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Review Article

Helminths in the lungs

J. M. CRAIG & A. L. SCOTT

Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA

SUMMARY

Parasitic helminths infect well over one billion people and typically cause chronic and recurrent infections that exert a considerable toll on human health and productivity. A significant number of important intestinal- and tissue-dwelling helminth parasites have evolved a scripted migration through select organ systems. Of specific interest here are the helminth parasites that interact with respiratory tissues and the pulmonary immune system. This review will consider the nature of the interactions between helminth parasites and the lung environment, as well as the consequences of these interactions on the evolution of parasitism and host immunity.

Keywords *filariasis, hookworm, innate immunity, lung inflammation, mucosal immunity, schistosomiasis*

INTRODUCTION

Significance of helminth infections – global burden/ morbidity

Over two-thirds of the human population is at risk of infection with one or more of the major helminth parasites (1). It is estimated that well over one billion people currently harbour helminth parasites worldwide, and it is likely that an equal number have a history of infection. These parasitic helminths, which are most prevalent in the tropical regions of Africa, Asia and Latin America, typically cause chronic and recurrent infections that have a sizeable impact on health and productivity. In addition to the direct tissue damage and immune-mediated pathology resulting from responses aimed at controlling larval and adult parasites, many of these infections are associated with chronic morbidities including anaemia, malnutrition, nutrient deficiencies, decrements in physical and mental growth in children, and a significant reduction in work productivity in adults (2, 3).

Common to all of the multicellular helminth parasites is the evolution of a multistage life cycle that includes a number of morphologically and antigenically distinct developmental stages that range from the microscopic transmission forms to the overtly macroscopic adult parasites. In many cases, after gaining entry to the host, the initial stages of parasite development are accompanied by a scripted migration through select tissues and organ systems. This migration culminates in positioning the adult males and females in an anatomical compartment where they can find each other, mate and efficiently disseminate the transmissible forms of the parasite. Of particular interest here is the subset of helminth parasites that have evolved a developmental scheme that includes interactions with the pulmonary environment (Table 1). Traditionally, the lung phase of the helminth life cycle has been viewed from the parasite's perspective as necessary for exposure to biochemical cues or acquisition of nutrients vital for normal development (4). Data derived from clinical observations and experimental animal models have demonstrated pathological and immunological consequences of lung–helminth interactions that point to complex relationships which go beyond simple issues of parasite development. This review will examine the interactions between helminth parasites and the pulmonary microenvironment, as well as the ramifications of these encounters on the evolution of parasitism and host immune responses.

Correspondence: Alan L. Scott, Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Baltimore, MD 21205, USA (e-mail: ascott@jhsph.edu).
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Table 1 Helminth parasites that interact with the lungs of humans

Disease	Parasite		Type	Route of entry	Pulmonary presentation
Nematodes					
Hookworm	*Ancylostoma duodenale* *Necator americanus*	H	1	Skin penetration	Loeffler syndrome
Ascariasis	*Ascaris lumbricoides*	H	1	Oral – food, liquid, soil	Loeffler syndrome
Strongyloidiasis	*Strongyloides stercoralis*	H	1, 2	Skin penetration	Acute infection – Loeffler syndrome; hyperinfection – eosinophilic pneumonia, coughing, wheezing
Lymphatic filariasis	*Wuchereria bancrofti*	H	1	Mosquito	Tropical pulmonary eosinophilia
	Brugia malayi	H	1	Mosquito	
Loiasis	*Loa loa*	H	1	Fly (*Chrysops*)	Eosinophilic pleural effusion
Dirofilariasis	*Dirofilaria immitis*	Z	3	Mosquito	Coin lesion
Toxocariasis	*Toxocara canis* *Toxocara catis*	Z	3	Oral – soil	Eosinophilic pneumonia, coughing, wheezing, dyspnoea
Trematodes					
Schistosomiasis	*Schistosoma mansoni* *Schistosoma japonicum* *Schistosoma haematobium*	H	1, 2	Skin penetration	Eosinophilic granuloma formation, pulmonary hypertension
Paragonimiasis	*Paragonimus sp.*	Z	3	Oral – infected crustaceans	Cough, chest pain, pleural lesions, haemoptysis
Cestodes					
Hydatid disease Alveolar echinococcosis	*Echinococcus granulosus* *Echinococcus multilocularis*	Z	3	Oral – food, liquids	Cough, chest pain, haemoptysis, pleural lesions

H = Infection restricted to humans; Z = Zoonotic infection.

Helminth–lung interactions

The lung-associated helminth parasites can be grouped into three major types according to the nature of their interactions with the pulmonary environment (Table 1). Type 1 interactions are associated with helminth species for which residence in the lung has evolved as an integral step in their life cycle. Type 1 interactions can be further divided into those that result in a transient (hours to days) presence in the lungs, typically as part of the early stages of larval development such as what is observed for hookworms, *Ascaris, Strongyloides* or *Schistosoma* sp., and those that have a more persistent (months to years) association exemplified by the filarial species *W. bancrofti*, *B. malayi* and *Loa loa*. In general, Type 1 interactions are well tolerated by the host. Type 2 interactions result from abnormally elevated parasite loads and/or a dysregulation of host homeostatic mechanisms. Type 2 interactions, such as those resulting from heavy *Schistosoma* infection or autoinfection by *Strongyloides,* are accompanied by significant pulmonary pathology. Lastly, Type 3 interactions are associated with zoonotic helminth infections where migration of larval and/or adult parasites to the lungs often results in pulmonary inflammation and damage. Examples of parasites that result in Type 3 interactions include *Dirofilaria*, *Toxocara*, *Paragonimus* and *Echinococcus.* Using these broad categories of helminth-lung interactions as a guide, we will now consider the implications of these migration behaviours on pulmonary immunity and pathology.

TYPE 1 INTERACTIONS

Hookworm

Human hookworm infections caused by *Necator americanus* and *Ancylostoma duodenale* are most commonly initiated when infective, third-stage larvae (L3) penetrate the skin of the feet or hands (5, 6). The larvae migrate to the lungs via the circulatory system and emerge into the alveolar spaces at the level of the pulmonary capillaries. In the process of entering the air spaces, hookworm larvae cause focal mechanical and enzymatic damage to the respiratory epithelium and vasculature. During residence in the lung, the larvae grow, differentiate, molt to a fourth-stage larvae (L4) and enter the conducting airway system by migrating up the bronchi to the trachea (7). The total residence time in the lung is typically 24–48 h (8), after which the L4 are coughed up, swallowed, and the parasite completes its developmental programme to the adult stage in the small intestine. The lifespan of adult parasites ranges from 1 to 18 years during which the females produce 5000–30 000 eggs per day (7).

During the pulmonary phase of hookworm infection, patients may present with fever, cough, wheezing and pulmonary eosinophilic inflammation (9, 10) – a condition

that has been classically described as Löfflers syndrome (11). Depending on the level and duration of larval exposure, hookworm-induced pneumonitis may last for months. Given the prevalence and importance of hookworm infection, it is notable that data from humans detailing lung pathology during this phase of infection are not available.

Strongyloides

Strongyloides stercoralis is endemic in the subtropics and tropics where it is estimated to infect over 350 million people (12). Similar to the hookworms, *S. stercoralis* infective filariform larvae are found in the soil and gain entry to a host by penetrating the skin or a mucosal surface. During the first 2 days of infection, the larvae migrate via tissues, lymph and blood to the lungs where they emerge into the alveolar spaces. After a brief period in the lungs, the larvae ascend the tracheobronchial tree and gain access to the gastrointestinal track where the larvae complete their development to adults (13). The adult form of *S. stercoralis* in the mammalian host is female and reproduction is by parthenogenesis (8). In most cases, the larvae differentiate into adults in the small intestine where they deposit eggs that develop in the intestinal mucosa. Eggs hatch in the intestine and the larvae migrate to the lumen where they have developmental options that are unique to most nematode species that parasitize vertebrates. A proportion of the larvae develop into the infective stage prior to exiting the intestine and can initiate the autoinfection cycle (13). Other larvae are passed in the faeces where they either undergo heterogonic development into free-living adult males and females in the soil, which produce a cohort of infective-stage larvae that are derived from sexual reproduction, or undergo homogonic development and transform directly into infective L3s (13).

The pulmonary symptoms associated with a limited Type 1 primary exposure to *S. stercoralis* are often absent, but some individuals experience a mild cough accompanied by bronchial and tracheal irritation (14). In contrast, more severe pulmonary symptomology accompanies the Type 2 *S. stercoralis* interactions that are associated with autoinfection or hyperinfection (outlined below).

Ascaris

Ascaris lumbricoides is the most common intestinal helminthic infection in humans (15). After 2 weeks of maturation in the soil, fertilized, infective eggs are swallowed and hatch in the small intestine. After migrating to the caecum and penetrating the intestinal mucosa, the larvae are carried by the portal circulation to the liver and then to the lungs (16). This hepato-pulmonary migration takes place over 10–14 days and culminates with the L3 parasites penetrating into the lung parenchyma where they grow, molt and develop for approximately 48 h. The larvae ascend the bronchial tree, are swallowed and mature to adult male and female parasites in the small intestine. Female *Ascaris* produce up to 200 000 eggs per day for a year or longer.

The respiratory symptoms induced by migration of *Ascaris* larvae through the lungs include burning substernal discomfort, dry cough with mucoid sputum, haemoptysis, shortness of breath and wheezing. Eosinophilic pneumonitis is an important laboratory finding and is the basis for diagnosis of Löfflers syndrome (17). Chest radiographs demonstrate unilateral or bilateral, transient, migratory, nonsegmental opacities of various sizes. The transient pulmonary disease caused by *A. lumbricoides* ordinarily does not require treatment. While there is a rough correlation between the severity of symptoms and larval burden, pulmonary symptoms are reported to be less common in regions with continuous transmission (18–20).

It is interesting to note that pulmonary symptoms and pathology have also been described for zoonotic infections with the highly related pig parasite *A. suum* (20–22). The extent to which the highly prevalent *A. suum* contributes to immunological activation and lung pathology in humans has not been defined.

Schistosoma

The schistosome species that cause the most human disease include *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*. Most commonly, schistosomiasis, also known as bilharzia, is initiated by direct contact with fresh water containing infective larvae (cercariae). Utilizing the content of specialized glands, the motile cercaria penetrates the skin and transforms into the tissue-traversing schistosomulum. Schistosomula enter the circulation and are carried to the lungs where they undergo developmental changes over 8–10 days, rendering the parasite competent to initiate the next phase of their migration. The larvae re-enter the blood flow and transit to the hepatic portal vein (*S. mansoni* and *S. japonicum*) or the venous system draining the bladder (*S. haematobium*). The parasites undergo additional development to sexually mature males and females. After pairing, the adults migrate along the hepatic portal vein to the mesenteric branches that surround the intestine and there the female releases embryonated eggs. A majority of these eggs pass through the gut wall and leave the host in the faeces. However, some eggs become lodged in intestinal tissues or are swept up by the

circulation and become trapped in the liver. The immune responses that lead to granuloma formation around these ectopically deposited eggs are the major causes of pathology in the chronic form of schistosomiasis. For *S. haematobium,* the eggs, which typically penetrate the bladder wall and are released with the urine, can become lodged within the wall of the bladder resulting in inflammation, bloody urine and an increased risk of bladder cancer (23). In fresh water, the eggs hatch and release motile miracidia that seek out the next host – a snail. Within the snail, the parasite undergoes asexual development giving rise to infective cercariae that are ultimately released back into the water.

Although the schistosomula reside in the lungs during the early stages of infection, pulmonary symptoms that include shortness of breath, wheezing and a dry cough typically occur 3–8 weeks after infection (24). The percentage of patients who present with pulmonary involvement in schistosomiasis is reported to be between 40% and 70% (25–27). While some have pulmonary symptoms coincident with the fever, chills, diarrhoea, abdominal pain and urticaria associated with Katayama syndrome (28), most schistosomiasis patients report the symptoms several weeks after the febrile disease subsides. Radiographic and CT scanning of the lungs following infection often reveals nodular lesions with diffuse borders (24).

Filarial nematodes

For a significant percentage of the over 100 million people harbouring one of the tissue-dwelling, vector-borne filarial nematode species, infection results in long-term debilitating morbidity including lymphatic blockage leading to elephantiasis and hydrocele, dermal lesions, blindness and respiratory complications (29). Of particular interest here is a subset of filarial species that includes *Wuchereria bancrofti*, *Brugia malayi* and *Loa loa*, all of which are major human pathogens that have evolved a pronounced circadian behaviour where larvae cycle between circulating in the blood and sequestering in the pulmonary vasculature.

Filarial nematode infections are initiated when an infective mosquito or haematophagous fly delivers the infective third-stage larvae to the bite wound. After a short period of development in host tissues, the larvae molt and migrate to various sites where male and female parasites mate. In the case of *W. bancrofti* and *B. malayi*, the adults take up residence in the lumen of an afferent lymphatic vessel often near a major lymph node cluster. *L. loa* adults are located within connective tissues layers of the skin and fascial tissues surrounding somatic musculature (30). The fertilized eggs develop and hatch within the uterus of the female and several thousand first-stage larvae, also referred to as microfilariae, are released daily from each gravid female directly into the lymph. Microfilariae follow the lymph flow and enter the peripheral circulation where they are available to be ingested by the insect vector during a blood meal. During their estimated 6- to 12-month lifespan, the population dynamics of microfilariae in the peripheral circulation are characterized by a remarkable periodicity in which peak parasite numbers coincide with the feeding behaviour of their corresponding vector species. Those filariae that are transmitted by mosquitoes that feed largely at night, such as *W. bancrofti* and *B. malayi*, exhibit nocturnal periodicity. In contrast, *L. loa* displays a diurnal periodicity in the peripheral blood corresponding with the peak feeding period of its tabanid fly vector. Microfilaremia can range from hundreds to thousands of parasites per mL of blood, and evidence suggests that microfilariae reside within the pulmonary arterioles when they are not in the circulation (31, 32).

The periodicity of microfilariae has been an abiding mystery since its description by Manson in 1879 (33). Despite this long-standing appreciation that the transmissible forms of most species of filarial worms exhibit a circadian rhythm, little is understood regarding the adaptive significance of limiting the time that the parasite is in the peripheral circulation or the reason why the pulmonary environment has evolved as the site of choice for sequestration. Furthermore, for a number of filarial species that parasitize mammals, microfilariae can be found in the blood at any time of the day. Given that there is no obvious regularly recurrent inflammation or symptoms that can be correlated with a nocturnal, diurnal or nonperiodic phenotype, it is unlikely that this behaviour has evolved to avoid innate or adaptive immune mechanisms.

While it is likely that the type of microfilarial periodicity displayed has a genetic basis which sets a baseline circadian rhythm for each species, it is hypothesized that this behaviour is also influenced by environmental factors. Environmental cues that have been suggested centre around host variables which occur during the 24-h wake–sleep cycle and include body temperature (34), oxygen and/or CO_2 levels in the blood and lungs (35), melatonin levels (36) and neurotransmitters (37). Interestingly, the zoonotic filarial species *Dirofilaria immitis* is marked by subperiodic microfilaremia that peaks diurnally in dogs and nocturnally in mice, indicating that the nature of the periodicity can also be dependent on the host (38). Additional outstanding questions include the exact location of the parasites in the lung vasculature, the mechanism used by the larvae to maintain a position in the lungs for several hours at a time, and how larvae navigate the small gauge vessels of the lungs without causing damage to the endothelial cells.

Filarial infections induce a robust, modified Th2 immune response and patients experience filarial fevers and acute and chronic lymphatic lesions (31, 39, 40). It is noteworthy that, despite the daily accumulation of millions of microfilariae in the lungs over the course of an infection that can last for decades, a vast majority of filariasis patients have no apparent parasite-induced pulmonary symptoms or lung pathology. On the other hand, a small number of filarial-infected individuals develop a severe pulmonary syndrome designated tropical pulmonary eosinophilia that is characteristic of a Type 2 interaction and is described below.

Animal models of type 1 interactions

As noted above, there are limited observations on the pathology and immunology of Type 1 lung–helminth interactions. However, numerous studies using animal models of hookworm infection have provided insights into the immediate and persistent pathological and immunological consequences of these interactions. A majority of the animal model studies have been carried out employing a murine-adapted strain of *Nippostrongylus brasiliensis* (Nb) (41). The results of these studies provide a level of detail on the pathogenesis of Type 1 helminth–lung interactions that cannot be achieved in humans. In experimental infections, the Nb L3 arrive in the lungs as early as 11 h post-infection and typically exit via the trachea by day 3 (41, 42). During this time, the larvae grow rapidly, differentiate and molt to fourth-stage larvae (L4). Adult parasites are harboured in the small intestine where they develop until gravid females release embryonated eggs. In immunocompetent mice, the adults are expelled from the intestine by day 11–12 of infection via a mechanism that relies on the production of IL-33, IL-13 and IL-4 (43–45). Worm entry into the lungs induces rapid activation of innate immune mechanisms. Nb larvae cause substantial mechanical and enzymatic damage to both endothelial and epithelial tissues as they enter the lung parenchyma via the pulmonary capillary vasculature. The resulting haemorrhage, which is most severe at day 2 of infection, is typically resolved within hours of the parasite exiting the lungs (42, 46). Neutrophils and monocytes are quickly recruited, presumably in response to this tissue damage. The infiltration of neutrophils is associated with an early increase in IL-17 production in the lungs (46). Damage to the lung epithelial cells also results in the release of molecules such as trefoil factor 2 (TFF2), which in turn promotes the production of IL-33 from epithelial cells, lung macrophages and dendritic cells (44, 47). IL-33 activates resident type 2 innate lymphoid cells (ILC2) to proliferate and produce IL-13 and IL-5 which are required to initiate a properly regulated systemic Th2 response that eventually results in the expulsion of Nb adults from the intestine (44). At the cellular level, IL-13 results in M2 activation of both resident and recruited mononuclear cells (42, 48). The initial monocyte and neutrophil response is followed by an influx of IL-4-producing eosinophils, basophils and T cells (42, 48, 49). The strongly polarized Th2 immunity initiated during the innate response is perpetuated for months after the larvae leave the lungs and the adults are expelled from the intestine as indicated by the persistent M2 phenotype adopted by resident lung macrophages (48, 50).

Although the Nb larvae are present for only a few hours, infection results in lasting changes to the immunological, physiological and structural architecture of the lungs (50, 51). Structurally, the initial damage inflicted by the larvae results in focal areas where the respiratory epithelium is destroyed causing the formation of emphysema-like lesions (50–52). As in emphysema, airspace enlargement is heterogeneous, widespread and progressive (51). Interestingly, this progressive lung destruction continues long after the host has eliminated Nb from the intestine and other tissues. Another long-term consequence of the transient presence of Nb larvae in the lungs is a change in the baseline reactivity threshold of the pulmonary microenvironment. Post-Nb lungs take on a heightened immunological status marked by increased transcription of both Th1 and Th2 cytokines/chemokines (50) and hyper-responsiveness to methacholine challenge (50, 51, 53). Paradoxically, allergen sensitization and challenge of the Nb-altered pulmonary immune environment results in a reduced level of reactivity (50). Thus, Nb larvae leave behind a complex reprogramming of the immunological set point in the lungs.

The anti-Nb immune response that develops during a primary exposure to the parasite confers partial protection against subsequent challenge with infective larvae (54, 55). It was long assumed that the reason for the reduced load of adult parasites in the in the gut upon secondary exposure was due to the elimination of most of the larvae in the skin, an assumption that is supported by recent data (56). However, other studies have also implicated the lungs as a significant site of larval attrition (52).

TYPE 2 INTERACTIONS

Several helminth species that have evolved Type 1 interactions as part of their canonical life cycle in the human host also exhibit a more pathogenic Type 2 lung–parasite interaction under circumstances where the parasite burden becomes excessive or the hosts immune response against the parasite becomes compromised or dysregulated.

Strongyloides

Strongyloides stercoralis can initiate a potentially lethal autoinfection cycle where precociously developing infective larvae penetrate the gut wall of the primary host, enter the circulatory system and migrate to the lungs. Successive generations of autoinfection in this same host result in a geometric expansion in worm burden and the development of a potentially life-threatening hyperinfection. Sputum from hyperinfected patients may contain adult worms, rhabditiform or filariform larvae, as well as eggs (57). Pulmonary manifestations include cough, wheezing, dyspnoea and, rarely, respiratory collapse [reviewed in (14)]. Imaging of the lungs reveals evidence of oedema, cellular infiltrates and pleural effusion (57–59). In general, the prognosis of patients with hyperinfection syndrome is poor with mortality rates that can exceed 80% (57, 60). This accelerated autoinfection is seen in patients undergoing treatment with immunosuppressive drugs and in individuals with acquired immune deficiency disorders. In a severe autoinfection, larvae become disseminated throughout the body and patients also present with severe gastrointestinal symptoms.

Schistosoma

A significant percentage of schistosomiasis patients develop pulmonary arterial hypertension (61, 62). In about 10% of patients, chronic schistosomiasis results in periportal fibrosis, portal hypertension and splenomegaly. As a consequence of the fibrosis, there is a progressive destruction of the portal venous system that leads to the formation of portosystemic shunts which allow eggs to embolize in the lungs (61). The presence of eggs in the lungs results in the formation of granulomas and a subsequent fibrotic reaction. It is thought that the presence of eggs and granulomas gives rise to an obliterative arteritis that ultimately may lead to severe pulmonary hypertension. Although data from humans are not available, in mouse models, the granulomas that surround the embolized eggs contain eosinophils and macrophages that play roles in eliminating parasite antigens and causing hepatic fibrosis (63).

Filarial parasites and tropical pulmonary eosinophilia

Tropical pulmonary eosinophilia (TPE) is typically included in the list of several pulmonary inflammatory syndromes that are accompanied by eosinophilia. The aetiology of most TPE cases is an immune hyper-responsiveness to the microfilarial stage of the *Wuchereria bancrofti* or *Brugia malay*i (64). Patients typically present with a peripheral blood eosinophilia of >3000/μL, high levels of antifilarial antibodies and exceedingly increased total IgE levels (65). The clinical presentation of TPE includes nocturnal paroxysmal cough, dyspnoea, wheezing, fever, weight loss and fatigue. Chest radiographs show diffuse lesions and interstitial mottling. Pulmonary function tests show decrements in lung capacity and lung volume that track with the levels of eosinophils recovered in bronchial alveolar lavage fluid and with alveolitis (66). Consistent with a filarial aetiology, patients show a dramatic clinical improvement after treatment with antifilarial drugs (65). For a significant percentage of patients, despite drug-mediated clearance of the parasite, alveolitis persists and leads to interstitial fibrosis (67).

TYPE 3 INTERACTIONS

In general, helminth parasites have a very limited host range. However, there are a number of notable examples of Type 3 zoonotic helminth infections where at least one of the parasite's developmental stages has an association with the lung. Several of these zoonotic infections result in serious lung disease.

Nematodes

Toxocara – visceral larva migrans

The parasites that cause visceral larva migrans in humans are a dog ascarid (*Toxocara canis*) and less commonly a cat ascarid (*T. cati*). The life cycle of *Toxocara* is similar to *Ascaris* (68). Toxocariasis in humans is initiated by ingestion of soil that contains embryonated eggs passed in the faeces of infected animals (69). The eggs hatch in the intestine and release larvae that traverse the intestinal wall and wander through the body with the potential to invade various tissues including the liver, central nervous system, eyes and lungs (68). The main pulmonary symptoms associated with visceral larva migrans are cough, dyspnoea and wheeze, which may present as asthma or bronchitis and are often accompanied by fever, eosinophilia, anaemia and fatigue (70). A chest radiograph may reveal focal patchy infiltrates and, in some cases, severe eosinophilic pneumonia that can be associated with respiratory distress.

Ascaris suum

Pigs, roundworms and people have lived together for millennia. As Linnaeus described *A. lumbricoides* from humans and Goeze described *A. suum* from pigs in 1782, the assumption has been that these are distinct species. However, the lack of morphological differences between these parasites has raised speculation that the two organisms may actually belong to a single species. In recent years, genomic-level analysis appears to support the idea that *A. lumbricoides* and *A. suum* are in fact the same

species (16, 71, 72). Genetic and phylogenetic issues notwithstanding, it is clear that pig-derived *Ascaris* is capable of infecting humans and causing pulmonary damage (20). The ability of pig-derived worms to progress through the lung stage of infection in humans suggests that special attention should be paid to potential *Ascaris*-induced pulmonary issues in individuals living and working in areas where the prevalence of infected pigs is high.

Trichinella

Of the five species of *Trichinella* (*T. spiralis*, *T. nativa*, *T. nelsoni*, *T. britovi* and *T. pseudospiralis*) that are capable of infecting humans, *T. spiralis* is clinically the most important (73). Humans acquire infection by consuming undercooked meat, typically pork, containing encysted larval worms. The larvae excyst and develop into adults in the small intestine where, during their short lifespan (approximately 4 weeks), the females release larvae that migrate to the peripheral musculature, encyst and remain infective for several years (73). Therefore, humans serve as both the definitive and intermediate host. Pulmonary symptoms, which are typically restricted to individuals with heavy exposure (74), include shortness of breath, dyspnoea and pulmonary infiltrates.

Dirofilaria

Dirofilariasis is caused by a group of mosquito-transmitted filarial nematodes that infect a large number of species in the families Canidae and Felidae (75). *Dirofilaria immitis* (heartworm) and *D. repens* are the most common zoonotic infections reported in humans (76). The adult parasites reside in the right ventricle of the heart where the females release microfilariae into the peripheral circulation. Humans are considered accidental hosts as *Dirofilaria* infections rarely reach patency. Infective-stage larvae pass through the heart and into the lungs where the parasites undergo partial development. It is likely that the parasite induces an inflammatory response that ultimately results in the death of the parasite and formation of a granuloma (75). While most patients are asymptomatic, some exhibit chest pain, cough, dyspnoea and fever (77). The clinical significance of this zoonosis is that it is often discovered by the presence of a solitary granuloma or coin lesion that requires an invasive and costly diagnostic work-up to exclude other infectious agents and neoplasia (75).

Trematodes

Paragonimus

Paragonimiasis (lung fluke disease) is caused mainly by *Paragonimus westermani* in South-East Asia, Latin America and Africa and mainly by *P. kellicotti* in North America. Members of the genus *Paragonimus* infect a spectrum of carnivorous species and utilize two intermediate hosts – snails and crustaceans (8). Humans typically acquire infection by eating raw or undercooked infected crab or crawfish. The larval stages are released during digestion, penetrate the gut wall and migrate via the diaphragm and pleura to the lungs where they mature into adult flukes in 6–8 weeks. The adults reside within cyst-like structures in the bronchiolar lumen and peribronchial tissues for up to 5 years. Eggs are either expelled by coughing, passed in faeces or are diverted into the lung parenchyma where they induce small tubercule-like lesions (8).

Pulmonary symptoms initiate with a dry chronic cough, which later becomes productive and yields blood-tinged sputum upon exertion. Reactions against the adults and entrapped eggs can lead to the development of an eosinophilic pneumonia (78). Chest imaging shows pleural lesions and patchy infiltrates, nodular opacities and fluid-filled cysts in the parenchyma of the lung (79). Protracted paragonimiasis can contribute to the development of bronchiectasis (80). The symptoms of paragonimiasis can be similar to those of tuberculosis or lung cancer (81, 82).

Cestodes

Echinococcus spp

Pulmonary hydatid disease is caused by *Echinococcus granulosus*. The definitive host is a canine, primarily dogs and foxes, and the intermediate hosts are sheep, cattle, horses, pigs and humans (83). Humans are considered accidental hosts when they ingest embryonated parasite eggs in contaminated food or water. *E. granulosus* oncospheres then hatch in the intestine where the parasites enter the portal circulation and travel to the liver or lungs before forming a fluid-filled, subspherical hydatid cyst. *E. granulosus* hydatids are unilocular and surrounded by a limiting membrane that expands radially to accommodate inward-budding daughter cysts and hundreds to thousands of protoscolices, each of which has the potential to develop into an adult within the intestine of a definitive host. Despite growing to an impressive size, most intact *E. granulosus* hydatid cysts cause minimal symptoms (84). While the liver is the primary location, approximately 30% of *E. granulosus* cysts are found in the lungs. If pulmonary cysts rupture into the pleural space or a bronchus, symptoms may include intense cough and vomiting of hydatid material and cystic membranes. Patients may also present with chest pain, chronic cough, pneumothorax, eosinophilic pneumonitis, pleural effusion, pulmonary embolism, haemoptysis or biliptysis (85).

Another species of *Echinocccus*, *E. multilocularis*, causes a disease referred to as human alveolar echinococcosis.

E. multilocularis is mainly a tapeworm of foxes, wolves and dogs with small mammals, deer, reindeer and bison serving as intermediate hosts (83). Human infection with *E. multilocularis* results in a slow-growing, irregular hydatid cyst in the liver that, unlike *E. granulosus*, lacks a limiting membrane. *E. multilocularis* hydatids contain outward-budding daughter cysts that form an invasive mass that can metastasize to other organs including the lungs in the later stages of the disease (85). The invasive daughter cysts of *E. multilocularis* also have the potential to rupture into the pleural space or the bronchi, resulting in severe symptoms similar to those outlined for pulmonary hydatid disease with *E. granulosus*.

PARADOX OF TISSUE MIGRATION

The general lack of pathology associated with type 1 interactions, when compared to that seen in types 2 and 3 interactions, underscores the high degree of co-adaptation that has taken place between humans and our helminths. The selective pressures that have been exerted both on the human host and on the helminth pathogen have generally meant that parasite-induced damage is limited. On the human side, the adaptations typically result in individuals harbouring long-term infection but with restricted morbidity. Major consequences of the parasite's adaptations appear to be a trade-off between the ability to establish a persistent infection (especially important for species with long generation times) and a significant restriction in host range. It is interesting to consider the specific role played by helminth–lung interactions in the evolution of human helminthiases.

For nearly a century, the seemingly paradoxical migration behaviours of helminth parasites – such as the enigmatic behaviour of the *Ascaris* larva ending its migratory tissue voyage in the intestine where it began – have bemused scientists. The evolutionary drivers of these complex migration patterns are not well understood. The apparent lack of functional significance for this behaviour has led some to characterize it as meaningless or an evolutionary relic harkening to the demands of an ancestral life cycle. Given our current understating of the mechanisms that govern evolution, the idea that tissue migration can be characterized as inherited behavioural baggage is untenable, as natural selection efficiently purges such unnecessary, hazardous and costly behaviours. It follows that helminths which have evolved migratory behaviour derive a survival benefit. Indeed, Read and Skorping (86) conclude, based on a meta-analysis of studies of developmental outcomes for a wide spectrum of parasitic nematodes of mammals, that migration confers a fitness advantage by significantly enhancing the size of the adults, thus enhancing fecundity (87). Cox (88), based on the observations that an immune response is elicited during tissue traversal, posited that larval migration evolved as a selective force that increased the fitness of both the parasite and the host by preventing overcrowding. It is likely that this migration-coupled enhancement of fitness is the product of a complex evolutionary give-and-take that required multiple adaptations on the part of both the host and the parasite. A major outstanding issue is defining the specific contributions that different components of these migrations, such as targeted interactions with the lungs, plays in promoting fitness.

WHY THE LUNGS?

From the parasite's perspective, it can be hypothesized that the lung may provide a nurturing environment with vital biochemical cues that trigger and/or promote proper development. While this may indeed be the case for some of the human parasites that have evolved Type 1 interactions, data from related animal helminths such as *A. suum* and *N. brasiliensis* indicate that, under the appropriate conditions, development from egg to adult can be accomplished in culture (89–92). The ability of *Strongyloides* to undergo a full life cycle as a free-living organism indicates that not all of the Type 1 species have an absolute requirement for residency in the lungs (13).

The lungs may also provide a protected environment that is important for the survival of vulnerable stages of worm development. The lower respiratory tract, although typically included as a full member of the common mucosal immune system, has immunological qualities that set it apart from other mucosal environments. While the upper airways resemble other mucosal surfaces such as the gut in having a significant population of commensal microorganisms, data show that the microbial bioburden diminishes progressively as one samples down the tracheobronchial tree, suggesting that bronchioles and alveoli could be essentially microbiome free (93). This putative germ-free environment is maintained by physical and chemical aspects of the upper airways including a mucus layer laden with antimicrobial factors that traps microorganisms and a mucociliary escalator mechanism on epithelial cells that transports the microbes away from the lower lung and out of the respiratory environment. In addition, the branching design of the conducting airways and the concentration of chemical barriers, immune cells and lymphoid tissues in the upper airways suggest a defence system that has evolved to anticipate first contact – thus first responses – to pathogens in the upper respiratory environment. The main immune cells found in the lower airways, lung macrophages and dendritic cells, appear to be programmed to maintain homeostasis and limit inflammation [reviewed in (94)]. The capacity to

minimize access of commensal and pathogenic microbes and to regulate inflammation that could result in damage to the delicate alveolar epithelium is essential for maintaining efficient gas exchange. The inherently regulated, microbe-limited environment of the lower lung may be an ideal setting for hookworms, *Strongyloides*, *Ascaris* and *Schistosoma* to initiate development. All of these parasites cause tissue damage as they breach epithelial and endothelial barriers to enter the lung. The lack of a significant microbial presence would minimize the exacerbating effects of exposure to bacterial/fungal antigens that would otherwise contribute to the innate immune responses elicited upon parasite entry. This back door entry into the alveolar environment via the lung's blood vasculature circumvents the innate immune mechanisms of the upper airways, thus providing the worms with a window of opportunity to develop. In this regard, it is interesting to note that, despite their size and complexity, intact helminth parasites appear to produce only a limited number of molecules that can activate known human innate receptors and initiate proinflammatory immune responses (95).

The physiological and fitness consequences of severe and prolonged inflammation in the lungs have required the evolution of a mechanism to strictly regulate these events. The helminth parasites under consideration here induce variants of an immune response that has been termed modified Th2 immunity (to distinguish it from the Th2 immunity classically associated with asthma and allergy) (96). For those helminths that are adept at establishing long-term chronic infections, the modified Th2 response appears to be an adaptive concession that trades limits on parasite burden and pathology for persistent infection. An important facet of helminth-induced modified Th2 responses is the increased production of IL-10 (97–99). A significant percentage of the IL-10 is derived from $CD25^{+}Foxp3^{+}$ regulatory T cells (Treg) (100). Tregs are critical for regulating the intensity and duration of pulmonary inflammation in the context of a variety of both infectious and immunological diseases (101). Results from studies in human and mouse models point to a major role for $CD25^{+}Foxp3^{+}$ Tregs in controlling pathology and immunity during geohelminth infection as well [reviewed in (96, 102)]. While it is clear that Tregs are effectively induced during the intestinal phase of several hookworm-like infections, there are no data on the contribution of the lung-phase response to the generation of Tregs. Given the inherent nature of the immunological environment of the lower lung, it is possible that the Treg response is actually initiated during the transient lung phase of infection so that it can expand and mature rapidly to promote adult survival and fecundity in the gut.

Further, helminth–lung interactions may have evolved as an important barrier for controlling parasite burden, especially in areas with high transmission. For a number of helminth species, initial exposure in the lungs results in an immune response that can provide partial or complete protection against reinfection. Responses directed against larvae result in a state of concomitant immunity in which the host harbours adult worms, but is refractory to subsequent infection. This aspect of the antihelminth adaptive immune response is thought to have evolved to avoid life-threatening parasite loads in high transmission settings. In the rodent hookworm model, the lung is implicated as the priming site for an IL-4-, STAT6- and CD4 T-cell-dependent protective immune response (52). In addition, studies of effector responses against *Ascaris* or *Strongyloides* infection point to a connection between an activation of the pulmonary immune compartment and a reduction in parasite load (103, 104). In schistosomes, activation of T cells in the lungs is critical for the protection induced by exposure to attenuated cercariae (105, 106).

A majority of the studies on innate and adaptive immunity against migrating helminths are designed and interpreted with the presumption that the cellular and humoral responses have the conventional emphasis of damaging, killing and eliminating the pathogen. Recently, with an increasing appreciation that there is considerable overlap between the modified antihelminth Th2 immunity and many aspects of the mechanisms of wound repair (107), it has been suggested that a key aspect of the response induced by helminth parasites may include acute wound healing as a reaction to the damage caused during tissue migration (108–111). This notion builds from the hypothesis that, in the response to persistent pressure from the helminth species that have coevolved with vertebrates, innate and adaptive Th2 responses evolved mechanisms that function in both tissue repair and reconstruction and in the control and expulsion of tissue-dwelling multicellular parasites (107, 108, 112). This idea has important implications for how we view immune responses to migrating helminths because it suggests that the main outcome of Th2-type immunity may not necessarily be to generate sterile immunity. In the context of helminth infections, it may be more fitting to consider modified Th2 immunity as a mechanism that mediates tolerance rather than a means for promoting resistance to challenge (113). This brand of tolerance appears to combine an element of protection, in that parasite loads tend to be limited, with a selective promotion of beneficial aspects of infection. The chronicity of helminth infections in conjunction with certain gene polymorphisms appears to result in an alteration in the immunological set point in mucosal and other tissues where regulatory molecules such as IL-10 and arginase 1 are increased and function to control inflammation that would otherwise cause disease (107). Indeed, the reduction in the incidence and prevalence of helminth infections has been connected with the dramatic increase in

allergic and inflammatory diseases in industrialized societies. Moreover, the severity of several inflammatory diseases, including allergic reactivity, inflammatory bowel disease and type 1 diabetes, is reduced in the context of a helminth infection (50, 114).

CONCLUSIONS

It is likely that during human evolution, helminth infections were omnipresent and exerted persistent selective pressure on the development of the human immune response. An intriguing outcome of this evolutionary give-and-take is the apparent adaptation by humans to exploit certain aspects of the antihelminth response to generate a regulatory network that has utility far beyond controlling the nature and intensity of antiparasite responses. Indeed, there is a growing appreciation that the immune strategies which have evolved over time to control many helminth parasites include a strong regulatory component that can significantly impact the induction and pathogenesis of a spectrum of chronic conditions such as allergic asthma and inflammatory bowel disease. Consistent with this notion that helminth-induced regulatory networks are important is the observation that the near elimination of helminth infections in developed areas coincides with a dramatic increase in the prevalence and intensity of allergic and autoimmune diseases. With this perspective, it is not unreasonable to consider expanding the way we view these multicellular organisms. In addition to playing their roles as parasites, helminths might also function as a macrobiome that influences critical aspects of the homeostatic mechanisms that regulate the immune response.

For lung-helminth interactions, a number of critical questions remain to be resolved. For example, enduring modifications to pulmonary immunity conferred by worm exposure may have important ramifications for the development of appropriate responses to concomitant or future infections with heterologous pathogens such as tuberculosis or influenza. This notion can also be extended to include diseases with genetic, environmental and occupational aetiologies beyond asthma and allergy, such as chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and lung malignancies. To date, human and experimental data relevant to these lung-specific co-morbidities are largely lacking, and assessing the implications of these interactions with helminths remains an important scientific venture. The results of such investigations could be used to inform clinical and public health practice particularly when assessing the indications for the use of antihelminthics.

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