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Immunological underpinnings of *Ascaris* infection, reinfection and co-infection and their associated co-morbidities

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Review

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Abstract

Human ascariasis is the most common and prevalent neglected tropical disease and is estimated that ~819 million people are infected around the globe, accounting for 0.861 million years of disability-adjusted life years in 2017. Even with the existence of highly effective drugs, the constant presence of infective parasite eggs in the environment contribute to a high reinfection rate after treatment. Due to its high prevalence and broad geographic distribution *Ascaris* infection is associated with a variety of co-morbidities and co-infections. Here, we provide data from both experimental models and humans studies that illustrate how complex is the interaction of *Ascaris* with the host immune system, especially, in the context of reinfections, co-infections and associated co-morbidities.

Introduction

Helminth parasites are infectious agents belonging to a diverse group of the phylum Nematoda (roundworms) and the phylum Platyhelminthes (flatworms). Among the nematodes is the group of the soil-transmitted helminths (STH), also known as geohelminths, classified as parasites which are infective agents, including embryonated eggs or larval stages are transmitted to the host by direct contact with the soil through either skin penetration or oral ingestion (Lustigman *et al.*, 2012). The STH, *Ascaris lumbricoides and Ascaris suum, Trichuris trichiura* and both *Necator americanus* and *Ancylostoma duodenale* are the most important etiological agents of the most common intestinal parasitic diseases of developing countries, being part of the neglected tropical diseases (NTD), such as ascariasis, trichuriasis and hookworm infections, respectively (Lustigman *et al.*, 2012). Among them, the most common and prevalent NTD is the human ascariasis caused by *A. lumbricoides* or *A. suum*, by which recent studies estimate that ~819 million people are infected worldwide (Pullan *et al.*, 2014). This high prevalence is associated with poverty and precarious health conditions, mainly in tropical and subtropical areas of developing countries such as sub-Saharan Africa, Southeast Asia and South America (Bethony *et al.*, 2006; WHO, 2015, 2019).

Human ascariasis is transmitted through the faecal–oral route. Infection occurs by ingestion of water or food contaminated with embryonated eggs containing the fully developed L3 larval stages. The eggs hatch in the intestine, and the L3 larvae that pass through the intestinal wall and migrate along the liver and heart, up to the lungs. In the lung tissue followed by the airways passage, the larvae are expectorated and then swallowed, passing through the gastrointestinal tract until they arrive at the small intestine, where they mature into adult worms, which after mating, females release millions of fertilized eggs with the faeces, contaminating the environment (Douvres *et al.*, 1969; WHO, 2011, 2019; CDC, 2019; Conterno *et al.*, 2020).

Clinically, ascariasis can be divided into 2 distinct phases in the human host because of its complex biological life cycle. The initial phase, known as larval or acute ascariasis, is caused by hepato-tracheal migration of the larval forms of the parasite in the first weeks of infection, characterized by a profound inflammatory response in the affected organs, mostly in the lungs, leading to diffuse lung disease as a consequence of the tissue damage provoked by the migrating larval stages (Weatherhead *et al.*, 2020). When the migrating larval stages complete their quest for program development with the maturation into adult worms in the intestine, the second phase of human ascariasis initiates, which is characterized by a chronic and long-term infection (Crompton, 1985).

Although the chronic infection in most cases is associated with light to moderate burden, with nonspecific symptoms, human ascariasis is considered a worldwide public health problem due to the clinical complications observed in individuals with a high parasitic burden. The severe form of the disease is associated with abdominal distension, nausea, diarrhoea and can be fatal due to intestinal obstruction by adult worms (Chan, 1997). Morbidity and mortality increase with the intensity of the disease (de Silva *et al.*, 1997). Moreover, in

moderate infections, ascariasis is correlated with nutritional deficit, growth retardation and cognitive deficit (Dold and Holland, 2011). Considering the limitation of data to quantify the complications of ascariasis, the estimated number of deaths worldwide in 2017 due to human ascariasis was 3206 (Vos *et al.*, 2017), causing a global burden of 0.861 million years of disability-adjusted life years (DALYs) in 2017 (Kyu *et al.*, 2018).

Moreover, due to its high prevalence and wide geographic distribution, a high rate of co-morbidities and co-infections associated with ascariasis is expected. In this review, we will provide insights about the immune response of *Ascaris* infection in the context of reinfection and co-morbidities such as lung fibrosis, allergic diseases, and co-infections.

Reinfections

Developing strategies to control the spread of *Ascaris* is a major challenge. The development of an integrated control strategy, consisting of preventive chemotherapy (PC), combined with health education and environmental sanitation is needed to interrupt transmission of STH (Jia *et al.*, 2012). Even with the existence of highly effective drugs (Keiser and Utzinger, 2008; Jia *et al.*, 2012; Moser *et al.*, 2017), the constant presence of infective parasite eggs in the environment guarantees reinfection months after treatment. Jia *et al.* (2012), in a meta-analysis study, showed that the prevalence of ascariasis tended to regress to the pretreatment levels 12 months post-treatment. On top of that, after decades of scientific discussion, currently, it has been a consensus that *A. suum*, the etiological agent of the swine ascariasis, with a massive cosmopolitan distribution among pigs, are also capable to infect human, causing human ascariasis. Although zoonotic infection is a rare event, *A. suum* infection represents a risk for farmers and farming areas worldwide, creating another obstacle for the control and elimination programs (Nejsum *et al.*, 2005; Thamsborg *et al.*, 2013; Alves *et al.*, 2016).

As an initiative to eliminate morbidities caused by STH infections, especially in children, World Health Organization (WHO) launched in 2012 a strategic plan aimed to increase the coverage of PC from 15 to 75% of school-age children and preschoolers (WHO, 2011). With the impact of increased PC coverage, in 2015 STH control programs prevented the loss of >500 000 DALYs (Kassebaum *et al.*, 2016). Therefore, the existence of a gap between PC and the prevention of reinfections, makes reinfection an extremely important phenomenon for ascariasis.

Despite its epidemiological importance, what is known about acute ascariasis was described based on experimental models, due to the difficulty of an early diagnosis in humans. Thus, in recent decades, a special focus has been given to the long-term ascariasis, with the assessment of immunological aspects of chronically infected individuals from endemic areas (McSharry *et al.*, 1999; Cooper *et al.*, 2000, 2004; Geiger *et al.*, 2002; Jackson *et al.*, 2004). In this way, there are many gaps in the understanding of how initial infection factors (such as larval migration) may influence the development of the immune response and the induction of resistance/susceptibility to infection. Therefore, the understanding of the immunobiological aspects of larval ascariasis in primary infection and reinfection, makes it possible to understand the type of initial immune response necessary for infection control.

The characterization of the mechanisms developed by the parasite to evade the host's immune response contribute to the basic scientific knowledge necessary for the development of more effective immunoprophylactic strategies to interrupt the parasite's transmission cycle before it establishes chronicity in the host.

In this sense, the use of an animal model for the study of larval ascariasis has been shown to be efficient, especially in understanding the mechanisms of the immune response and pathophysiology after multiple exposures (Fig. 1). Initially, with the use of pigs as an experimental model, it was demonstrated that repeated infections with *A. suum* would generate resistance to new infections. This finding was evidenced by the reduction in the number of larvae found at intestinal, hepatic and pulmonary levels after reinfection, and with the reduction in the number of milk-spots in the liver in necropsy (Urban *et al.*, 1988; Eriksen *et al.*, 1992; Nejsum *et al.*, 2009*b*). Afterwards, Eriksen *et al.* (1992) in an elegant paper demonstrated that the protective immune response was dose dependent, with the highest first inoculum leading to a lower final burden after reinfection. In addition, it was verified by analyzing the sizes of the worms in the small intestine, that the adult worms established themselves mainly from the first doses of inoculated eggs, giving rise to a patent infection, while the newly inoculated larvae were less successful (Eriksen *et al.*, 1992; Mejer and Roepstorff, 2006; Nejsum *et al.*, 2009*b*).

The protective phenotype in the reinfection of *A. suum* had been also previously demonstrated by Urban and collaborators in pigs inoculated orally with UV-irradiated eggs, leading to protection against infection (Urban and Tromba, 1984). Such findings also corroborate with studies that demonstrated that previous exposure to other helminths contributed to the reduction of the parasitic burden, of *Strongyloides ratti* (Dawkins and Grove, 1982), of *Neodiplostomum seoulensis* (Yu *et al.*, 1995), *Clonorchis sinensis* (Sohn *et al.*, 2006), *S. stercoralis* (Rotman *et al.*, 1996) and *Trichuris suis* (Nejsum *et al.*, 2009*a*).

The immune pathways responsible for controlling the parasitic burden of *Ascaris* are not fully understood. Prolonged helminth infections have been shown to induce the generation of specific antibodies to the parasite, with a predominance of IgG1 and IgA; on the other hand, recent primary infections generate polyreactive IgG and IgE antibodies (McCoy *et al.*, 2008). And, although it is not clear, the passive transfer of immune serum, or IgG, showed that the humoral immune response plays an important role in resistance to *Ascaris*, contributing to the control of the parasitic burden in animals challenged after the transfer (Khoury *et al.*, 1977; Gazzinelli-Guimarães *et al.*, 2018). Interestingly, it was demonstrated *in vitro* that circulating eosinophils degranulated in direct contact with larvae, in the presence of serum from reinfected animals, which means that specific antibodies and complement components can contribute to protection *via* eosinophils (Masure *et al.*, 2013). In addition to IgG, animals infected with *A. suum* have high levels of specific IgA, which contributes to the control of the weight and size of parasites in the intestinal lumen (Marbella and Gaafar, 1989; Kringel *et al.*, 2015).

Several studies suggested that the immune response triggered in the mucosal tissue contribute to control *Ascaris* larvae migration; with an increase in the number and activation status of eosinophils in lung tissue as well as in the intestine, suggesting an important role of eosinophils in reducing *Ascaris* burden (Masure *et al.*, 2013; Nogueira *et al.*, 2016; Gazzinelli-Guimaraes *et al.*, 2019). Masure *et al.* (2013), demonstrated that recruitment of eosinophils to the caecum of reinfected animals was further supported by increased levels of interleukin-5 (IL-5), interleukin-13 (IL-13), C-C motif chemokine ligand 11 (CCL11) and eosinophil peroxidase transcripts in the cecal mucosa of reinfected swine. In the same work, using a porcine model demonstrated that the reduction in the number of larvae in reinfected animals was associated with eosinophilia, mastocytosis and hyperplasia of goblet cells in the cecum (Masure *et al.*, 2013).

Recently, using the murine model, it has been demonstrated that *A. suum* reinfected mice showed an important and significant reduction in parasitic burden at the pulmonary level (Nogueira *et al.*, 2016), however, reinfected mice have greater tissue damage. After multiple exposures to *A. suum*, Nogueira *et al.* (2016)

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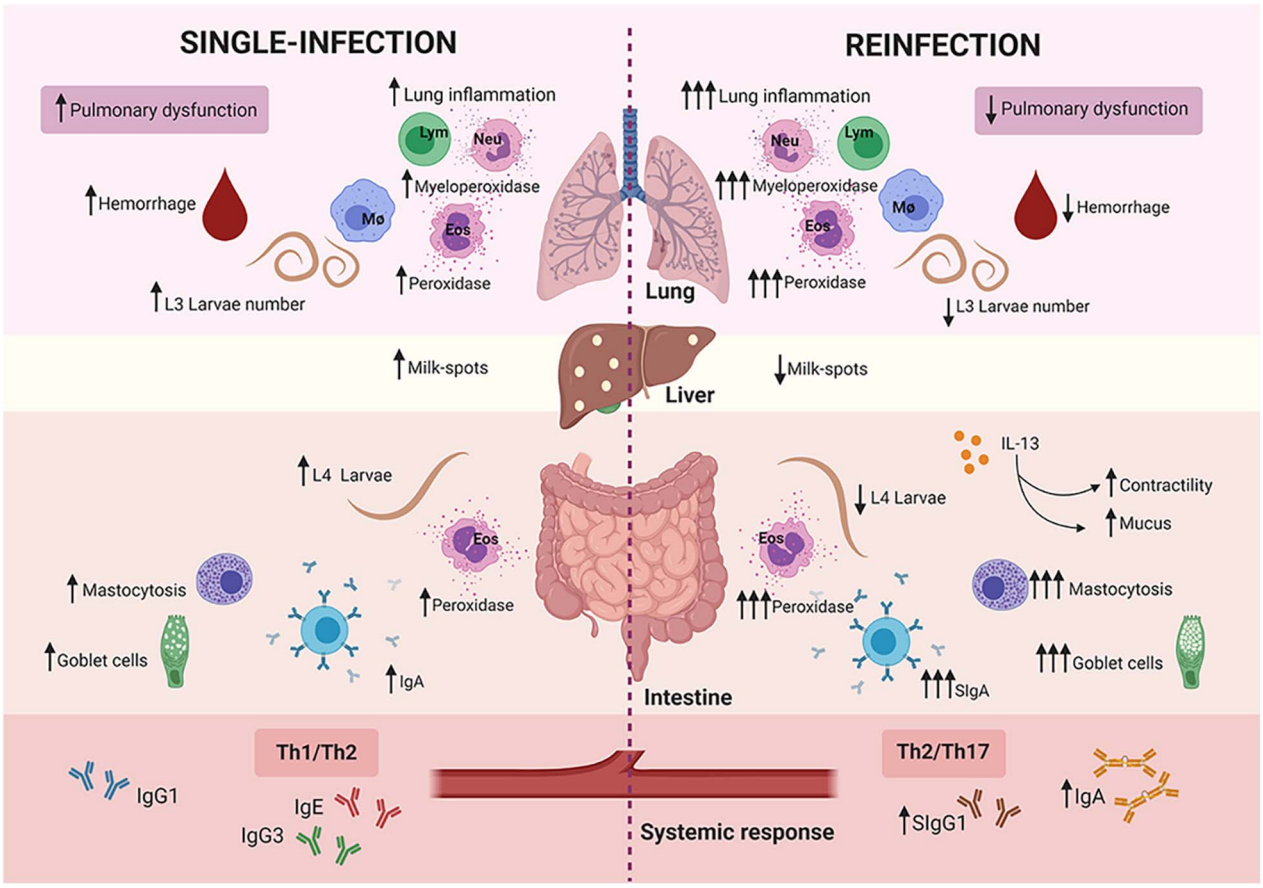

Fig. 1. *Ascaris* reinfection. Figure compiles the data obtained from the different experimental model for 1 or multiple infections with *A. suum*. In the lungs, repeated infection leads to higher lung inflammation and cellularity with increase number and activation status of neutrophils, eosinophils, lymphocytes and macrophages. Nevertheless, reinfected animals display lower larvae burden, less haemorrhage and pulmonary impairment. Necropsy also evidenced a reduction in the number of milk spots in the liver from reinfected animals. In the intestine, reinfected animals show an increase in number and activation status of eosinophils, mastocytes and goblet cells with higher expression of IL-13 that leads to increased contractility and mucus secretion. All those factors culminate with lower L4/young adult's larvae. The prolonged infection has been shown to induce the generation of specific antibodies to the parasite, with a predominance of IgG1 and IgA, while recent primary infection generates polyreactive IgG1, IgG3 and IgE. The cytokine response also differs from single to reinfection models. With a predominance of a Th2/Th17 response in the latter compared to Th1/Th2 phenotype in primo-infected animals.

observed a significant increase in lung tissue and airways cellularity, characterized by an increase in lymphocytes and macrophages, in addition to a marked eosinophilic and neutrophilic inflammation of the lungs. In addition, it was observed that induction of a mixed Th2/Th17 systemic response defined by elevated levels of IL-4, IL-5, IL-10, IL-6, tumor necrosis factor (TNF) and IL-17A compared to single-infected mice. Similar to what was observed in *Toxocara canis* infection (Resende *et al.*, 2015).

The presence of eosinophils can also be implicated in tissue repair and remodelling due to the extensive mechanical injury and haemorrhage associated with larvae migration (Isobe *et al.*, 2012). It was also highlighted that reinfection induced a larger area of lung injury when compared to primary infection, also suggesting that multiple exposures can lead to repeated tissue injury and chronic inflammation (Nogueira *et al.*, 2016). The contribution of the inflammatory response in the control of parasitic burden has been evidenced in models of susceptibility and resistance to single infection by *A. suum* (Lewis *et al.*, 2007; Dold *et al.*, 2010). Hepatic inflammation has been associated with infection control seen in animals resistant to *A. suum* infection (Dold *et al.*, 2010). Pulmonary inflammation, on the other hand, was considered important for the control of *A. suum* infection, but directly associated with tissue repair induced by larval migration (Lewis *et al.*, 2007).

In general, previous studies have shown that the mechanism of protection against helminth reinfection is mediated by an eosinophil dominated-type 2 immune response, and susceptibility is associated with the Th1 immunity (Gause *et al.*, 2003; Hayes *et al.*, 2007). During experimental *Ascaris* reinfection, elevated levels of IL-4 and IL-10 in serum (Nogueira *et al.*, 2016) was also observed. The combination of these 2 cytokines was crucial for the control of the damage caused by *Nippostrongylus brazilien-sis* larvae migration through the host's organs (Chen *et al.*, 2012). However, the findings by Nogueira *et al.* (2016), demonstrated that the protection driven by reinfection was associated with a mixed Th2/Th17 response pattern (). In fact, the increase in IL-17A levels after multiple exposures to *A. suum* may reflect intense and chronic inflammation, analogous to the pulmonary fibrosis model (Wilson *et al.*, 2010).

The pulmonary physiological changes observed in *A. suum* infected mice, such as loss of lung volume, airway flow and elasticity, were observed due to intense parenchymal injury, haemorrhage and edema (Nogueira *et al.*, 2016). After multiple exposures, the persistence of physiological modulation and chronic lung parenchymal injury, associated with intense eosinophilia, were consistent with human ascariasis associated with Loeffler syndrome/eosinophilic pneumonitis (Nutman, 2007; Kunst *et al.*, 2011). Such findings demonstrate that collagen deposition and fibrogenesis is a cumulative effect of larval ascariasis, and together with the persistence of eosinophils in the tissue, those factors can lead to restrictive lung disease. It is worth mentioning, acute injury to the lung parenchyma caused by the migration of the larvae,

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detected mainly in simple infections, and tissue remodelling by fibrogenesis, detected in prolonged simple and multiple infections, can lead to increased pulmonary resistance, and decrease complacence, accentuated in single infected animals (Nogueira, *et al.*, 2016). The fibrogenesis caused due to tissue healing induced by the Th2/Th17 immune response and already proven in the larval ascariasis model (Oliveira *et al.*, 2019).

Ascaris comorbidities

Pulmonary fibrosis

Pulmonary fibrosis is a chronic and progressive lung condition caused by excessive collagen deposition in the lung parenchyma that can severely disrupt lung function and contribute to the development of lethal fibrotic pathology (Wilson and Wynn, 2009; Gause *et al.*, 2013). After acute injury or infection, resolution of inflammation is important to restore normal tissue architecture. However, the healing process can become pathogenic when important checkpoints are missed and chronic inflammation can result in scar tissue formation (Wynn, 2004; Wilson and Wynn, 2009).

Cytokines such as ransforming growth factor beta 1 (TGF-β1), IL-1β, IL-8 and IL-17A have already been recognized and is well characterized as important mediators in the development process of pulmonary fibrosis, inducing fibroblast proliferation and consequent type I collagen deposition (Russo *et al.*, 2009, 2011; Wilson *et al.*, 2010). In addition, contributing to collagen deposition, type 2 responses are linked to fibrogenic processes of tissue regeneration and repair following injury. Several studies have shown the involvement of cytokines IL-4, IL-5 and IL-13 in the resolution of inflammation, with the participation of macrophages, eosinophils, mast cells, basophils, T helper type 2 cells and type 2 innate lymphoid cells. In response to persistent chronic insults and injury, the wound healing process can become pathogenic (Van Dyken and Locksley, 2013; Guo *et al.*, 2015; Minutti *et al.*, 2017; Gieseck *et al.*, 2018). The participation of these cells in type 2 fibrosis defines whether type 2 response results in a beneficial tissue repair or fibrogenic process with associated pathology. ILC2 and Th2 cells promote fibrosis contributing to the local secretion of type 2 cytokines such as IL-4, IL-5 and IL-13, which support cell recruitment and activation. Eosinophils can be important promoters of inflammatory and tissue damage, releasing type 2 cytokines and TGFβ1, a potent profibrotic eosinophil secretory cytokine that stimulates fibroblasts to promote the synthesis and direct deposition of many extracellular matrix proteins (Raghow, 1991; Rosenberg *et al.*, 2013; Aceves, 2014). Alternatively, activated macrophages are substantial to regulate the initiation, maintenance, and resolution of inflammation, contributing to repair the following injury by clearance of matrix and cell debris along with the production of cytokines, growth and angiogenic factors that promote fibroproliferation and angiogenesis (Leibovich and Ross, 1976; Martin and Leibovich, 2005; Gieseck *et al.*, 2018).

Chronic helminth infections are considered potent inducers of type 2 immunity, which is the main protective immune response against helminth parasites, important for worm expulsion and to regulate tissue repair that are frequently related to fibroproliferative response during chronic stages of disease (Van Dyken and Locksley, 2013; Gieseck *et al.*, 2018). Studies have shown that IL-13 is crucial for lung and liver fibrosis induction in schistosomiasis. An IL-13 inhibitor was able to block the development of liver fibrosis in a murine model of schistosomiasis (Chiaramonte *et al.*, 1999). In another study, IL-13 receptor α1 (IL-13Rα1) – deficient mice infected with *Schistosoma mansoni* showed an increased survival rate due to fibrosis suppression (Ramalingam *et al.*, 2008).

Experimental infections by *Ascaris* have contributed to the understanding of the elements involved in the immune response, inflammatory process, and pathogenesis of ascariasis, especially in the acute phase. However, there are few studies investigating the relationship of *Ascaris* sp. infection with the process of developing fibrosis in affected organs after larval migration. Studies reported by our group, as previously mentioned, demonstrate in a murine experimental model that in the larval migration phase, there is a polarization of the immune response in ascariasis, with a mixed profile of Th2/Th17 cytokines (Gazzinelli-Guimarães *et al.*, 2013, 2018; Nogueira *et al.*, 2016; Oliveira *et al.*, 2019). Notably, most of the cytokines present in *Ascaris* infection are known to contribute effectively to the production and deposition of collagen (IL-17A and TGF-β1) (Leask and Abraham, 2004; Wilson *et al.*, 2010; Gieseck *et al.*, 2018) or to have a fibrogenic potential (IL-4, IL-6, IL-13 and IL-33), contributing indirectly for the fibrosis development (Gharaee-Kermani *et al.*, 2001; Saito *et al.*, 2008; Wilson *et al.*, 2010; Gause *et al.*, 2013; Li *et al.*, 2014; Gieseck *et al.*, 2018).

Indeed in *A. suum* infection, it was reported collagen deposition around the lower airways, blood vessels and in the alveolar wall as a result of injuries caused by larval migration, followed by tissue remodelling (Nogueira *et al.*, 2016; Gazzinelli-Guimarães *et al.*, 2018; Oliveira *et al.*, 2019). These findings suggest that ascariasis could predispose or contribute to the worsening of the progressive development of pulmonary fibrosis.

Recently, using the bleomycin experimental model of pulmonary fibrosis (Benítez, 2006; Walters and Kleeberger, 2008; Liu *et al.*, 2017) and Ascariasis (Gazzinelli-Guimarães *et al.*, 2013), our group shed light on the comorbidity environment generated by these 2 pathologies. In this study, it was observed that the co-existence of lung fibrosis and *Ascaris* infection led to the exacerbation of lung damage, evidenced by a loss of pulmonary physiological parameters that were related to the increase in exudative phenomena and haemorrhage induced by larval migration (Oliveira *et al.*, 2019). Although the comorbidity directed the immune response to a profibrogenic profile with increased cytokines IL-1, IL-4, IL-6, IL-13, and IL-33, the study did not observe collagen deposition alteration or change in the levels of IL-17A and TGF-β1 expression. In addition, the previous fibrosis in the pulmonary parenchyma, around airways, blood vessels and thickening of alveolar septa, did not impair the larval migration, which was carried out in preserved areas of the lung parenchyma (Fig. 2). (Oliveira *et al.*, 2019). There is a clear need for further studies addressing comorbidities produced by helminth infections and pulmonary fibrosis, considering different association times to elucidate and a better understanding of immunopathological changes, which directly affect the progression of the diseases involved.

Pulmonary allergic inflammation

The comorbidities associated with Ascariasis and other helminth infections can be triggered by 2 important features of their parasites' biologies, including the progressive larval development in the host – characterized by a transient larval migration through organs and tissues – and their molecular and structural similarities with other pathogens or agents, including common environmental allergens. Over the years, many studies have examined the interface between allergic diseases and helminth infections (Van Den Biggelaar *et al.*, 2001; Daniłowicz-Luebert *et al.*, 2011; Gazzinelli-Guimarães *et al.*, 2016). These largely immunoepidemiologic studies associate chronic helminth infections with the modulation of allergic responses through the induction of IL-10, expansion of regulatory T cells, and blockade of IgG4 antibodies (Van Den Biggelaar *et al.*, 2000; Satoguina *et al.*, 2005;

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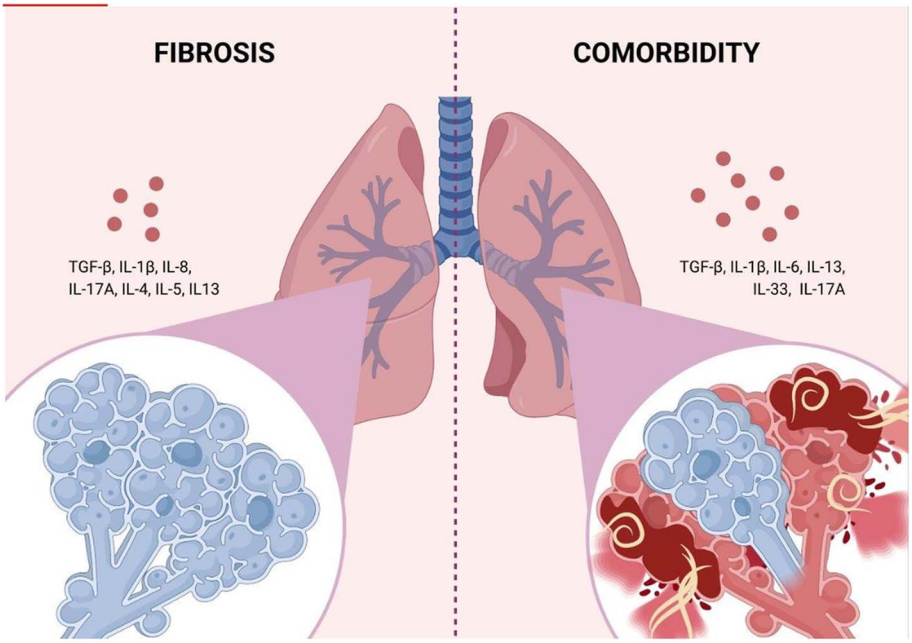

Fig. 2. Pulmonary fibrosis. The association of previous pulmonary fibrosis and *A. suum* infection increases lung damage, characterized by an increase in exudative phenomena and haemorrhage induced by larval migration. The presence of *A. suum* in pulmonary parenchyma that already present fibrosis increased the expression of IL-1, IL-4, IL-6, IL-13, IL-17A, IL-33 and TGF-β1 cytokines. Despite the increase in the expression of cytokines with a profibrogenic profile during comorbidity, this did not contribute to the worsening of lung fibrosis. Larval migration is not impaired by pulmonary fibrosis. The success of the loss cycle in comorbidity occurs due to *A. suum* larvae migration non-fibrous areas in the lung parenchyma.

Yazdanbakhsh and Wahyuni, 2005). On the other hand, there are studies in humans and in experimental models which demonstrate that helminth infections are associated with increased allergenicity. Notably, the allergy-like reactions and syndromes seen in helminth-infected patients (e.g. urticaria in *Strongyloides* infection (Zubrinich *et al.*, 2019); angioedema and tropical pulmonary eosinophilia in filarial infections (Van Dellen, 1985; Ottesen and Nutman, 1992; Rakita *et al.*, 1993); atopic dermatitis and asthma-like syndrome in ascariasis (Caraballo *et al.*, 2015; Qualizza *et al.*, 2018); and swimmer's itch in schistosomiasis (Kolářová *et al.*, 1999)) have been associated with the acute stages of the infections. These allergic-type inflammatory responses are normally a consequence of the helminth-driven, dominant type-2 immune response orchestrated by the host as an attempt to kill or expel these early stages of parasites (Cruz *et al.*, 2017). Notably, *A. lumbricoides* infection has been implicated in inducing asthma and wheezing (Leonardi-Bee *et al.*, 2006), while other murine studies have indicated that the pre-sensitization to *Ascaris* antigens triggers mite-specific IgE responses upon subsequent mite antigen inhalation (Suzuki *et al.*, 2016).

Ascaris parasites have transient life cycles in which migration through the lung tissue is a necessary step for development in the host. The migrating lung-stage larvae lead to diffuse lung infiltrates (Gazzinelli-Guimarães *et al.*, 2013; Weatherhead *et al.*, 2020) and eosinophilic pneumonia, termed Löeffler's Syndrome (Gelpi and Mustafa, 1968).Gazzinelli-Guimaraes *et al.* (2019) demonstrated by using a controlled model of multiple timepoints of early *Ascaris* infection that in primary exposure to *Ascaris*, the L3-stage larvae migrate to the lung parenchyma in their quest to reach the airways, leading to a marked influx of neutrophils and associated levels of IL-6, and penetrate into the alveolar spaces, causing bleeding and mechanical damage in the organ. These migrating *Ascaris* larvae, while growing in size towards the L4 stage of development (Douvres *et al.*, 1969), induce a tissue inflammatory type 2 immune response in the lungs characterized by increased IL-5 levels followed by the production of IL-4 and IL-13, culminating in the differentiation of M2 macrophages and eosinophilia in the tissue. Very similar to a severe allergic airway disease, this diffuse lung inflammation induced by *Ascaris* infection is characterized by an eosinophil-dominated type-2 immune response and manifests clinically as coughing, wheezing and in severe cases, respiratory failure (Aleksandra *et al.*, 2016). Notwithstanding, Weatherhead *et al.* (2018) using a murine model, demonstrated that *Ascaris* larval migration in the lung tissue induces significant pulmonary damage, including airway hyperresponsiveness and type 2 inflammatory lung pathology resembling an extreme form of allergic airway disease. These authors and others, given similar clinical features, support the idea that ascariasis may be an important cause of allergic airway disease in regions of high endemicity. Moreover, immunoepidemiologic studies suggest that children with *Ascaris*-induced allergic airway disease have increased cross-reactivity to bystander antigens such as house dust mites (HDM) (Acevedo and Caraballo, 2011).

Many studies have shown that helminth infection promotes type 2-associated immune polarization that converges into IgE antibody production (Jarrett and Bazin, 1974; Urban, 1982). As a result of the structural similarities of helminth and common allergen B-cell epitopes, helminth antigens eventually drive allergen-specific cross-reactive IgE antibodies (Sereda *et al.*, 2008; Acevedo *et al.*, 2009; da Costa Santiago and Nutman, 2016). Indeed, it has been shown that the allergic sensitization with environmental common allergens, including HDM, drives cross-reactive immune responses to homologous helminth proteins (Santiago *et al.*, 2011; Da Costa Santiago *et al.*, 2015). Several molecules from common aeroallergens, including those from the dust mites *Dermatophagoides pteronyssinus* (Der p 1, Der p 8 and Der p 10) have been characterized as having significant IgE cross-reactivity with helminth proteins from a variety of parasites including *Ascaris* (Santos *et al.*, 2008; Acevedo *et al.*, 2009; Santiago *et al.*, 2011). A recent study investigating the interface between *Ascaris* infection and pulmonary allergic inflammation induced by HDM identified the *Ascaris* larval antigens recognized by HDM-specific antibodies as *Ascaris* tropomyosin and enolase based on high sequence and structural similarity to HDM homologs (Gazzinelli-Guimarães *et al.*, 2021). In this study, it was shown that HDM-triggered IgE cross-reactive antibodies were functional as they mediated hypersensitivity responses in skin testing. Moreover, helminth tropomyosin was capable of inducing a severe type-2-associated pulmonary inflammation following sensitization with the homologous HDM

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tropomyosin (Der p 10), indicating a potential mechanism to understand how helminth infections induce or exacerbate allergic inflammation.

The immunobiology of *Ascaris* co-infections

Individuals are continuously exposed to multiple pathogens with co-infections being extremely likely during life. Nevertheless, there is still poor knowledge about how combinations of co-infections may impact our immune response and can influence disease outcomes. Generally, in infections that affect humans, the prevalence of parasites in each region depends not only on the climate or the presence of susceptible hosts but also on the social, political and economic conditions of the population that can favour the spread and perpetuation of diseases. That explains how certain regions tend to be more affected by parasites (Murray *et al.*, 2015; Osakunor *et al.*, 2018).

Therefore, there are several studies that aim to evaluate the mechanisms of interaction among different pathogens and their implication in the outcome of diseases (Salgame *et al.*, 2013). However, it is worth mentioning the importance of helminth infections, in the context of coinfections, since helminth infections are present in all tropical regions of the planet, and may influence the course, diagnosis, and treatment of various infections by different pathogens. As mentioned before, among the NTDs commonly encountered, ascariasis is by far the most prevalent (Bethony *et al.*, 2006; Brooker, 2010).

Since helminths stimulate Th2 type of response, many researchers have focused on the investigation of the relationship between helminths and pathogens that require a Th1 immune response, such as Mycobacterium tuberculosis (MTB). Helminth infections appear to indirectly affect the diagnosis of tuberculosis by modulating the immune response of MTB antigens (Babu and Nutman, 2016). In South Africa, children with IgE antibodies against *Ascaris* are less likely to mount a positive response to the tuberculin skin test (Gebreegziabiher *et al.*, 2014).

Patients with tuberculosis and infected with *S. mansoni* had lower sputum bacterial loads (Mhimbira *et al.*, 2017). In agreement with this, *Mycobacterium bovis* bacterial loads are also decreased in cattle co-infected with *Fasciola hepatica* (Garza-Cuartero *et al.*, 2016). A study with Brazilian patients showed that coinfection with *Ascaris* and MTB does not alter the clinical evolution of pulmonary tuberculosis, though it may influence the severity of pulmonary lesions. The coinfection also did not influence the Th1, Th2 and Th17 responses or the percentage of innate and adaptative cell subpopulations (Santos *et al.*, 2019). In a recent article, the exposure to *A. lumbricoides* proteins induced an enhanced capacity to control MTB growth in human monocyte-derived macrophages but the minimal effect in human PBMCs (Togarsimalemath *et al.*, 2020).

Another well-studied interaction is the co-infection between *Ascaris* and *Plasmodium*. Literature suggests that there is a biological association between *Plasmodium* and helminths when they coexist in a host (Mwangi *et al.*, 2006; Nacher, 2011; Degarege and Erko, 2016). Studies as early as 1978 indicated that anti-helminth treatment of ascariasis in a high-transmission area was followed by an increase in symptomatic malaria (Murray *et al.*, 1978; Spiegel *et al.*, 2003). Conversely, other studies showed a beneficial effect in co-infections between helminths and *Plasmodium* (Tshikuka *et al.*, 1996; Nacher *et al.*, 2002; Lyke *et al.*, 2006). *Ascaris* infection has been associated with protection from cerebral malaria in Thailand (Nacher *et al.*, 2000) and with the occurrence of severe malaria attack in a case-control study in Senegal (Le Hesran *et al.*, 2004). It was suggested that helminth infection might reduce the number and frequency of mature schizonts and therefore reducing severe malaria, although the mechanisms are yet not understood (Nacher *et al.*, 2001). A randomized controlled trial was performed in Madagascar. The study showed a negative interaction between *Ascaris* and *Plasmodium* in children older than 5 years of age, with an increase in *Plasmodium* density after anti-helminthic treatment (Brutus *et al.*, 2006). Of note, although *Ascaris* and *Plasmodium* were the predominant parasites, the presence of other helminths such as *S. mansoni* or hookworms may have interfered in the results observed.

Another possible consequence of the immune alterations driven by helminth infection is based on the impact of vaccines. The protective efficacy of BCG against pulmonary tuberculosis presents great variation around the globe, ranging from 80% in the United Kingdom to 0–50% in countries where helminths are often endemic (Roy *et al.*, 2014). The lower cellular immune response against MTB antigens in individuals co-infected with helminths, together with the skew to a Th2 phenotype may explain, at least in parts, the effect of helminth infection on BCG efficacy (Elias *et al.*, 2001, 2008). A similar effect could play a role in a malaria vaccine, by affecting the induction of an efficient Th1 immune response (Hartgers and Yazdanbakhsh, 2006). Recently, using a model of *Litomosoides sigmodontis*-infected mice it was demonstrated that concurrent helminth infection reduces the efficacy of vaccination against seasonal influenza and H1N1 influenza A virus. Importantly, the impaired response was also observed after helminth clearance. The suppression of vaccination efficacy was mediated by sustained IL-10 levels and abrogated by IL-10 receptor blockade (Hartmann *et al.*, 2019). In a similar way, *A. suum* infection negatively affected the protection after *Mycoplasma hyopneumoniae* in pigs. Infected animals display a higher percentage of lung pathology after challenge and lower sero-conversion after vaccination. The effect was mediated by a skewed Th2 response induced by *A. suum* infection (Steenhard *et al.*, 2009).

In addition to MTB and malaria, it has been hypothesized that helminth infections may increase susceptibility to the human immunodeficiency virus (HIV). Infection with *Ascaris*, *S. mansoni* and *Trichuris* were linked to increased frequencies of activated HLA-DR + T cells and a potential higher risk of HIV-1 transmission in patients from Tanzania (Chachage *et al.*, 2014). HIV + patients with high *Ascaris* IgE display high viral loads and lower CD4 + counts compared with the HIV negative group in South Africa (Mkhize-Kwitshana *et al.*, 2011). Furthermore, a randomized, double blind, placebo-controlled trial conducted in Kenya showed that treatment of *A. lumbricoides* with albendazole in HIV co-infected adults resulted in significantly increased CD4 counts and may potentially reduce plasma HIV-1 RNA viral load (Walson *et al.*, 2008). Similar results were obtained in *Ascaris*/HIV co-infected patients from Southern Ethiopia (Abossie and Petros, 2015). Albendazole treatment in co-infected patients was associated with decrease IL-10 plasma levels (Blish *et al.*, 2010). In another study, egg excretion and/or *Ascaris* specific IgE was associated with lower proliferative capacity and reduced Th1 cytokines in HIV-1 + patients (Mkhize-Kwitshana *et al.*, 2014). Although promising, more studies are needed to better clarify the importance of deworming in HIV progression. Our group has demonstrated that concomitant infection with *Ascaris* and Vaccinia virus (VACV) in experimental model induces a reduction in interferon gamma (INFγ) produced by CD4 + T cells and a robust pulmonary inflammation that were associated with increased morbidity/mortality in the coinfected compared to single infected mice (Gazzinelli-Guimarães *et al.*, 2017).

To better understand how *Ascaris* and other helminth infection may influence the course of a concurrent viral infection, and the mechanisms of immunoregulation present during co-infection is an important field that needs further investigation. Indeed, it is possible that larvae migration, as well as, immune modulation during *Ascaris* infection may influence the clinical

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outcome of COVID-19. Indeed, very recently papers have attempted to argue if helminth SARS CoV-2 coinfection would be beneficial or detrimental to the host. Bradbury *et al.* (2020) suggested that immune modulation by helminths could reduce the resistance to SARS CoV-2 infection. Nonetheless, Hays *et al.* (2020) argue that the Th2 immunomodulation observed during helminth infection may have a mitigating effect. Indeed, Fonte *et al.* (2020) point out that the great variability in COVID-19 lethality rate between countries and regions might be related to helminth prevalence, particularly the low COVID-19 lethality in Sub-Saharan Africa. It is important to note that, as described earlier, the immune modulation driven by helminth infection could also interfere with the efficacy of a SARS CoV-2 vaccine. In agreement with others, we do believe that it is key to investigate the influence of helminth co-infection on COVID-19 outcome and vaccine efficacy.

Conclusion

Animals and humans are continuously exposed to different pathogens. A better understanding of how different pathogens interact in the same host, as well as how chronic infection may impact the response to injuries and immunological challenges is crucial. Increasing data indicate that *Ascaris* infection consequences are beyond ascariasis and may influence the clinical outcome of a variety of conditions. Conflicting results and conclusions from different studies illustrate that there are still many unknown factors involved, and this is a promising field with a complexity of factors.

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