrophage phenotypes. Thus, their role cannot easily be assessed by taking snapshot measurements of individual activation markers. In addition, Finlay & Allen highlight that macrophages do not act in isolation but are embedded in a network of immune cell interactions and control mechanisms as well as dependencies on the tissue niche and stromal cell-derived cues. Thus, future research is necessary to untangle cause and consequence of macrophage heterogeneity in helminth infection and the relative contribution of macrophage subsets to individual resistance mechanisms.

Pessenda and da Silva focus on the innate immune response to Leishmania species and in particular the role of the enzyme arginase in rendering hosts susceptible. In helminth infections, as discussed above, Arg1 provides essential wound healing elements and helps to trap worms. However, in the context of Leishmania spp. this becomes detrimental and heightened IL-4 responses, Arg1 expression and expansion of tissue-resident macrophages have all been linked to disease progression. Currently, the predominant explanation for this finding is the competition of Arg1 with nitric oxide synthase (Nos2) within infected macrophages for their shared substrate L-Arginine, limiting killing of Leishmania parasites. Challenging this paradigm, Pessenda and da Silva point out that many functions of arginase seem to extend beyond this simplistic view. On one hand, Leishmania parasites express their own arginase, essential for growth and proliferation, and inhibition of arginase alters susceptibility without necessarily altering Nos2-mediated mechanisms. Moreover, Arg1 has a profound effect on T cells indicating a regulatory capacity outside of macrophages. Indeed, human macrophages do not readily express arginase, but many of the detrimental effects of the enzyme seem to be mimicked in human patients. Lastly, Pessenda and da Silva highlight the highly complex regulation of Arg1 expression in vivo. Although typically associated with M2 activation, Arg1 expression during Leishmania infection can occur in a strong Th1 environment and interferon-γ can even synergize with IL-4 to induce Arg1. In addition, macrophages of different origin, tissue resident vs. monocyte-derived, but also macrophages from different tissues (eg liver vs spleen), show different propensity to express Arg1 leading to tissue-specific resistance/susceptibility patterns within the same host. Thus, dissecting the tissue- and subset-specific regulatory mechanisms governing macrophage activation will be essential for future therapeutic approaches.

Taken together these reviews emphasize the multi-layered, intricate and sometimes confusing interaction of parasitic pathogens with macrophages. Eliminating the threat seems often not to be the prime objective of the immune response, but rather containment and limitation of pathological sequelae. This may allow parasites to infest, proliferate and propagate, but ensures the best possible chances for host survival. Moreover, a beneficial response in one setting may be detrimental in another and so macrophage responses have to be balanced across a variety of scenarios. Thus, macrophages are both, partners in crime as well as mortal enemies of these disease-causing agents and future research will need to dissect these two sides of the coin.

**KEYWORDS**
cell, macrophage, parasite

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