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Lessons from studying roundworm and whipworm in the mouse: common themes and unique features

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Abstract

Ascaris lumbricoides, the roundworm, and *Trichuris trichiura*, the whipworm, are human intestinal nematode parasites; both are soil-transmitted helminths, are often placed together in an epidemiological context and both remain neglected despite high prevalence. Our understanding of parasitic disease continues to be enhanced through animal models. Despite the similarities between whipworm and roundworm, there are key differences between the two species and these have influenced the application of their respective animal models. In the case of *T. trichiura*, the fact that a murine equivalent, *T. muris* completes its life cycle in a mouse model has greatly enhanced our knowledge of whipworm biology, pathogenicity and immunology. In contrast, *A. lumbricoides* and its porcine equivalent, *Ascaris suum*, lack a rodent model in which the life cycle is completed. However, evidence continues to accumulate demonstrating that mice represent useful models of early *Ascaris* infection, a key stage of the life cycle. The use of mouse models for both *Ascaris* and *Trichuris* has a long history with early pioneers discovering fundamental aspects of each parasite's biology. Novel technologies and perspectives, as outlined in this special issue, demonstrate how through the prism of mouse models, we can continue to explore the similarities and differences between roundworms and whipworms.

Introduction

Why study parasite infections in mice? The house mouse, *Mus musculus*, is a powerful model organism given its similar anatomy, physiology and immunology to humans, its short breeding cycle and the availability of a whole 'toolbox' of reagents, transgenic mice and advanced methodologies. In the context of parasitic infection, one of the key research imperatives is a desire to alleviate the ill-health caused by infection in humans and their domestic animals, and research into the soil-transmitted helminth parasites is no exception to this. A variety of gut helminth mouse models exist, including the rodent hookworms *Heligomosomoides polygyrus* and *Nippostrongylus brasiliensis*, the whipworm *Trichuris muris* and the roundworm *Ascaris spp*. This special edition of *Parasitology* focuses on the latter two parasites with articles focused upon immunology, immunoregulation, co-morbidities, the microbiome and vaccine development.

Despite whipworms and roundworms sharing certain commonalities, for example, an association with humans for several thousand years and an ability to trigger a similar quality of immune response (reviewed in Else *et al.*, 2020), these two nematode species also have many differences. *Ascaris* worms are large; up to 35 cm in length whilst whipworms are small (up to 5 cm in length); whipworms live in the large intestine whilst *Ascaris* inhabits the small intestine. More than 70 *spp.* of *Trichuris* are described, including *T. muris* in the mouse, whilst in the genus *Ascaris* only two species are known, *A. suum* in pigs and the human parasite *A. lumbricoides.* Notably, whipworms are entirely enteric in their life style whilst *Ascaris* parasites have a migratory larval phase that contributes to pathology in the liver and lungs in addition to the intestine (Holland, 2021). In the context of mouse models, a key difference between the two parasites is that the mouse is a natural host of whipworm infection but not of *Ascaris* infections, and this difference plays out in some of the ways that mouse models have been used to understand whipworm and roundworm infections, as described within this special collection. Collectively, the articles in this special issue explore the application of these two important nematode parasites, in both basic and applied research, and describe some of the recent advances made through the use of the mouse model.

Historical aspects

Trichuris muris in the mouse has been used as a model system by parasitologists for well over half a century with Shikhobalova reporting studies in 'white mice' as long ago as 1937 (Shikhobalova, 1937). Detailed studies of the whipworm life cycle in the mouse were published in 1954 (Fahmy, 1954) and at that time there was a growing desire to understand the host–parasite interaction better. Thus, a number of studies reporting strain variation in the ability

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Table 1. Mouse models of *Trichuris* and *Ascaris* infections: a selection of the early pioneers

Pioneers	Research focus	Reference
Stewart	First evidence of hepatic-pulmonary migration of *Ascaris* in mice	Stewart (1916, 1917)
Ransom and Foster	Conclusion that rats and mice were abnormal hosts for *Ascaris*	Ransom and Foster (1920)
Shikhobalova	*Trichuris* infection in white mice	Shikhobalova (1937)
Sprent	Distribution of *Ascaris* larvae in mice	Sprent (1952)
Fahmy	Investigation of whipworm life cycle	Fahmy (1954)
Worley	Uses *Trichuris* in mice to evaluate anthelmintics	Worley *et al.* (1962)
Campbell	Describes how resistance to whipworm is suppressed by cortisone treatment	Campbell (1963)
Bindseil	Fate of *Ascaris* larvae in immune and non-immune mice	Bindseil (1969)
Douvres and Tromba	Comparative development of *Ascaris* in various animal models	Douvres and Tromba (1971)
Wakelin	Explores the concept of immunity to whipworm infection	Wakelin (1967, 1970*a*, 1970*b*)
Mitchell	Establishes resistance and susceptibility to *Ascaris* in inbred mice	Mitchell *et al.* (1976)
Pike	Notes that a *Trichuris* infection alters the bacterial flora in the ceca of mice	Pike (1976)

to carry a chronic infection were published, including Keeling (1961) and Worley *et al.* (1962), leading to a debate as to whether the inability to carry an infection through to the adult stage represented an incompatibility between the host environment and the parasite, or immune-mediated resistance (or both). Important work by Campbell in 1963 discussed the concept of immune-mediated worm expulsion which was then built upon by numerous elegant studies by Wakelin in the 1960s and 70s (see Wakelin, 1967, 1970*a*, 1970*b*). It is interesting, however, to reflect on the early debate around a host environment incompatibility *vs* immunity, given our new knowledge of the important contribution of the host microbiome to the success of the parasite, a topic discussed by Lawson *et al.* (2021) in this volume, and the fact that Pike had noted changes in the bacterial flora in the caeca of *Trichuris*-infected mice as long ago as 1976 (Pike, 1976) (Table 1).

In contrast to *Trichuris*, *Ascaris* does not have a species that infects a natural rodent host where the life cycle is completed. Animal models in which *Ascaris* does not complete its life cycle but mimic the all important hepato-tracheal migration are described as abnormal hosts. Larval stages of *Ascaris* do not return successfully to the small intestine to mature into adult worms (Holland, 2021). This has undoubtedly hindered research into what is regarded by some as the most neglected of the neglected tropical diseases (Hotez, 2013). However, it is clear that this phase of infection is likely to be crucial in the manifestation of susceptibility and resistance and successful adult worm establishment (Nogueira *et al.*, 2016) and this is one of the reasons why mice serve as a useful model for the assessment of vaccine candidates (see Gazzinelli-Guimaraes *et al.*, 2021).

As early as 1916, investigators used *A. suum*-infected mice to make novel and important observations concerning the biology of the ascarid (Stewart, 1916; Holland, 2021) (Table 1). Since then, mouse models of early *Ascaris* infection have been used for such diverse investigations as the intestinal hepatic migratory pattern (e.g. Ransom and Foster, 1920; Slotved *et al.*, 1998; Dold *et al.*, 2010). Of particular note are the findings of Slotved *et al.* (1998) who demonstrated, in important comparative work, that the migratory pattern of *A. suum* is similar in murine and porcine hosts; the hepatic-pulmonary migratory pattern (e.g. Sprent, 1952; Douvres and Tromba, 1971; Song *et al.*, 1985; Lewis *et al.*, 2006); hepatic pathology (e.g. Bindseil, 1969; Dold *et al.*, 2010; Deslyper *et al.*, 2016, 2019); immunological responses (Mitchell *et al.*, 1976; Kennedy *et al.*, 1987; Gazzinelli-Guimaraes *et al.*, 2013; Nogueira *et al.*, 2016) and host–parasite genetics (e.g. Mitchell *et al.*, 1976; Nejsum *et al.*, 2008; Dold *et al.*, 2011; Peng *et al.*, 2012). Furthermore, Gazzinelli-Guimaraes *et al.* (2021) describe the mouse model as the primary *in vivo* animal system for the evaluation of vaccine candidates for *A. lumbricoides* and provide a detailed historical perspective on the studies performed from 1957 to 2021.

Wild immunology

Whilst the early drivers to study *T. muris* in the mouse were largely driven by curiosity, the majority of the articles in this collection focus on the use of mouse models of infection to further our understanding of human disease, and the article by Mair *et al.* (2021) is no exception covering the most recent immunological knowledge gained from studying *T. muris* in the laboratory mouse. However, in addition, Mair *et al.* move on to extend the beneficiaries of whipworm research beyond the medical community, highlighting contributions made by mouse whipworm research to the field of host–parasite co-evolutionary relationships, ecology and parasite genetic diversity, enabled by the fact that, unlike *Ascaris spp.*, *T. muris* is a natural parasite of wild mice. Of course the study of parasites in wild populations is not new and one early pioneer in the context of whipworm research was Behnke who assessed the epidemiology of *T. muris* in its natural host, the wild house mouse (Behnke and Wakelin, 1973). The new and growing field of Eco-Immunology or 'Wild Immunology' is also enabled by the fact that, as mentioned above, *T. muris* naturally infects mice. Eco-immunologists aim to study immunity to infection in real-world settings rather than the highly controlled laboratory environments where most studies on the immune response to infection are conducted. A number of elegant mouse model systems have recently been developed which move from fully wild settings, to the semi-wild enclosure-based systems pioneered by Graham (reviewed by Graham, 2021) and a system where inbred strains of mice carry a 'wild' microbiome (Rosshart *et al.*, 2019). Gut-dwelling helminth parasites live in intimate association with their host and with a large diverse microbial community with which they share their niche. The intricate relationship between the host, its parasites and the gut microbiota is extremely well illustrated by studies using *T. muris* infection of mice, and these complex relationships are described by Lawson *et al.* (2021). Indeed research in this area has illuminated a

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dependency of the parasite on the host microbiome for maintenance of its life cycle, with *T. muris* parasites evolving to respond to microbial cues within the host gut as well as harbouring their own unique microbiome.

Vaccine development

Given the persistently high prevalence of *A. lumbricoides* and *Trichuris trichiura* globally, research focussing on vaccine development is a priority. A historical perspective by Gazzinelli-Guimaraes *et al.* (2021) highlights the challenges associated with the development of a vaccine against a complex helminth infection like *Ascaris* that produces resistant eggs into the environment, promotes rapid re-infection and has the potential to induce anthelmintic resistance. This is despite the clear imperative to identify immunogenic *Ascaris* antigens that can enhance larval killing and/or larval expulsion, in order to prevent maturation and the successful establishment of adult worms that induce both chronic and acute ascariasis. Promising recombinant *Ascaris* antigens such as As14, As16 and As37 (Tsuji *et al.*, 2001, 2002) have been identified and a recent study by de Castro *et al.* (2021) outlines the use of a more intricate vaccine target, an adjuvanted chimeric protein derived from the three recombinants with an efficacy of 73.54% in BALB/c mice. Our continued paucity of knowledge of the totality of the *Ascaris* immune responses and the possibility that other undiscovered proteins may exist and act as better vaccine targets remains an ongoing challenge.

Research advances in whipworm antigen discovery are reviewed in Hayon *et al.* (2021) which ends with a view of the global health policy needs if we are to develop and implement vaccine delivery in the field. Whilst a case can be made for anti-whipworm vaccine research based on the impact the parasite itself has on human health, whipworm infections also have substantial, widespread systemic effects despite being localized within the large intestine.

Co-morbidities, immunomodulation and co-infection

Hayes and Grencis (2021) highlight these body-wide influences of *Trichuris* infection which, in addition to affecting the progression of bowel inflammation, can also worsen stroke outcome, suppress lung inflammation and inhibit anti-tumour immunity. Given the far-reaching effects whipworm has on disease progression at sites distal from the site of infection, unsurprisingly *Trichuris* parasites are a source of immunoregulatory molecules, in keeping with many other helminth parasites; our current understanding of these molecules is reviewed by Bancroft and Grencis (2021) including the quantitatively dominant single novel protein *T. muris* p43.

Mouse models have also provided an opportunity to understand the role of *Ascaris* infection in the exacerbation of other conditions such as pulmonary fibrosis and pulmonary allergic inflammation as discussed by Magalhães *et al.* (2021). Evidence from a mouse model of both larval ascariasis and lung fibrosis revealed an exacerbation of lung damage and an associated diminishment of pulmonary physiological parameters (Oliveira *et al.*, 2019). Furthermore, allergic airway disease can be observed in *Ascaris*-infected mice experiencing tissue damage in the lungs (Weatherhead *et al.*, 2018). As with whipworm infection, an infection with roundworm can exacerbate lung disease. However, the effects of *Ascaris* on diseases of the lung do not necessarily evidence a systemic reach, unlike whipworm, given that *Ascaris* migrates through the lung whilst whipworm is entirely enteric. The role of *Ascaris* infection in liver inflammation lags behind that of the lungs as outlined by Holland (2021). In contrast to other animal models of ascariasis, mice are the only model for which the basis of resistance and susceptibility has been defined (Holland *et al.*, 2013). Furthermore, two inbred strains of mice with highly consistent and diverging larval burdens in their lungs represent the extremes of the host phenotype displayed in the aggregated distribution of *Ascaris* adult worm burdens in humans (Holland *et al.*, 1989; Holland, 2009). The establishment of this model provided an opportunity to explore the mechanistic basis that confers resistance and predisposition to light and heavy *Ascaris* infection with a particular emphasis on the liver. In resistant mice, the most pronounced inflammatory response was observed on day 4 post-infection, a day that coincides with the migration of larvae from the liver to the lungs whereas in susceptible mice occurred later on day 6 post-infection when the majority of the larvae are known to have successfully migrated to the lungs (Dold *et al.*, 2010). These observations led to several proteomic analyses of hepatic tissues in this mouse model that demonstrated intrinsic differences between the two strains, suggesting that resistance might be associated with the oxidative phosphorylation pathway and reactive oxygen species production (Deslyper *et al.*, 2016) and differential expression of components of the complement system (Deslyper *et al.*, 2019). There is obviously a clear need for further investigation of the role of *Ascaris* infection in tissue damage to key organs such as the liver and the lungs, a pathology which sets *Ascaris* apart from any of the other soil-transmitted helminths.

The role of helminths including *Ascaris* in co-infection and the possible perturbation of other infections particularly microparasites has received considerable attention and conflicting observations (Kirwan *et al.*, 2010; Vaumourin *et al.*, 2015). A recent paper by Vieira-Santos *et al.* (2021) explored concomitant infections of *Plasmodium berghei* and *A. suum* in a mouse model and found that co-infection exacerbated reduced respiratory function. As with *Trichuris*, the immunomodulatory properties of *Ascaris* parasites have received attention given their potential development as therapeutic tools. Caraballo *et al.* (2021) provide a review of the cystatins as cysteine protein inhibitors with a particular emphasis on the A1-CPI nematode type 2 cystatin in *A. lumbricoides*. The production of a recombinant form of A1-CPI has been found to be safe in mice and to manifest intestinal anti-inflammatory properties (Coronado *et al.*, 2017) and anti-inflammatory properties in the context of an allergic airway inflammatory mouse model (Coronado *et al.*, 2019). The authors conclude that A1-CPI may prove useful in the immunotherapy of asthma (Caraballo *et al.*, 2021).

Conclusion

To conclude, as outlined above, the use of mouse models to understand the complex interplay between two important soil-transmitted helminths – *A. lumbricoides* and *T. trichiura* and their human hosts – has a long history. However, novel technologies and perspectives, as illuminated in this volume, demonstrate the continued relevance of such animal model systems and how they can help us to fill some of the gaps in our knowledge. We hope that this special edition will stimulate and enhance scientific interest in two parasites that remain among the neglected tropical diseases.

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