Review article

Reflections upon immunological mechanisms involved in fertility, pregnancy and parasite infections

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A B S T R A C T

During a pregnancy, the mother accepts her semi-allogeneic fetus with no signs of immunological rejection. Therefore, some modulation of the maternal immune system must occur. Similarly, changes in the host's immune system occurs during infections with parasites. In a study conducted in an endemic area in Bolivia, it has been reported that women infected with either the helminthic parasite roundworm or hookworm were estimated to give birth to either two more, or three fewer, children than uninfected, endemic women, respectively. Immune regulation by helminthic parasites is a rather well-researched concept, but there are few reports on the effects on human fecundity. The current review focuses on mechanisms of possible importance for especially the increased fertility rates in women infected with roundworm. The host immune response to roundworm has been hypothesized to be more favourable for a successful pregnancy because it bears resemblance to the anti-inflammatory immunological responses observed in pregnancy, steering the immunological response away from a pro-inflammatory state that seem to suppress fecundity. Further research into parasitic worm interactions, fertility, and the molecular mechanisms that they unfold may widen our understanding of the immunomodulatory pathways in both helminthic infections and in fertility and pregnancy.

1. Introduction

The immunological network is a fascinating and complex system of organized effector cells and molecules that together protect the human organism against infections, toxic substances and malfunctioning cells. Despite the complexity, an immune response often follow conserved pathways, of which Th1 and Th2 responses are well described. Although variation in details do exist, the division of the immune response into such more general response pathways seems common regardless of the initial cause of immune activation.

The immune system of the mother must play dual roles by keeping up the immune defences to protect the mother and fetus from infections, while simultaneously tolerating implantation and growth of the fetus expressing immunogenic allo-antigens inherited from the father during pregnancy (Dahl and Hviid, 2012; Munoz-Suano et al., 2011). Fetus and parasite alike, depends upon its host to survive. The maintenance of pregnancy requires establishment of temporal immunological tolerance throughout the pregnancy, involving the suppression of effector functions and induction of tolerance, originally

described as a Th2 skewing (Chavan et al., 2017; Gleicher et al., 2017; Lin et al., 2016; Mor et al., 2011; Wegmann et al., 1993) (Fig. 1).

Globally, approximately 1.5 billion citizens, corresponding to 24% of the world's population are infected with soil-transmitted helminths, commonly known as parasitic worms (WHO, 2018, 2016). In general, helminth infections are often asymptomatic and rarely fatal. Infections are, however, chronic in nature and can lead to significant morbidity as they contribute to malnutrition. As seen during pregnancy, helminths have been shown to induce type 2 immunity in its host and to downregulate host immunity, protecting themselves from elimination and minimizing severe pathology in the host during long-term and chronic infections (Jackson et al., 2008; Johnston et al., 2014; Maizels et al., 2004; Maizels and McSorley, 2016; van Riet et al., 2007). As such, they can be considered as successful xenotransplants in the human body (Johnston et al., 2014; Maizels and McSorley, 2016).

This review will focus on highlighting some of the shared immunomodulating mechanisms in helminth infections and pregnancy. More specifically, we will try to shed some light on the immunological mechanisms exerted in hookworm and roundworm infections with

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Ascaris lumbricoides
Mechanisms of immune regulation:
- Studies show highly polarized Th2-type cytokine responses hypothesized to promote protective immunity
- IgE-production, mast cell activation and mucus secretion
- One study has reported reduced cellular reactivity and reduced Th1-type responses (TNF-α, IFN-γ, IL-12) reflecting a down-regulation of inflammatory responses. Such a mechanism might support parasite survival in the host

Necator americanus
Mechanisms of immune regulation:
- Studies of cytokine levels show conflicting results but overall a mixed Th1/Th2 response cuntering parasitic infection
- Increased levels of parasite-specific and total IgE together with eosinophilia, systemic and in the lungs
- Haemoglobinases enable degradation of human haemoglobin for use as an essential nutritional source

The placenta as an immunological contact zone

Mechanisms of immune regulation during pregnancy:
- Closely regulated expression of HLA/MHC molecules
- Initial inflammatory state at implantation and in early pregnancy; later in pregnancy Th2-type response
- Uterine NK cells – a distinct type of NK cells
- Special subtypes of regulatory T cells
- Complement regulatory proteins expressed on the trophoblast
- Apoptosis of potentially harmful effector T cells
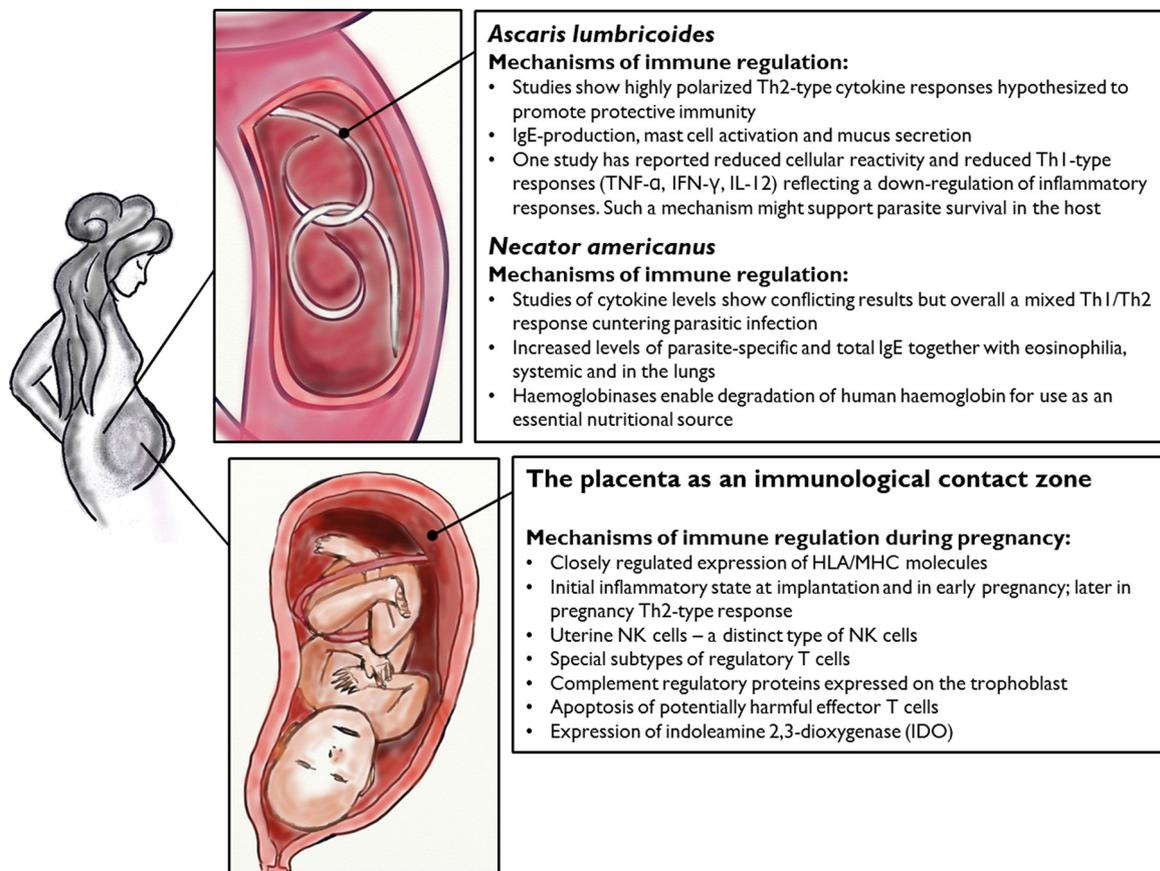- Expression of indoleamine 2,3-dioxygenase (IDO)

Fig. 1. Schematic representation of immune evasion strategies of hookworm and roundworm in the human host and the maternal immune system during pregnancy. The maternal immune system needs to maintain immune reactivity to invading pathogens while simultaneously tolerating paternal allo-antigens on the semi-allogeneic fetus. This balancing act requires several regulatory immunological mechanisms besides the carefully regulated milieu in and around the placenta that also aids in establishing the maternal tolerance towards the fetus.

particular emphasis on the regulatory immune cell responses and induction of tolerance. Interestingly, changes in fertility and fecundity in a population of Bolivian women following helminth infection have been observed by Blackwell et al. (2015). Infection with intestinal helminths might increase fecundity due to the associated immunological changes, resembling those occurring during a successful pregnancy. Application of this knowledge of immunomodulation to the existing field of reproductive immunology might be important in a broadening of our current knowledge of immunomodulation in pregnancy as well as in parasite infections.

2. The immunological paradox of pregnancy in relation to parasites

2.1. A potential role of parasites and helminth infections in human fertility

Our current knowledge of how different adaptive immune responses evolved in order to interact with and thereby protect the body from various external and internal attacks is in its broadest sense based on the recognition of a foreign entity, something that is not *us*. The reaction to foreign tissue will be carried out by a coalition of antigen-presenting and –recognising immune molecules ultimately leading to either the destruction or inactivation of the antigen. In the case of reproduction, where one of the greatest enigmas is when a mother accepts her semi-allogeneic fetus without causing immunological rejection, evidently some modulation of the maternal immune system must occur. The fetus equates to a 'foreign' tissue that is grafted and tolerated, despite the fact that the fetus carries paternal major histocompatibility complex (MHC) molecules, in humans designated human

leukocyte antigens (HLA), and minor histocompatibility antigens.

Several mechanisms have been identified and appear to play a protective role in the acceptance of the fetus. On one hand, the maternal immune system must tolerate implantation of partly foreign, allogenic fetal cells, while simultaneously on the other hand limit disproportionate spread of invading fetal trophoblast cells into the maternal tissue, and actively prevent infections that could harm both mother and fetus. Likewise, improper immune regulation has been linked to recurrent abortions, recurrent implantation failures and preeclampsia (Dahl and Hviid, 2012; Hviid, 2006; Redman and Sargent, 2005).

Along with this delicate balance between tolerance and attack orchestrated by the maternal immune system during pregnancy, some parasites can directly affect human reproduction by e.g. infecting the reproductive organs, affecting the genital immune response, or the fetus (Crespillo-Andujar et al., 2017; Leutscher et al., 2005; Mahande and Mahande, 2016; Pellati et al., 2008). It is important to stress that parasitic infections is not without a cost to the pregnant female and her offspring. Helminth infection can negatively affect pregnancy and nursing by a diversion of energy and resources from gestation and lactation towards immune defense mechanisms, thus constraining reproductive success. Moreover, maternal infection might alter the health and immunity of the child through transfer of parasitic antigens and immune effector molecules such as antibodies and cytokines *in utero* and by breastfeeding. The consequences for the child includes altered defense against both related and unrelated infections, altered response to vaccination and modified risk for allergy and eczema (reviewed by Dewals et al., 2018). However, alterations in the host's immune response during infection might also play a role for reproductive success.

This could explain the results of a recent and very interesting study of women living in Bolivia that found that different species of helminth infections were associated with contrasting effects on fecundity of the women (Blackwell et al., 2015). The authors took advantage of nine years of longitudinal data on Bolivian forager-horticulturalists, the Tsimane people, experiencing natural fertility and a helminth prevalence as high as 70%. After correcting for likely confounding effects that could influence fecundity, they showed that women infected with the roundworm *Ascaris lumbriocoides* achieved pregnancy for the first time at an earlier age and showed significantly increased chances for pregnancy under the age of 32 years compared with non-infected women (hazard ratio (HR) = 3.06; confidence interval (CI): 1.91–4.91; $P < 0.001$). Moreover, seen across the life span of the women, an infected woman was expected to give birth to two more children than women, who were never infected. In contrast, infection with the hookworm (*Ancylostoma duodenale* or *Necator americanus*) was significantly associated with a delay in first pregnancy (HR = 0.33; CI: 0.20-0.54; $P < 0.001$), a reduced chance of subsequent pregnancy at all ages (HR = 0.71; CI: 0.58-0.86; $P < 0.001$), and the women could expect to give birth to three fewer children across the life span compared with uninfected women.

These results clearly indicate that parasitic infections have the potential of influencing natural fertility. Blackwell et al. hypothesized that in the various ways infection with *Ascaris lumbricoides* bears resemblance to the immune state during pregnancy as opposed to inflammatory states, potentially mediated by hookworm infection that might hinder fertility, this might also be the mechanisms behind the observed increase in fecundity. It can be speculated that when the female body inhabits an *Ascaris lumbricoides* infection, the following immune response might simply turn the immunological environment surrounding the uterus into a more advantageous milieu for implantation of the embryo. Confirming this theory, a study investigating the immune response in *Schistosoma mansoni* infected BALB/c mice, indicates that the effect on fertility is dependent on the phase of the infection (Straubinger et al., 2014). As will be discussed in the next section, the immune response towards helminth infections is dynamic going from a Th1 response towards a Th2 response until a regulatory environment is established during chronic infection. Interestingly, the authors found that pregnancy rates in female mice mated during the initial Th1 phase of infection was significantly lower than the pregnancy rates of both un-infected mice and mice mated during the Th2 or regulatory phase. Thus indicating that not only the species of helminth but also the phase of infection might have an impact on fecundity.

2.2. Dynamics of Th1, Th2, and regulatory responses during pregnancy and parasite infection

The placenta is comprised of cells of maternal as well as fetal origin; maternal decidual cells and immune cells, and fetal trophoblast cells. Development of the placenta is critically dependent on the ability of the invading trophoblast cells to interact with cells of the maternal immune system to induce tolerance and protect the fetus from maternal immune attacks. A variety of immune cells are found in the decidua in the feto-maternal interphase, including natural killer (NK) cells, T cells, and dendritic cells (Liu et al., 2017; Munoz-Suano et al., 2011). All contributing to the establishment of a suitable environment for placental and fetal development (Fu et al., 2013; Liu et al., 2017; Munoz-Suano et al., 2011).

While early studies point towards an immune response during pregnancy skewed towards Th2 immunity with increased numbers of Th2 cells and cytokines in the early decidua (Piccinni et al., 1998; Tsuda et al., 2001), others have not been able to confirm these findings (Mjösberg et al., 2010). The Th1/Th2 paradigm has therefore been widened to comprise Th1, Th2, Th17 and regulatory T cells as important players in maintaining fetal tolerance (Saito et al., 2010). Moreover, during recent years several authors have argued that the

immunological environment shifts during pregnancy. It has been proposed that a Th1 inflammation-like condition is required for proper implantation early in pregnancy, shifting towards a state of temporal Th2-skewed immune-tolerance for maintenance of pregnancy mostly during the second trimester, followed by a second shift in immune response towards yet another phase of inflammation during parturition (Chavan et al., 2017; Mor et al., 2011).

Similar dynamics of the immune response have been observed in helminth infections, in which immune regulation vary over the life cycle of the parasite with phases resembling those occurring during implantation, maintenance of pregnancy and parturition. Early stages of infection, including those comprising the larvae and filarial form of the parasite, as well as clearance of infection, seems to be associated with activation of a Th1 response (Lawrence et al., 1994; Terrazas et al., 1998), and immune responses to the adult worm during chronic infection is dominated by a Th2-like response and the selective loss of effector T cell activity, against a background of regulatory T cells, alternatively activated macrophages and Th2-inducing dendritic cells (Maizels et al., 2004). Mice splenocytes isolated at different time points after infection of BALB/c mice with *S. mansoni*, and stimulated with soluble egg antigen (SEA) showed that the first weeks of infection were characterized by a Th1 dominant response with low levels of IL-4, IL-5 and IL-10, and high levels of IFN-γ. This initial response was followed by a Th2 dominant response with decreased levels of IFN-γ and increased levels of both IL-4 and IL-5. Sixteen weeks post infection this developed into a regulatory response characterized by low levels of IFN-γ, IL-4 and IL-5 and high levels of IL-10 that could be detected until 29th week post infection (Straubinger et al., 2014). Although, different helminth parasites display a wide variation in life cycles and host niches, the outcome, i.e. the induction of Th2 response, is often commonly conserved; this indicates that establishment of an anti-inflammatory milieu indeed provides more favourable living conditions and ultimately secure the survival of the parasite. It has been argued, on the other hand, that creating a tolerogenic environment might also be beneficial to the host as it protects the host against the deleterious effects of an otherwise chronic inflammatory environment, and in doing so, aids in dampening responses to unrelated immunological diseases including allergy and autoimmunity as well as enhancing allograft tolerance (Johnston et al., 2014; McSorley and Maizels, 2012). Consequently, strict immune regulation during helminth infections might have been established as a consequence of reciprocal co-adaption during evolution (Jackson et al., 2008).

This review will mainly focus on the induced tolerogenic responses during pregnancy and long-term or chronic parasite infections.

3. Immunobiology of pregnancy and of parasite infections

Although being associated with abnormal immune regulation, including increased Th1 and Th17 responses, fertility and pregnancy complications such as implantation failure, recurrent spontaneous abortion and preeclampsia are poorly defined clinical conditions due to a limited understanding of the underlying pathogenesis (Gleicher et al., 2017). While many have drawn parallels to immune regulatory pathways in autoimmune disease, cancer and transplantation, few have studied the effect of helminthic immunomodulation in relation to the potential role for human fecundity. Immune regulation by invading helminthic parasites is a rather well-researched area that includes the conquering and turning of the host immune response to the benefit of the invading parasite (Maizels et al., 2004). Importantly, in most individuals long-term helminth infections are asymptomatic with increased immune Th2 and regulatory responses, suggesting that the helminth employ immunomodulatory mechanisms ensuring their survival and chronic existence. In contrast, cases with pathology have a low number of Tregs, and a string Th1 and Th17 response (McSorley and Maizels, 2012), thus resembling the scenario seen for pregnancy complications (Fig. 2).
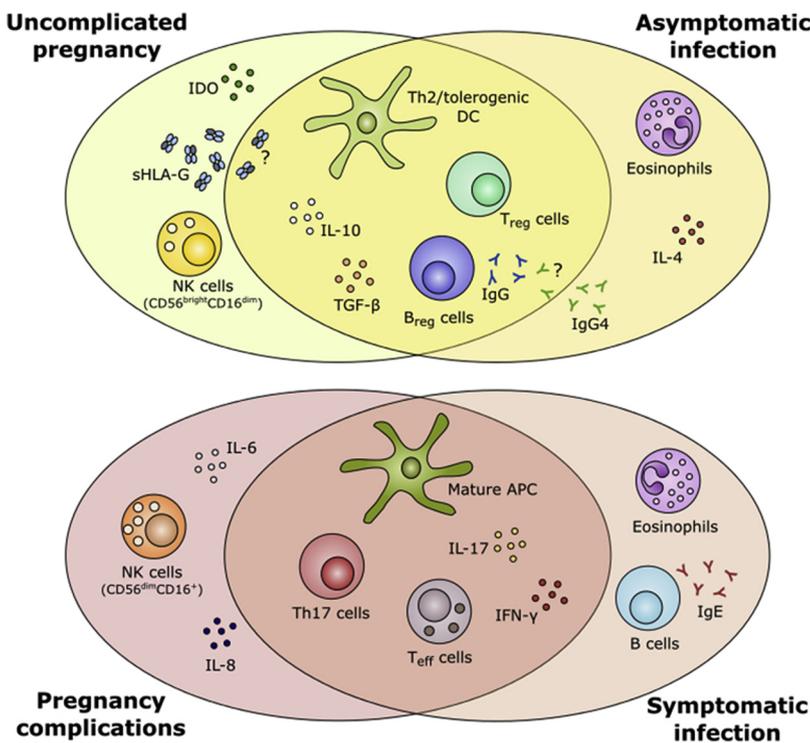
Fig. 2. Similarities and differences in asymptomatic and symptomatic helminth infection and uncomplicated pregnancy and in pregnancy complications. An uncomplicated pregnancy is characterized by a tolerogenic milieu, including Th2-skewed/tolerogenic dendritic cells (DC), regulatory T cell (Treg) and B (Breg) cells, decidual CD56^{bright}CD16^{dim} NK cells, and secretion of soluble tolerogenic molecules such as indole-2,3-dioxygenase (IDO), soluble (s)HLA-G, IL-10, TGF-β and antibodies. Many asymptomatic helminth infections share many of the features observed in pregnancy, but are also characterized by increased numbers of eosinophils, IL-4 and IgG4. In contrast, pregnancy complications and symptomatic helminth infections are characterized by increased effector T cells (Teff), Th17 cells, mature antigen presenting cells (APC) and secretion of IL-17 and IFN-γ. In addition, increased levels of cytotoxic CD56^{dim}CD16^{+} NK cells, IL-6 and IL-8 are observed in pregnancy complications, while eosinophilia and increased secretion of IgE is observed in symptomatic helminth infections. See text for references.

Below, the immunomodulation during pregnancy and in parasitic infections, with special attention directed towards roundworm infection (*Ascaris*) and hookworm infection (*Ancylostoma duodenale* and *Necator americanus*) will be discussed in an attempt to demonstrate similarities that could explain the results obtained by Blackwell et al. (2015). Immune regulation by other helminth species will only be included, when information about the aforementioned species is scares or when it is relevant.

3.1. Expression of immunomodulatory molecules by fetal trophoblast cells and parasites

The maternal and host immune cells interact with a number of immunomodulatory molecules expressed and secreted by both the fetal trophoblast cells and parasites, some of which will be highlighted below.

Trophoblast cells strictly regulate their expression of HLA/MHC genes so that the highly polymorphic HLA/MHC class Ia antigens, HLA-A and -B, are down-regulated by extravillous cytotrophoblast tissue during pregnancy (Apps et al., 2009; Hunt et al., 1987; Kovats et al., 1990; Ober et al., 2003; Redman et al., 1984). Instead, human trophoblast cells express the moderately polymorphic class Ia molecule (HLA-C) and all three non-classical HLA class Ib molecules, HLA-E, -F, and -G, showing limited polymorphism (Hviid et al., 1997; Ishitani et al., 2003; King et al., 2000; Kovats et al., 1990). The paradigm is that this will make the trophoblast resistant to direct alloantigen recognition by maternal effector T and NK cells (Persson et al., 2017).

In contrast to HLA-E and -F, HLA-G has been well studied and a number of immunomodulatory functions have been ascribed to HLA-G. In summary, HLA-G inhibits both cytotoxic T cell responses and NK cell functions by preventing the activation and proliferation of alloreactive CD4^{+} T cells, facilitating apoptosis while inducing immunosuppressive CD4^{+} T cells (Contini et al., 2003; Kapasi et al., 2000; Pérez-Villar et al., 1997; Persson et al., 2017; LeMaoult et al., 2004). The shift from a Th1 type pro-inflammatory immune response to a Th2 response during pregnancy may also partly be regulated by HLA class Ib molecules, especially HLA-G that is expressed in the placenta and in the endometrium (Kapasi et al., 2000; Kofod et al., 2017; Kovats et al.,

1990; Persson et al., 2017). In addition, CD8^{+} T cell apoptosis can be induced by soluble HLA-G through the Fas/FasL pathway (Fournel et al., 2000). The expression of Fas will increase the likelihood of the T cells undergoing apoptosis and therefore not performing their usual cytolytic functions. Indeed, it has been proposed that Fas-mediated apoptosis may be one of the most important mechanisms influencing the balance of Th1/Th2 cells (Reinhard et al., 1998). Among CD4^{+} T cells, it is believed to be mostly the Th1 cells that express FasL (CD95 L), whereas Th2 cells tend to express only little FasL (Hahn et al., 1995; Ju et al., 1994). Increased Fas expression on Th1 cells leading to apoptosis might participate in eliminating allo-reactive T cells that can potentiate cytotoxic effects directed against fetal tissues.

Only a few studies have studied the expression of HLA-G in relation to parasite infection. A newly published study indicates a positive correlation between hookworm infection with *A. duodenale* and/or *N. americanus* and high plasma levels of sHLA-G in pregnant women (Avokpaho et al., 2019) Likewise, increased sHLA-G levels have been observed in active and transitional stages of cysts in cystic echinoccosis caused by the helminth *Echinococcus ganulosus* in which humans can serve as an intermediate host (Mariconti et al., 2016). It is unknown, whether the increased level of sHLA-G in the blood of infected individuals is an immune-evasion strategy caused by the helminth or if it is an immune modulation of the host to counteract an inflammatory response (Sabbagh et al., 2018). The role of HLA-G in other helminth infections remains to be studied.

The enzyme indoleamine 2,3-dioxygenase (IDO) that degrades the essential amino acid tryptophan generating downstream biological active tryptophan metabolites, such as kynurenine, is hypothesized to be important for maintaining a pregnancy (Chang et al., 2018). IDO inhibits maternal T cell activation, as T cells starved of tryptophan show reduced responsiveness, and induce Treg formation (Chang et al., 2018; Munn et al., 1998). Multiple cell types in the placenta express IDO, including trophoblast cells, as well as decidual CD14^{+} cells, dendritic cells, decidual stromal cells and vascular endothelial cells (Chang et al., 2018). Moreover, IFN-γ-dependent M1 macrophages have been shown to protect against pathology and mortality through the secretion of IDO in *Schistosoma mansoni*-infected mice (Rani et al., 2012). Although the exact mechanisms behind IDO immunosuppression is not known, IDO

expression is induced by pro-inflammatory mediators such as IFN-γ, indicating a counter-regulatory role (Chang et al., 2018; Vacca et al., 2010). Interestingly, HLA-G has also been shown to be up-regulated by pro-inflammatory cytokines such as IFN-γ, indicating a similar counteracting role of HLA-G for maintenance of a tolerant environment (Svendsen et al., 2017a; Persson et al., in preparation).

Galactin-9 (Gal-9) and other beta-galactoside lectin proteins, are secreted by both human trophoblast cells, *Ascaris* and the human hookworm *Necator americanus* (Cuadro Mogollon et al., 2018; Jex et al., 2011; Li et al., 2016; Tang et al., 2014). Gal-9 is the ligand for the T cell immunoglobulin domain and mucin domain (Tim-3), a negative regulator of both adaptive and innate immune responses. Tim-3 is expressed on cells of both the innate and adaptive immune system. Engagement of Tim-3 with Gal-9 has been shown to activate the alternative activated macrophage (AAM/M2), induce FoxP3 expression in Tregs, promote apoptosis and/or inhibit Th1 and Th17 cell differentiation (Han et al., 2013). In pregnancy, Tim-3 expression is associated with IL-4$^+$perforin^{low} expressing dNK cells, and reduced number of Tim3$^+$ dNK cells with reduced expression of IL-4 and IL-10, and increased TNF-α, IFN-γ and perforin expression were found in cases of miscarriage (Li et al., 2016). Although the exact role for Gal-9 secretion by helminth parasites is unknown, it is likely to assume that it is involved in immunomodulation of the host to secure its longevity.

Yet another protein worth mentioning shared between man and parasite is the latent TGF-β binding protein LTBP-1 that also play a role in immune regulation. LTBP is a family of large glycoproteins with structural homology to fibrillin-1 and -2 (Govinden and Bhoola, 2003). Both *in vitro* and *in vivo* TGF-β is secreted in an inactive form as part of a large latent complex with its pro-peptide, also referred to as latency associated peptide (LAP), and LTBP. LTBP-1 is involved in sequestering of TGF-β by targeting the complex to extracellular matrices, and is involved in the conversion of TGF-β to its active form, i.e. when free TGF-β is released from LAP (Nunes et al., 1997). TGF-β$_1$, -β$_2$ and -β$_3$ mRNA and protein have been identified in decidua, placenta and trophoblast (Bowen et al., 2002b). Also, LTBP-1 is expressed in the placenta and has been found to be down-regulated in pre-eclampsia (Feng et al., 2018). Interestingly, a range of helminth species including the *Haemonchus contortus*, *Teladorsagia circumcincta* (hookworms of sheep), *Nippostrongylus brasiliensis* (hookworm of rats) and *Heligmosomoides polygyrus* (mouse intestinal nematode) have been found to secrete TGF-β homologs (McSorley, 2008). Excretory/secretory products of adult *H. polygyrus* were able to induce Treg formation, suppress naïve CD4$^+$ T cells and in combination with IL-6 drive production of IL-17A from naïve CD4$^+$ T cells via TGF-β pathway signaling (Grainger et al., 2010; McSorley, 2008). Additionally, proteomic analysis of *Ascaris suum* revealed expression of LTBP-1 (Wang et al., 2013). Interestingly, blocking of host TGF-β receptors in *H. polygyrus*-chronically infected mice led to reduced worm burden, showing that it is likely that TGF-β homologs, probably linked to LTBP-1, are also involved in regulation of the host immunity. Parasites do also express unique immune modulatory molecules not shared with the fetal trophoblast cells, one example hereof is the strong immunomodulatory PAS-1 (suppressor protein of *A. suum*-1), a homologue of ABA-1 produced by *A. lumbricoides* (Xia et al., 2000). It is an important immunomodulatory molecule not shared between parasites and trophoblast. In mice, PAS-1 has been shown to limit LPS-induced inflammation by inhibition of neutrophil migration, strong suppression of LPS-induced production of TNF-α, IL-1β and IL-6 and induction of IL-10 and TGF-β synthesis, most likely through the induction of CD4$^+$CD25^{hi}FoxP3$^+$ T cells (Oshiro et al., 2005; Titz et al., 2017).

From this is it is clear that parasites have evolved to express molecules that interact with and regulate the host immune response very much like the fetus that secures its survival in the womb of the mother. The following sections will concentrate on shared responses against the parasite and fetus.

3.2. Regulatory immune cells in the decidua

Regulatory populations of immune cells present in the decidua comprise specialized CD56^{bright}CD16$^-$ NK cells, regulatory CD4$^+$ T cells and dendritic cells (recently reviewed in details by Ghaebi et al., 2017; Liu et al., 2017; Negishi et al., 2018; Zenclussen, 2013).

Dendritic cells (DC) are key initiators of the adaptive immune response by providing presentation of antigen and expression of co-stimulatory molecules such as CD40, CD80, CD83 and CD86. The conventional mature myeloid (m)DC is highly phagocytic, specialized in presenting antigen and associated with a Th1 polarization of the T cell response and production of pro-inflammatory cytokines (Wakkach et al., 2003). The immature (iDC) express low levels of MHC class I and II and co-stimulaory molecules. The iDCs are also involved in tolerogeneic responses, as they are very ineffective in activation of the T cells (Kämmerer et al., 2003). Decidualization upon conception is associated with an increase in tolerogeneic DC-SIGN$^+$ iDCs and a decline in CD83$^+$ mDCS (Kämmerer et al., 2003). The decidual DCs secrete lower levels of IL-12 and higher levels of IL-10, which could push the CD4$^+$ T cells towards a Th2 phenotype and has been shown to be able to induce Treg formation during pregnancy (Blois et al., 2004; Miyazaki et al., 2003; Wakkach et al., 2003). IL-12 and IL-15 production by dendritic cells also promote increased secretion of IFN-γ and proliferation of the CD56^{bright}CD16$^-$ NK cells, respectively (Ferlazzo et al., 2004). Likewise, characterization of the DCs during helminth infection have revealed that they have an increased expression of the co-stimulatory receptor CD86 and of OX40 L, both of which are involved in the Th2 response. Moreover, the Th2-skewed DCs have been shown to produce IL-6, IL-12p40, but not IL-12p70 (Maizels et al., 2004). Also, there is evidence of important effects on other innate cell types, particularly expansion of eosinophilic cell populations during parasite infections (Mawhorter, 1994; Meeusen and Balic, 2000). Furthermore, eosinophils show evidence of an activated state during helminth infection (White et al., 1986).

The immunomodulatory function of regulatory T cells (Treg) have been acknowledged in relation to transplantation, cancer, autoimmune diseases, allergies and infections. Induced levels of regulatory T cells are seen during pregnancy and associations between increased levels and activity of Tregs and parasite infection have been noted (Heikkinen et al., 2004; Maizels and McSorley, 2016; Rowe et al., 2012; Sasaki et al., 2004). Naturally arising regulatory CD4$^+$ T cells, described as constitutively expressing the IL-2R α-chain (CD25) and the transcription factor forkhead box protein 3 (FOXP3), are recognized to be involved in the regulation of immune responses and play indispensable roles in the maintenance of natural self-tolerance (Cobbold et al., 2006; Sakaguchi, 2005). In both mice and humans, it has been reported that the population of CD4$^+$CD25$^+$ Tregs expand during pregnancy and are required to prevent immunological rejection of the fetus (Aluvihare et al., 2004). In contrast, reduced levels of Tregs have been associated with pregnancy complications (Santner-Nanan et al., 2009; Sasaki et al., 2007). The cytokine milieu at the feto-maternal interface contributes to fetal tolerance with a combination of cytokines that suppresses the development of effector T cells in favour of Tregs (Aluvihare et al., 2004). In parasite infections, it has been proposed that the induction of regulatory T cells may direct the immune responses toward immune-anergy in the human host, in time leading to immune hypo-responsiveness (Ludwig-Portugall and Layland, 2012; Maizels and McSorley, 2016). Asymptomatic carriers show increased levels of Tregs and CD4$^+$IL-10$^+$ cells compared to patients with pathology, indicating a role in maintenance of tolerance and dampening of inflammatory responses. In contrast, symptomatic patients showed elevated Th17 immune cell and cytokine profile (Babu et al., 2009; Katawa et al., 2015). Moreover, Tregs have been shown to prolong pathogen survival (Maizels et al., 2004), thus playing a dual role in host evasion and protection against deleterious effects to the host as a result of inflammation.

In peripheral blood most NK cells are characterized by moderate expression of CD56 and expression of CD16 (CD56^{dim}CD16^{+}), whereas only a minor population are characterized as CD56^{bright}CD16^{-}. Unlike in the peripheral blood, CD56^{bright}CD16- NK cells are found in high numbers before implantation in the late secretory phase of the endometrium, and represents the majority (˜70%) of the lymphocytes present in the decidua during early pregnancy (Biswas Shivhare et al., 2015; Moffett-King, 2002). These maternal NK cells, known as uterine (u) or decidual (d) NK cells have been proposed to play a critical role in the balance between acceptance or rejection of the fetus, owing to their increased presence in the early decidua and their direct contact with trophoblast cells. Studies have shown that the dNK cells play important roles in early pregnancy by promoting trophoblast growth, differentiation, invasion and spiral arterial formation in the early decidua, primarily through secretion of growth factors and chemokines such as IL-8, interferon-inducible protein (IP)-10, vascular endothelial growth factor (VEGF) and placental growth factor (PLGF) (Hanna et al., 2006; Hazan et al., 2010). The dNK cells are only weakly cytotoxic and do not normally kill trophoblast cells, although they can become cytotoxic, e.g. by activation by IL-15 or in response to infection, such as by human cytomegalovirus (Tilburgs et al., 2015). Moreover, dNK cells have also been shown to be important regulators of other immune cells; including depressing inflammatory T$_H$17 cell responses through IFN-γ production (Fu et al., 2013) and induce development of CD25^{+}FOXP3^{+} Tregs (Vacca et al., 2010). Therefore, the dNK cells represent an important regulator of immune cells, angiogenesis and trophoblast invasion, especially in early pregnancy (Moffett-King, 2002; Poli et al., 2009).

In contrast to their important function in immunomodulation during pregnancy, NK cells have not yet been ascribed any particular role in helminth infections. Although increased IFN-γ production by NK cells has been noted, Katawa et al. (2015) showed that both CD56^{dim}CD16^{+} and CD56^{bright}CD16^{dim} NK cell populations were decreased in patients with onchocerciasis compared to uninfected individuals (Hsieh et al., 2004; Katawa et al., 2015). However, studies analysing the local host immune response to the helminth parasite are lacking, and it is possible that NK cells play a role in the local environment as seen in the decidua during pregnancy.

The regulatory counterpart of Tregs, the Bregs, have also been found to play important functions during helminth infection (Hussaarts et al., 2011). Most studies on the regulatory B cells (Breg), identified by their ability to secrete IL-10, are primarily performed in relation to cancer and autoimmunity, and many are performed in mouse models. Nevertheless, Bregs seem to be able to alter the cytokine production by T cells and drive the formation of Tregs (Carter et al., 2011; Tedder et al., 2018). Moreover, DCs cultured together with Bregs have reduced capacity to induce antigen-specific proliferation of CD4^{+} T cells (Tedder et al., 2018). B cells of infected individuals have been shown to protect against allergy and suppress autoimmunity (Correale et al., 2008; Hussaarts et al., 2011; van der Vlugt et al., 2012). *In vitro*-activated Bregs from pregnant women have been shown to inhibit TNF-α production by T cells, and the level of Bregs and their ability to produce IL-10 was lower in women experiencing spontaneous abortion that in pregnant women (Rolle et al., 2013).

Helminths also induce elevated antibody responses in naturally infected populations, including total IgG, IgG subtypes, IgM, IgA and IgE (Croese et al., 1996; Palmer et al., 1996; Quinnell et al., 2004). Elevated levels of parasite-specific and total IgE have been found in individuals infected with *Necator americanus* (Pritchard, 1995). Consistently, increased levels of antigen-specific total IgG, IgG1, IgG2, IgG3, IgM and IgE have been observed in *A. lumbricoides* infections (Cooper et al., 2000; Geiger et al., 2004). Although B cell numbers are low in the decidua during pregnancy, anti-paternal asymmetrical antibodies have been suggested to play a protective role during pregnancy (Gutierrez et al., 2005). These are antibodies having two different antigen-binding sites as a result of half-molecule exchange making them less effective in triggering immune responses. Characterization of the placental

immunoglobulins (Ig) has shown that they, like milk, consist of different subclasses of IgG (IgG1-4), IgM, and IgA, all undergoing extensive half-molecule exchange (Lekchnov et al., 2015). The exact role for Bregs and antibodies in human pregnancies remains to be studied.

Clearly, active local regulation of the immune system is important for a successful pregnancy as well as for the survival of the parasite within the host. Many similar immune regulatory effector cells and molecules are seen during certain parasitic infections, and understanding immune regulation in parasitic infections might help broaden our understanding of immunological mechanisms operating during early pregnancy, and vice versa.

3.3. Cytokine networks in pregnancy and helminth infections

As previously discussed immunomodulation during both pregnancy and helminth infections seem to involve a complex and dynamic interaction of Th1, Th2 and regulatory cytokines. Common for both scenarios is a Th2 and regulatory environment during the most of the pregnancy and during prolonged or chronic helminth infection (cf. Section 2.2).

Helminths have originally been described to induce Th2-biased immune responses, orchestrated through a range of cytokines, including IL-4, IL-5, IL-9, IL-13, IL-21, IL-25 and IL-33 (Finkelman et al., 2004; Jackson et al., 2008; Maizels et al., 2004; Urban et al., 1996). In the same way, the cytokine network during pregnancy has been described to be biased towards a Th2 response (Wegmann et al., 1993). In fact, a range of both anti-inflammatory and inflammatory cytokines are found in the placental bed, being secreted from the decidual immune cells, the placenta and its associated membranes. Their expression varies with gestational age, thus implying different function of the cytokines during the course of pregnancy (Bowen et al., 2002a, 2002b; Hauguel-de Mouzon and Guerre-Millo, 2006). The exact role of the cytokines once pregnancy is established is not so clear. The complex network of cytokines expressed during pregnancy has been reviewed by Bowen et al. (2002a/b) and Haugel-de Mouzon and Guerre-Millo (2006) and will only be summarized here based on these reviews. In conclusion, successful pregnancy is most likely a result of a balance of the effect of pro-inflammatory, anti-inflammatory and regulatory cytokines. Although controversies do exist, most studies point towards an increase in concentration of inflammatory cytokines with gestational age, while anti-inflammatory cytokines decrease towards term and labor. Pro-inflammatory cytokines such as IL-1β, IL-6, IL-15 and TNF-α seem to be involved in invasion mediated by the trophoblast cells in early pregnancy by inducing proliferation and secretion and activity of metalloproteases, as well as in the protection of the fetus against pathogenic infections. The anti-inflammatory cytokines IL-4, IL-10, IL-13, TGF-β and the IL-1 receptor agonist (IL-1RA) are in general expressed throughout pregnancy, although their main function seem to be in the first trimester of pregnancy. As previously mentioned the pro-inflammatory cytokine IFN-γ is able to induce expression of the regulatory molecules IDO and HLA-G (Ban et al., 2013; Svendsen et al., 2017b). Hence, the sub-division of cytokines into pro-inflammatory and anti-inflammatory during pregnancy is not straight forward, and the presence of classical pro-inflammatory cytokines might rather paradoxically contributes to the establishment of an immunological tolerant milieu.

The exact mechanisms of how helminth parasites might contribute in suppressing the immune reactions have not yet been fully explained, and many controversies exists. Although a number of studies have assessed cytokine responses to hookworm antigens in naturally infected individuals, the results are not consistent. Geiger et al. (2004) found that high levels of IL-10 was associated with reduced levels of IFN-γ, IL-5, and IL-13 and reduced proliferative responses in hookworm-infected Brazilian patients. The high levels of IL-10 in infection point towards an important role for regulatory cell subsets in controlling potential pathogenic effects of exacerbated Th1 or Th2 responses (Geiger et al.,

2004; Maizels and Yazdanbakhsh, 2003). Geiger et al. (2004) hypothesized that enhanced IL-10 production in *Necator*-infected patients may be a mechanism to down-regulate possible damage inflicted by inflammatory responses elicited by the infection, hence protecting the parasite from destruction. However, another study found that incubation of purified NK cells with *Necator americanus* secretory products stimulated the production of augmented (4- to 30-fold) levels of IFN-γ, whereas IL-4, IL-5, IL-10 and TNF-α levels were below the limit of detection (Hsieh et al., 2004). Furthermore, Falcone et al. (2004) found evidence that proteinases in *Necator americanus* secretions induced a Th2 cytokine profile (IL-4, IL-5 and IL-13) in a KU812 human basophilic cell line and the production of IL-4 from purified human peripheral blood basophils (Falcone et al., 2004). The above mentioned cytokine results showed that hookworm infection are able to induce a mixed Th1/Th2/regulatory response with production of both Th1 (IFN-γ, TNF-α, IL-12), Th2 cytokines (IL-4, IL-5, IL-13) and the regulatory cytokine IL-10, most likely depending on the age of the host, stage of infection and method for measurement. Clearly, these contrasting results call for more research to firmly establish the cytokine profile of *Necator americanus* infection.

Likewise, for roundworm infections discrepancies in relation to the cytokine response exist. It has been shown that patients with an *Ascaris lumbricoides* infection present a highly polarized type 2 cytokine response with parasite infection linked to lower type 1, e.g. TNF-α and IL-12 responses, higher frequencies of parasite antigen-stimulated peripheral blood mononuclear cells (PBMC) expressing either IL-4 or IL-5, and increased Th2/Th1 ratio (IL-4/IFN-γ: uninfected 0.7, infected 7.6), but with unchanged IL-10 and IL-13 levels compared to uninfected individuals (Cooper et al., 2000; Geiger et al., 2004). Also, it has been described how this type of immune response leads to IgE production, mast cell activation, mucus secretion, and ultimately in theory, parasite elimination (Finkelman et al., 1999). However, the two studies by Cooper et al. (2000) and Geiger et al. (2004) show conflicting results regarding IFN-γ production, the proliferative response to infection and IgG4 production. While Cooper et al. (2000) observed increased proliferation and no difference in neither IFN-γ nor IgG4 production in infected individuals, Geiger et al. reported reduced cellular reactivity, lower levels of IFN-γ and increased levels of IgG4 when compared with endemic controls. Likewise, a study from 2008 made by Matera et al., showed a trend towards decreased levels of IFN-γ, TNF-α and TGF-β levels although not significant, and significant increase of IL-4 levels in infected individuals. They also showed increased number of CD25⁺ T cells, but decreased levels of IL-10 (Matera et al., 2008). Conflicting with the above mentioned studies yet another study from 2010 showed increased levels of TNF-α, IL-5 and IL-10 and unchanged levels of IL-4 in *Ascaris* infected individuals. Additionally they found that children between six and ten years of age had the highest parasite load and that the intensity of infection was positively correlated with TNF-α, IL-4 and IL-5, and negatively correlated with IL-10 (Goddey et al., 2010).

To this point there is no clear picture of the induced cytokine network during helminth infection nor pregnancy. Most likely, the cytokine responses are dynamic and dependent on characteristics of the study population, stage of infection or pregnancy, and possible co-infection with other pathogens.

4. Conclusion and future prospects

4.1. The broad perspective

In a very broad perspective looking at parallels between induction of tolerance in helminth infections and induction of tolerance during pregnancy, it is also interesting to speculate about further similarities and discrepancies regarding immunomodulatory mechanisms in tumor development and in organ transplantation (Wilczyński, 2006). Traditionally, the semi-allogenic fetus has been recognized as 'nature's own transplant' and has been compared with the artificial situation of an organ transplant. However, transplantation is the 'odd one out' in this regard. For pregnancy, parasite infections and tumor development, the process starts from a small number of cells that either enter the body or develops from unusual, specific host cells. The blastocyst implants and develops to a fetus, the parasite egg develops to the full parasite, and the tumor cell clone develops to a cancer. It is rather slow and dynamic processes. The immunological responses seem to undergo different stages and involve active and specific immunomodulatory mechanisms, although much is still not known in details. The amount of allogenic load is different in these situations but the antigen presentation is gradual, and immune tolerance is most often obtained. On the other hand, an organ allograft is not developed in the host in a similar dynamic way, and there is no gradual dialogue in different stages with the recipient's immune system. This is the schism of organ transplantation: suddenly there is a new situation, where the immune response of the recipient must immediately be suppressed, which can only be done – for the moment – artificially by drugs with side effects and limitations for the recipient. However, in the cases of pregnancy and of a parasite infection there is a rather long and dynamic immunological adaptation by the mother or by the host to the intruder. Furthermore, there have been a very long evolutionary development with selection and optimization of the underlying immunological mechanisms. A similar process may be relevant in a malignant tumor: however, in this case concentrated in constant mutations and selection mechanisms in a few unstable tumor clone cells that may develop into a tumor mass interacting with the patient's immune system, which leads to either eradication of the tumor or to tumor escape. Thereby, it might be more fruitful to investigate and compare immunoregulatory mechanisms in tumor microenvironments, parasite infections and pregnancy, and remember that organ transplantation is a very special situation.

4.2. Parasites and pregnancies

The original study on the Tsimane population conducted by Blackwell et al. produced some striking observations in terms of associations between parasitic infections and human fertility. Hypothesized by the authors, the association that led to the observed increased fecundity of two children in the group of women with *Ascaris lumbricoides* infection was connected to the immune responses launched by the mothers in accordance with the parasitic infection. In contrast to this, women infected with either *Necator americanus* or *Ancylostoma duodenale* were estimated to reduce their fecundity with three children.

Altogether, both hookworm and roundworm are fully capable of modulating the host immune response; however, further studies are needed to fully elucidate the specific immune responses. The launched immune responses to helminths are intriguing not only from the perspective of understanding protective immunity and immunopathology, but also because, as pointed out by Hotez et al.: a major branch of the mammalian immune system, type 2 immunity, seems to have evolved specifically to handle this class of pathogens (Hotez et al., 2008). Also, it has been described how immune hyporesponsiveness or anergy in humans as a result of helminth infection is linked with reduced proliferative responses and increased production of IL-10 in peripheral lymphocytes (Maizels et al., 2004; Reina Ortiz 2011).

Importantly, the idea that an infection with different helminths will cause the exact same cascade of immunological responses is incorrect. As described above, different helminthic species, despite the overall similarities, will launch different responses. Observational studies found a skewed Th2 to Th1 cytokine ratio in *Ascaris*-infected subjects (Cooper et al., 2000; Geiger et al, 2002). This contrasts with several findings in conducted studies on *Necator americanus*- or *Ancylostoma duodenale*-infected individuals (Geiger et al., 2004; Falcone et al., 2004; Hisieh et al., 2004; Pritchard, 1995; Ottesen, 1991), who presented with a less clear or polarized cytokine profile.

One possible explanation could be that hookworms and roundworms have different life cycles that most likely also has an impact on

the way they modulate the immune system in the host as consequences on the health of the women and thereby on fecundity. Adult *Necator* hookworms parasitize the proximal small intestine, where they attach to the intestinal microvilli and mucosa and secrete enzymes that enable them to invade submucosal tissues and cause the erythrocytes to erupt whereupon the released haemoglobin is degraded by proteolytic pathways (Loukas et al., 2006, Bungiro et al., 2004, Don, 2004). Clinical disease finally manifests when the blood loss associated with hookworm infection exceeds the nutritional reserves of the host, resulting in iron-deficiency anaemia (Loukas et al., 2005). Because children and women of reproductive age due to menstruation have reduced iron reserves, both are at particular risk (Loukas et al., 2005). As Blackwell et al. speculated, there is the possibility that the decreased fecundity of the mothers infected with *Necator americanus* and *Ancylostoma duodenale* might be caused by the depletion of the iron reserves of the mother instead of a direct change of the immunological environment in the host. The costs inflicted by infections are high, and anaemia and nutritional losses might outweigh any effect of immunomodulation. The immunological mechanisms may play a role, but this needs to be elucidated further.

Conversely, *Ascaris lumbricoides*, which also mature into adult worms in the small intestine, is often asymptomatic and infection does not deplete the iron reserves of the infected mother (Hlaing, 1993). Also for *Ascaris*, much of the information regarding immunomodulation is known from studies of the pig counterpart *Ascaris suum*, whereas the exact mechanisms of the human-specific *A. lumbricoides* is not very well-studied in the literature. The evolutionary relationship between the two species has been a matter of debate, and it has been argued that *A. lumbricoides* and *A. suum* are in fact a single species as they are morphologically indistinguishable and closely related genetically (Leles et al., 2012; Nejsum et al., 2012). It can thus only be assumed that the two *Ascaris* (sub)species share similar immunomodulatory mechanisms.

The idea that a parasitic infection with *Ascaris lumbricoides* in any way would have the potential to actually make the women infected more fertile, is equally intriguing and difficult to ignore. Additionally, that the anaemia associated with hookworm infection together with a less polarized Th2/Th1 balance seems to play a role in the markedly decrease of fecundity is also worth investigating to a greater extent. The fact that the hookworm actually *attach* to the intestinal microvilli may itself lead to a more pro-inflammatory response in the host, thereby causing the mixed Th1/Th2 response, alongside with the anaemia. Interestingly, it seems that infection with *Ascaris lumbricoides* is negatively correlated with hookworm infection in the same host (Cooper et al., 2004, 2001; Nguyen et al., 2006). Moreover, a study conducted in Vietnam analysing the infection status among more than 5000 non-pregnant women in the reproductive age found a strikingly high prevalence of 59% infected with *A. lumbricoides* compared to 36% infected with hookworm (Nguyen et al., 2006). This situation may benefit fertility in female hosts and may be viewed as a symbiotic co-evolutionary advantage for both parasite and host.

Much research has been conducted in order to firmly understand the mechanisms at play in the establishment of the maternal tolerance of the semi-allogeneic fetus. One prominent concept is a down-regulation of the cellular immune response that is dependent upon the suppression of Th1 cells and the up-regulation of Th2 cells (Lin et al., 1993; Wegmann et al., 1993). The unique HLA expression of HLA-E, -F, and -G, with a very limited polymorphism, on extra-villous trophoblast cells may at least partly be involved in the maternal Th2 cytokine-skewed immune response (Djurisic et al., 2015; Ishitani et al., 2003; Kovats et al., 1990; Ober et al., 2003; Redman et al., 1984). Especially, HLA-G has been shown in several in vitro experiments to induce a Th2 cytokine profile and down-regulate Th1 cytokines (Maejima et al., 1997; Kapasi et al., 2000; Melsted et al., 2017). It can be speculated that this shift to Th2, which seems to play an important role in maternal tolerance, may be manipulated or exploited in the case of a parasitic infection. As pregnancy is equally affected by and alters immunity, parasitic

infections with helminths that result in systemic immunological changes may be expected to affect fertility by altering the immune response of the host.

It is well-known, that the hyporesponsiveness created by helminths does not only benefit the parasite, but also affect the immune response to non-related antigens such as co-infections, autoimmunity, allergy and in the defence against other pathogens (Chamone et al., 1990; Nacher et al., 2000; van Riet et al., 2007). Autoimmune diseases, allergies and pregnancy complications show an over-active or misdirected immune response as a result of an imbalance between immune effector cells and regulatory cells. The" Old Friend" hypothesis was first proposed by Graham A. W. Rook in 2003 and state that exposure and interaction with our microbiome, including helminths, commensal bacteria and the environmental microbiome contribute to shaping and developing our immune system (Rook et al., 2003). This hypothesis was proposed in the light of increased incidences of autoimmune related diseases and allergies in developed countries compared to countries in which helminth infections are endemic (Asher et al., 2006; Bach, 2002). In regions with helminth infections, including *Ascaris lumbricoides* infection, the burden of infection has been associated with lower frequencies of allergic symptoms and skin test positivity (Alcantara-Neves et al., 2012). In a systematic review and meta-analysis made by Leonardi-Bee et al. (2006) an association between decreased risk of asthma in hookworm infection and increased risk in *A. Lumbricoides* infection were seen (Leonardi-Bee et al., 2006). Thus, the inflammatory process is counterbalanced by regulatory pathways and influenced by the presence or absence of "Old Friends". Whether the lack of commensal helminths in modern urban areas can explain some cases of infertility or hinder pregnancy remains to be studied.

A major limitation of the studies analysing immune responses in helminth infected individuals is the inconsistent experimental design. The discrepancies observed in immune responses to *Ascaris* might therefore reflect differences in analysis and/or sampling method, the age of the infected individuals studied, stage of infection and co-infections. Further studies, especially focusing on infected individuals of the reproductive age could cast some interesting light of the role of the immune response in relation to the observed increased fecundity observed in the *Ascaris* infected women (Blackwell et al., 2015). Thus, the observed increase in fecundity for the women with *Ascaris lumbricoides* infection is only an association. Clear evidence for causality and the exact biological mechanisms are still lacking. Further research into worm interactions, fertility, and the possible molecules that the parasites carry or secrete is necessary to widen our understanding of all of the factors that influences the immune system of the (female) host. The use of helminths or helminth-derived products are already being exploited for therapeutic trials targeting a range of autoimmune diseases (summarized by Fleming and Weinstock, 2015; Kahl et al., 2018; Sobotková et al., 2019). Also summarized by Sobotková et al. (2019) the use of *Necator americanus* live larvae has shown to have favourable outcome against allergy and celiac disease but not inflammatory bowel disease in in vitro models. The effect was ascribed an inhibition of Th1 responses and induction of Th2 and regulatory responses. The use of adult live *Ascaris lumbricoides* worms and the use of a recombinant cystatin from *A. lumbricoides* also showed a favourable outcome in in vitro cell models of dextran sodium sulfate induced colitis and multiple sclerosis. Likewise, *A. suum* adult/egg antigen and parasite derived products (PAS-1 and pseudocoelomic fluid) showed beneficial effect by inhibiting Th1 and inducing regulatory responses of adjuvant induced airway inflammation and arthritis. These findings may also have the potential of being exploited medically and pharmacologically in treatment options for infertility and recurrent miscarriages. By studying the ability of such biological and molecular factors to manipulate the immune system, we may learn not only how to intervene and cure infections but also perhaps to imitate helminths in regulating deleterious responses in the body, as well as to learn more about possible parallels to the immunomodulatory mechanisms during pregnancy.

Declaration of Competing Interest

None.

Acknowledgements

References

Alcantara-Neves, N.M., Veiga, R.V., Dattoli, V.C.C, Fiaccone, R.L., Esquivel, R., Cruz, Á.A., Cooper, P.J., Rodrigues, L.C., Barreto, M.L., 2012. The effect of single and multiple infections on atopy and wheezing in children. J. Allergy Clin. Immunol. 129, 359–367. https://doi.org/10.1016/j.jaci.2011.09.015. e3.

Aluvihare, V.R., Kallikourdis, M., Betz, A.G., 2004. Regulatory T cells mediate maternal tolerance to the fetus. Nat. Immunol. 5, 266–271. https://doi.org/10.1038/ni1037.

Apps, R., Murphy, S.P., Fernando, R., Gardner, L., Ahad, T., Moffett, A., 2009. Human leucocyte antigen (HLA) expression of primary trophoblast cells and placental cell lines, determined using single antigen beads to characterize allotype specificities of anti-HLA antibodies. Immunology 127, 26–39. https://doi.org/10.1111/j.1365-2567.2008.03019.x.

Asher, M.I., Montefort, S., Björkstén, B., Lai, C.K., Strachan, D.P., Weiland, S.K., Williams, H., 2006. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases one and three repeat multicountry cross-sectional surveys. Lancet 368, 733–743. https://doi.org/10.1016/S0140-6736(06)69283-0.

Avokpaho, E., d'Almeida, T.C., Sadissou, I., Tokplonou, L., Adamou, R., Sonon, P., Milet, J., Cottrell, G., Mondière, A., Massougbodji, A., Moutairou, K., Donadi, E.A., Mendes, Teixeira, Junior, C., Favier, B., Carosella, E., Moreau, P., Rouas-Freiss, N., Garcia, A., Courtin, D., 2019. HLA-G expression during hookworm infection in pregnant women. Acta Trop. 196, 52–59. https://doi.org/10.1016/j.actatropica.2019.04.026.

Babu, S., Bhat, S.Q., Kumar, N.P., Lipira, A.B., Kumar, S., Karthik, C., Kumaraswami, V., Nutman, T.B., 2009. Filarial lymphedema is characterized by antigen-specific Th1 and Th17 proinflammatory responses and a lack of regulatory T cells. PLoS Negl. Trop. Dis. 3. https://doi.org/10.1371/journal.pntd.0000420.

Bach, J.-F., 2002. The effect of infections on susceptibility to autoimmune and allergic diseases. N. Engl. J. Med. 347, 911–920.

Ban, Y., Chang, Y., Dong, B., Kong, B., Qu, X., 2013. Indoleamine 2,3-dioxygenase levels at the normal and recurrent spontaneous abortion fetal-maternal interface. J. Int. Med. Res. 41, 1135–1149. https://doi.org/10.1177/0300060513487642.

Biswas Shivhare, S., Bulmer, J.N., Innes, B.A., Hapangama, D.K., Lash, G.E., 2015. Menstrual cycle distribution of uterine natural killer cells is altered in heavy menstrual bleeding. J. Reprod. Immunol. 112, 88–94. https://doi.org/10.1016/j.jri.2015.09.001.

Blackwell, A.D., Tamayo, M.A., Beheim, B., Trumble, B.C., Stieglitz, J., Hooper, P.L., Martin, M., Kaplan, H., Gurven, M., 2015. Helminth infection, fecundity, and age of first pregnancy in women. Science 350 (80-), 970–972. https://doi.org/10.1126/science.aac7902.

Blois, S.M., Alba Soto, C.D., Tometten, M., Klapp, B.F., Margni, R.A., Arck, P.C., 2004. Lineage, maturity, and phenotype of uterine murine dendritic cells throughout gestation indicate a protective role in maintaining Pregnancy1. Biol. Reprod. 70, 1018–1023. https://doi.org/10.1095/biolreprod.103.022640.

Bowen, J.M., Chamley, L., Keelan, J.A., Mitchell, M.D., 2002a. Cytokines of the placenta and extra-placental membranes: roles and regulation during human pregnancy and parturition. Placenta. https://doi.org/10.1053/plac.2001.0782.

Bowen, J.M., Chamley, L., Mitchell, M.D., Keelan, J.A., 2002b. Cytokines of the placenta and extra-placental membranes: biosynthesis, secretion and roles in establishment of pregnancy in women. Placenta. https://doi.org/10.1053/plac.2001.0781.

Carter, N.A., Vasconcellos, R., Rosser, E.C., Tulone, C., Munoz-Suano, A., Kamanaka, M., Ehrenstein, M.R., Flavell, R.A., Mauri, C., 2011. Mice lacking endogenous IL-10-Producing regulatory B cells develop exacerbated disease and present with an increased frequency of Th1/Th17 but a decrease in regulatory t cells. J. Immunol. 186, 5569–5579. https://doi.org/10.4049/jimmunol.1100284.

Chamone, M., Marques, C.A., Atuncar, G.S., Pereira, A.L.A., Pereira, L.H., 1990. Are there interactions between schistosomes and intestinal nematodes? Trans. R. Soc. Trop. Med. Hyg. 84, 557–558. https://doi.org/10.1016/0035-9203(90)90039-H.

Chang, R.Q., Li, D.J., Li, M.Q., 2018. The role of indoleamine-2,3-dioxygenase in normal and pathological pregnancies. Am. J. Reprod. Immunol. 79. https://doi.org/10.1111/aji.12786.

Chavan, A.R., Griffith, O.W., Wagner, G.P., 2017. The inflammation paradox in the evolution of mammalian pregnancy: turning a foe into a friend. Curr. Opin. Genet. Dev. https://doi.org/10.1016/j.gde.2017.08.004.

Cobbold, S.P., Adams, E., Graca, L., Daley, S., Yates, S., Paterson, A., Robertson, N.J., Nolan, K.F., Fairchild, P.J., Waldmann, H., 2006. Immune privilege induced by regulatory T cells in transplantation tolerance. Immunol. Rev. https://doi.org/10.1111/j.1600-065X.2006.00428.x.

Contini, P., Ghio, M., Poggi, A., Filaci, G., Indiveri, F., Ferrone, S., Puppo, F., 2003. Soluble HLA-A,-B,-C and -G molecules induce apoptosis in T and NK CD8 + cells and inhibit cytotoxic T cell activity through CD8 ligation. Eur. J. Immunol. https://doi.org/10.1002/immu.200390015.

Cooper, P.J., Chico, M., Sandoval, C., Espinel, I., Guevara, A., Levine, M.M., Griffin, G.E., Nutman, T.B., 2001. Human infection with Ascaris lumbricoides is associated with suppression of the interleukin-2 response to recombinant cholera toxin B subunit following vaccination with the live oral cholera vaccine CVD 103-HgR. Infect. Immun. 69, 1574–1580. https://doi.org/10.1128/IAI.69.3.1574-1580.2001.

Cooper, P.J., Chico, M.E., Sandoval, C., Espinel, I., Guevara, A., Kennedy, M.W., Urban Jr., J.F., Griffin, G.E., Nutman, T.B., 2000. Human infection with Ascaris lumbricoides is associated with a polarized cytokine response. J. Infect. Dis. 182, 1207–1213. https://doi.org/10.1086/315830.

Cooper, P.J., Chico, M.E., Sandoval, C., Nutman, T.B., 2004. Atopic phenotype is an important determinant of immunoglobulin e–Mediated inflammation and expression of t helper cell type 2 cytokines to Ascaris antigens in children exposed to Ascariasis. J. Infect. Dis. 190, 1338–1346. https://doi.org/10.1086/423944.

Correale, J., Farez, M., Razzitte, G., 2008. Helminth infections associated with multiple sclerosis induce regulatory B cells. Ann. Neurol. 64, 187–199. https://doi.org/10.1002/ana.21438.

Crespillo-Andujar, C., Díaz-Menéndez, M., Mora-Rillo, M., 2017. Evidence for previously unidentified sexual transmission of protozoan parasites. Emerg. Infect. Dis. 23, 602–603. https://doi.org/10.3201/eid2311.171049.

Croese, J., Opdebeeck, J., Prociv, P., Loukas, A., 1996. Immunoglobulin g subclass antibodies against Excretory/Secretory antigens of ancylostoma caninum in human enteric infections. Am. J. Trop. Med. Hyg. 54, 672–676. https://doi.org/10.4269/ajtmh.1996.54.672.

Cuadro Mogollon, O.F., Florez, R.P., Duran, A.R., Gonzalez Lopez, J.S., 2018. Ascaris spp antigens. Contemp. Eng. Sci. 11, 333–355. https://doi.org/10.12988/ces.2018.8122.

Dahl, M., Hviid, T.V.F., 2012. Human leucocyte antigen class Ib molecules in pregnancy success and early pregnancy loss. Hum. Reprod. Update 18, 92–109. https://doi.org/10.1093/humupd/dmr043.

Dewals, B.G., Layland, L.E., Prazeres Da Costa, C., Horsnell, W.G., 2018. Maternal Helminth Infections and the Shaping of Offspring Immunity. https://doi.org/10.1111/pim.12599.

Djurisic, S., Skibsted, L., Hviid, T.V.F., 2015. A phenotypic analysis of regulatory t cells and uterine NK cells from first trimester pregnancies and associations with HLA-G. Am. J. Reprod. Immunol. 74, 427–444. https://doi.org/10.1111/aji.12421.

Falcone, F.H., Loukas, A., Quinnell, R.J., Pritchard, D.I., 2004. 2004. The Innate allergenicity of helminth parasites. Clin. Rev. Allergy Immunol. 26 (1), 61–72. https://doi.org/10.1385/CRIAI:26:1:61.

Feng, Y., He, Y., Wang, J., Yuan, H., Zou, J., Yang, L., Xu, J., 2018. Application of iTRAQ proteomics in identification of the differentially expressed proteins of placenta of pregnancy with preeclampsia. J. Cell. Biochem. 120, 5409–5416. https://doi.org/10.1002/jcb.27819.

Ferlazzo, G., Pack, M., Thomas, D., Paludan, C., Schmid, D., Strowig, T., Bougras, G., Muller, W.A., Moretta, L., Münz, C., 2004. Distinct roles of IL-12 and IL-15 in human natural killer cell activation by dendritic cells from secondary lymphoid organs. Proc. Natl. Acad. Sci. 101, 16606–16611. https://doi.org/10.1159/000186059.

Finkelman, F.D., Shea-Donohue, T., Morris, S.C., Gildea, L., Strait, R., Madden, K.B., Schopf, L., Urban, J.F., 2004. Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. Immunol. Rev. 201, 139–155. https://doi.org/10.1111/j.0105-2896.2004.00192.x.

Finkelman, F.D., Wynn, T.A., Donaldson, D.D., Urban, J.F., 1999. The role of IL-13 in helminth-induced inflammation and protective immunity against nematode infections. Curr. Opin. Immunol. 11, 420–426. https://doi.org/10.1016/S0952-7915(99)80070-3.

Fleming, J.O., Weinstock, J.V., 2015. Clinical trials of helminth therapy in autoimmune diseases: rationale and findings. Parasite Immunol. 37, 277–292. https://doi.org/10.1111/pim.12175.

Fournel, S., Aguerre-Girr, M., Huc, X., Lenfant, F., Alam, A., Toubert, A., Bensussan, A., Le Bouteiller, P., 2000. Cutting edge: soluble HLA-G1 triggers CD95/CD95 ligand-mediated apoptosis in activated CD8 + cells by interacting with CD8. J. Immunol. 164, 6100–6104. https://doi.org/10.4049/jimmunol.164.12.6100.

Fu, B., Li, X., Sun, R., Tong, X., Ling, B., Tian, Z., Wei, H., 2013. Natural killer cells promote immune tolerance by regulating inflammatory TH17 cells at the human maternal-fetal interface. Proc. Natl. Acad. Sci. 110, E231–E240. https://doi.org/10.1073/pnas.1206322110.

Geiger, S.M., Massara, C.L., Bethony, J., Soboslay, P.T., Corrêa-Oliveira, R., 2004. Cellular responses and cytokine production in post-treatment hookworm patients from an endemic area in Brazil. Clin. Exp. Immunol. 136, 334–340. https://doi.org/10.1111/j.1365-2249.2004.02449.x.

Ghaebi, M., Nouri, M., Ghasemzadeh, A., Farzadi, L., Jadidi-Niaragh, F., Ahmadi, M., Yousefi, M., 2017. Immune regulatory network in successful pregnancy and reproductive failures. Biomed. Pharmacother. https://doi.org/10.1016/j.biopha.2017.01.016.

Gleicher, N., Kushnir, V.A., Barad, D.H., 2017. Redirecting reproductive immunology research toward pregnancy as a period of temporary immune tolerance. J. Assist. Reprod. Genet. 34, 425–430. https://doi.org/10.1007/s10815-017-0874-x.

Goddey, N.O.P., Osagie, I.D., Maliki, A., 2010. Serum cytokines profiles in Nigerian children with Ascaris lumbricoides infection. Asian Pac. J. Trop. Med. 3, 288–291. https://doi.org/10.1016/S1995-7645(10)60070-3.

Govinden, R., Bhoola, K.D., 2003. Genealogy, expression, and cellular function of transforming growth factor-β. Pharmacol. Ther. 98, 257–265. https://doi.org/10.1016/S0163-7258(03)00035-4.

Grainger, J.R., Smith, K.A., Hewitson, J.P., McSorley, H.J., Harcus, Y., Filbey, K.J., Finney, C.A.M., Greenwood, E.J.D., Knox, D.P., Wilson, M.S., Belkaid, Y., Rudensky, A.Y., Maizels, R.M., 2010. Helminth secretions induce de novo T cell Foxp3 expression and regulatory function through the TGF-β pathway. J. Exp. Med. 207,

2331–2341. https://doi.org/10.1084/jem.20101074.

Gutierrez, G., Gentile, T., Miranda, S., Margni, R.A., 2005. Asymmetric antibodies: a protective arm in pregnancy. Chem. Immunol. Allergy 89, 158–168. https://doi.org/10.1159/000087964. [pii]\r10.1159/000087964.

Hahn, S., Stalder, T., Wernli, M., Bürgin, D., Tschopp, J., Nagata, S., Erb, P., 1995. Down-modulation of CD4+ T helper type 2 and type 0 cells by T helper type 1 cells via Fas/Fasligand interaction. Eur. J. Immunol. 25, 2679–2685. https://doi.org/10.1002/eji.1830250942.

Han, G., Chen, G., Shen, B., Li, Y., Hajishengallis, G., Filep, J.G., 2013. Tim-3: An Activation Marker and Activation Limiter of Innate Immune Cells. https://doi.org/10.3389/fimmu.2013.00449.

Hanna, J., Goldman-Wohl, D., Hamani, Y., Avraham, I., Greenfield, C., Natanson-Yaron, S., Prus, D., Cohen-Daniel, L., Arnon, T.I., Manaster, I., Gazit, R., Yutkin, V., Benharroch, D., Porgador, A., Keshet, E., Yagel, S., Mandelboim, O., 2006. Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat. Med. 12, 1065–1074. https://doi.org/10.1038/nm1452.

Hauguel-de Mouzon, S., Guerre-Millo, M., 2006. The placenta cytokine network and inflammatory signals. Placenta 27, 794–798. https://doi.org/10.1016/j.placenta.2005.08.009.

Hazan, A.D., Smith, S.D., Jones, R.L., Whittle, W., Lye, S.J., Dunk, C.E., 2010. Vascular-leukocyte interactions: mechanisms of human decidual spiral artery remodeling in vitro. Am. J. Pathol. 177, 1017–1030. https://doi.org/10.2353/ajpath.2010.091105.

Heikkinen, J., Möttönen, M., Alanen, A., Lassila, O., 2004. Phenotypic characterization of regulatory T cells in the human decidua. Clin. Exp. Immunol. 136, 373–378. https://doi.org/10.1111/j.1365-2249.2004.02441.x.

Hlaing, T., 1993. Ascariasis and childhood malnutrition. Parasitology 107, S125–S136. https://doi.org/10.1017/S0031182000075557.

Hotez, P., Brindley, P., Bethony, J.M., King, C.H., Pearce, E.J., Jacobson, J., 2008. Helminth infections: the great neglected tropical diseases. J. Clin. Invest. 118, 1311–1321. https://doi.org/10.1172/JCI34261.tion.

Hsieh, G.C.-F., Loukas, A., Wahl, A.M., Bhatia, M., Wang, Y., Williamson, A.L., Kehn, K.W., Maruyama, H., Hotez, P.J., Leitenberg, D., Bethony, J., Constant, S.L., 2004. A Secreted Protein from the Human Hookworm Necator americanus Binds Selectively to NK Cells and Induces IFN- Production. J. Immunol. 173, 2699–2704. https://doi.org/10.4049/jimmunol.173.4.2699.

Hunt, J.S., Andrews, G.K., Wood, G.W., 1987. Normal trophoblasts resist induction of class I HLA. J. Immunol. 138, 2481–2487.

Hussaarts, L., Van Der Vlugt, L.E.P.M., Yazdanbakhsh, M., Smits, H.H., 2011. Regulatory B-cell induction by helminths: implications for allergic disease. J. Allergy Clin. Immunol. 128, 733–739. https://doi.org/10.1016/j.jaci.2011.05.012.

Hviid, T.V.F., 2006. HLA-G in human reproduction: aspects of genetics, function and pregnancy complications. Hum. Reprod. Update 12, 209–232. https://doi.org/10.1093/humupd/dmi048.

Hviid, T.V.F., Meldgaard, M., Sørensen, S., Morling, N., 1997. Polymorphism of exon 3 of the HLA-G gene. J. Reprod. Immunol. 35, 31–42. https://doi.org/10.1016/S0165-0378(97)00051-X.

Ishitani, A., Sageshima, N., Lee, N., Dorofeeva, N., Hatake, K., Marquardt, H., Geraghty, D.E., 2003. Protein expression and peptide binding suggest unique and interacting functional roles for HLA-E, F, and g in Maternal-Placental immune recognition. J. Immunol. 171, 1376–1384. https://doi.org/10.4049/jimmunol.171.3.1376.

Jackson, J.A., Friberg, I.M., Little, S., Bradley, J.E., 2008. Review series on helminths, immune modulation and the hygiene hypothesis: Immunity against helminths and immunological phenomena in modern human populations: Coevolutionary legacies? Immunology 126, 18–27. https://doi.org/10.1111/j.1365-2567.2008.03010.x.

Jex, A.R., Liu, S., Li, B., Young, N.D., Hall, R.S., Li, Y., Yang, L., Zeng, N., Xu, X., Xiong, Z., Chen, F., Wu, X., Zhang, G., Fang, X., Kang, Y., Anderson, G.A., Harris, T.W., Campbell, B.E., Vlaminck, J., Wang, T., Cantacessi, C., Schwarz, E.M., Ranganathan, S., Geldhof, P., Nejsum, P., Sternberg, P.W., Yang, H., Wang, Jun, Wang, Jian, Gasser, R.B., 2011. Ascaris suum draft genome. Nature 479, 529–533. https://doi.org/10.1038/nature10553.

Johnston, C.J.C., McSorley, H.J., Anderton, S.M., Wigmore, S.J., Maizels, R.M., 2014. Helminths and immunological tolerance. Transplantation 97, 127–132. https://doi.org/10.1097/TP.0b013e3182a53f59.

Ju, S.T., Cui, H., Panka, D.J., Ettinger, R., Marshak-Rothstein, A., 1994. Participation of target Fas protein in apoptosis pathway induced by CD4+ Th1 and CD8+ cytotoxic T cells. Proc. Natl. Acad. Sci. U. S. A. 91, 4185–4189. https://doi.org/10.1073/pnas.91.10.4185.

Kahl, J., Brattig, N., Liebau, E., 2018. The Untapped Pharmacopeic Potential of Helminths. https://doi.org/10.1016/j.pt.2018.05.011.

Kämmerer, U., Eggert, A.O., Kapp, M., McLellan, A.D., Geijtenbeek, T.B.H., Dietl, J., Van Kooyk, Y., Kämpgen, E., 2003. Unique appearance of proliferating antigen-presenting cells expressing DC-SIGN (CD209) in the decidua of early human pregnancy. Am. J. Pathol. 162, 887–896. https://doi.org/10.1016/S0002-9440(10)63884-9.

Kapasi, K., Albert, S.E., Yie, S.M., Zavazava, N., Librach, C.L., 2000. HLA-G has a concentration-dependent effect on the generation of an allo-CTL response. Immunology 101, 191–200. https://doi.org/10.1046/j.1365-2567.2000.00109.x.

Katawa, G., Layland, L.E., Debrah, A.Y., von Horn, C., Batsa, L., Kwarteng, A., Arriens, S.W., Taylor, D., Specht, S., Hoerauf, A., Adjobimey, T., 2015. Hyperreactive Onchocerciasis is Characterized by a Combination of Th17-Th2 Immune Responses and Reduced Regulatory T Cells. PLoS Negl. Trop. Dis. 9. https://doi.org/10.1371/journal.pntd.0003414.

King, A., Burrows, T.D., Hiby, S.E., Bowen, J.M., Joseph, S., Verma, S., Lim, P.B., Gardner, L., Le Bouteiller, P., Ziegler, A., Uchanska-Ziegler, B., Loke, Y.W., 2000. Surface expression of HLA-C antigen by human extravillous trophoblast. Placenta 21, 376–387. https://doi.org/10.1053/plac.1999.0496.

Kofod, L., Lindhard, A., Bzorek, M., Eriksen, J.O., Larsen, L.G., Vauvert, T., Hviid, F.,

2017. Endometrial immune markers are potential predictors of normal fertility and pregnancy after in vitro fertilization. Am. J. Reprod. Immunol. 78. https://doi.org/10.1111/aji.12684.

Kovats, S., Main, E., Librach, C., Stubblebine, M., Fisher, S., DeMars, R., 1990. 1A class I antigen, HLA-G, expressed in human trophoblasts. Science 248 (80-), 220–223. https://doi.org/10.1126/science.2326636.

Lawrence, R.A., Allen, J.E., Osborne, J., Maizels, R.M., 1994. Adult and microfilarial stages of the filarial parasite Brugia malayi stimulate contrasting cytokine and Ig isotype responses in BALB/c mice. J. Immunol. 153, 1216–1224. https://doi.org/10.4049/jimmunol.171.12.6723.

Lekchnov, E.A., Sedykh, S.E., Dmitrenok, P.S., Buneva, V.N., Nevinsky, G.A., 2015. Human placenta: Relative content of antibodies of different classes and subclasses (IgG1-IgG4) containing lambda- and kappa-light chains and chimeric lambda-kappa-immunoglobulins. Int. Immunol. 27, 97–306. https://doi.org/10.1093/intimm/dxv003.

Leles, D., Gardner, S.L., Reinhard, K., Īiguez, A., Araujo, A., 2012. Are Ascaris lumbricoides and Ascaris suum a single species? Parasit. Vectors. https://doi.org/10.1186/1756-3305-5-42.

LeMaoult, J., Krawice-Radanne, I., Dausset, J., Carosella, E.D., 2004. HLA-G1-expressing antigen-presenting cells induce immunosuppressive CD4+ T cells. Proc. Natl. Acad. Sci. 101, 7064–7069. https://doi.org/10.1073/pnas.0401922101.

Leonardi-Bee, J., Pritchard, D., Britton, J., 2006. Asthma and current intestinal parasite infection: systematic review and meta-analysis. Am. J. Respir. Crit. Care Med. 174, 514–523. https://doi.org/10.1164/rccm.200603-331OC.

Leutscher, P.D.C., Pedersen, M., Raharisolo, C., Jensen, J.S., Hoffmann, S., Lisse, I., Ostrowski, S.R., Reimert, C.M., Mauclere, P., Ullum, H., 2005. Increased prevalence of leukocytes and elevated cytokine levels in semen from Schistosoma haematobium-Infected individuals. J. Infect. Dis.

Li, Y.H., Zhou, W.H., Tao, Y., Wang, S.C., Jiang, Y.L., Zhang, D., Piao, H.L., Fu, Q., Li, D.J., Du, M.R., 2016. The Galectin-9/Tim-3 pathway is involved in the regulation of NK cell function at the maternal-fetal interface in early pregnancy. Cell. Mol. Immunol. 13, 73–81. https://doi.org/10.1038/cmi.2014.126.

Lin, H., Mosmann, T.R., Guilbert, L., Tuntipopipat, S., Wegmann', T.G., 2016. Synthesis of T helper 2-type cytokines at the Synthesis of T Helper 2-Type Cytokines at the Maternal-Fetal Interface. J Immunol J. Immunol. Sch. Vet. Med. Hann. Febr. J. Immunol. Copyr. 151, 4562–4573.

Liu, S., Diao, L., Huang, C., Li, Y., Zeng, Y., Kwak-Kim, J.Y.H., 2017. The role of decidual immune cells on human pregnancy. J. Reprod. Immunol. 124, 44–53. https://doi.org/10.1016/j.jri.2017.10.045.

Loukas, A., Constant, S.L., Bethony, J.M., 2005. Immunobiology of hookworm infection. FEMS Immunol. Med. Microbiol. https://doi.org/10.1016/j.femsim.2004.11.006.

Ludwig-Portugall, I., Layland, L.E., 2012. TLRs, treg, and B cells, an interplay of regulation during helminth infection. Front. Immunol. 3. https://doi.org/10.3389/fimmu.2012.00008.

Mahande, A.M., Mahande, M.J., 2016. Prevalence of Parasitic Infections and Associations with Pregnancy Complications and Outcomes in Northern Tanzania: a Registry-based Cross-sectional Study. https://doi.org/10.1186/s12879-016-1413-6.

Maizels, R.M., Balic, A., Gomez-Escobar, N., Nair, M., Taylor, M.D., Allen, J.E., 2004. Helminth parasites – masters of regulation. Immunological 201, 89–116.

Maizels, R.M., McSorley, H.J., 2016. Regulation of the host immune system by helminth parasites. J. Allergy Clin. Immunol. 138, 666–675. https://doi.org/10.1016/j.jaci.2016.07.007.

Maizels, R.M., Yazdanbakhsh, M., 2003. Immune regulation by helminth parasites: cellular and molecular mechanisms. Nat. Rev. Immunol. https://doi.org/10.1038/nri1183.

Mariconti, M., Meroni, V., Badulli, C., Brunetti, E., Tinelli, C., De Silvestri, A., Tamarozzi, F., Genco, F., Casulli, A., Martinetti, M., 2016. Correlation of serum sHLA-G levels with cyst stage in patients with cystic echinococcosis: is it an immune evasion strategy? Parasite Immunol. 38, 414–418. https://doi.org/10.1111/pim.12328.

Matera, G., Giancotti, A., Scalise, S., Pulicari, M.C., Maselli, R., Piizzi, C., Pelaia, G., Tancrè, V., Muto, V., Doldo, P., Cosco, V., Cosimo, P., Capicotto, R., Quirino, A., Scalzo, R., Liberto, M.C., Parlato, G., Focà, A., 2008. Ascaris Lumbricoides-induced Suppression of Total and Specific IgE Responses in Atopic Subjects Is Interleukin 10-independent and Associated With an Increase of CD25 + Cells. https://doi.org/10.1016/j.diagmicrobio.2008.06.015.

Mawhorter, S.D., 1994. Eosinophilia caused by parasites. Pediatr. Ann. 23 (405), 409–413.

McSorley, H., 2008. TGF-beta Homologues From Parasites: Inducers of Immune Regulation? University of Edinburgh.

McSorley, H.J., Maizels, R.M., 2012. Helminth infections and host immune regulation. Clin. Microbiol. Rev. 25, 585–608. https://doi.org/10.1128/CMR.05040-11.

Meeusen, E.N.T., Balic, A., 2000. Do eosinophils have a role in the killing of helminth parasites? Parasitol. Today 16, 95–101. https://doi.org/10.1016/S0169-4758(99)01607-5.

Miyazaki, S., Tsuda, H., Sakai, M., Hori, S., Sasaki, Y., Futatani, T., Miyawaki, T., Saito, S., 2003. Predominance of Th2-promoting dendritic cells in early human pregnancy decidua. J. Leukoc. Biol. 74, 514–522. https://doi.org/10.1189/jlb.1102566.

Mjösberg, J., Berg, G., Jenmalm, M.C., Ernerudh, J., 2010. FOXP3+ Regulatory T Cells and T Helper 1, T Helper 2, and T Helper 17 Cells in Human Early Pregnancy Decidua1. Biol. Reprod. 82, 698–705. https://doi.org/10.1095/biolreprod.109.081208.

Moffett-King, A., 2002. Natural killer cells and pregnancy. Nat. Rev. Immunol. 2, 656–663. https://doi.org/10.1038/nri886.

Mor, G., Cardenas, I., Abrahams, V., Guller, S., 2011. Inflammation and pregnancy: the role of the immune system at the implantation site. Ann. N. Y. Acad. Sci. 1221, 80–87. https://doi.org/10.1111/j.1749-6632.2010.05938.x.

Munn, D.H., Zhou, M., Attwood, J.T., Bondarev, I., Conway, S.J., Marshall, B., Brown, C., Mellor, A.L., 1998. Prevention of allogeneic fetal rejection by tryptophan catabolism. Science 281 (80-), 1191–1193. https://doi.org/10.1126/science.281.5380.1191.

Munoz-Suano, A., Hamilton, A.B., Betz, A.G., 2011. Gimme shelter: the immune system during pregnancy. Immunol. Rev. 241, 20–38. https://doi.org/10.1111/j.1600-065X.2011.01002.x.

Nacher, M., Gay, F., Singhasivanon, P., Krudsood, S., Treeprasertsuk, S., Mazier, D., Vouldoukis, I., Looareesuwan, S., 2000. Ascaris lumbricoides infection is associated with protection from cerebral malaria. Parasite Immunol. 22, 107–113. https://doi.org/10.1046/j.1365-3024.2000.00284.x.

Negishi, Y., Takahashi, H., Kuwabara, Y., Takeshita, T., 2018. Innate immune cells in reproduction. J. Obstet. Gynaecol. Res. 1–12. https://doi.org/10.1111/jog.13759.

Nejsum, P., Betson, M., Bendall, R.P., Thamsborg, S.M., Stothard, J.R., 2012. Assessing the Zoonotic Potential of Ascaris suum and Trichuris Suis : Looking to the Future From an Analysis of the Past Assessing the Zoonotic Potential of Ascaris suum and Trichuris Suis : Looking to the Future From an Analysis of the Past. cambridge.orghttps://doi.org/10.1017/S0022149X12000193.

Nguyen, P.H., Nguyen, K.C., Nguyen, T.D., Le, M.B., Bern, C., Flores, R., Martorell, R., 2006. Intestinal helminth infections among reproductive age women in Vietnam: prevalence, co-infection and risk factors. Southeast Asian J. Trop. Med. Public Health 37, 865–874. https://doi.org/10.1007/10703040_45.

Nunes, I., Gleizes, P.E., Metz, C.N., Rifkin, D.B., 1997. Latent transforming growth factor-β binding protein domains involved in activation and transglutaminase-dependent cross-linking of latent transforming growth factor-β. J. Cell Biol. 136, 1151–1163. https://doi.org/10.1083/jcb.136.5.1151.

Ober, C., Aldrich, C.L., Chervoneva, I., Billstrand, C., Rahimov, F., Gray, H.L., Hyslop, T., 2003. Variation in the HLA-G promoter region influences miscarriage rates. Am. J. Hum. Genet. 72, 1425–1435. https://doi.org/10.1086/375501.

Oshiro, T.M., Macedo, M.S., Macedo-Soares, M.F., 2005. Anti-inflammatory activity of PAS-1, a protein component of Ascaris suum. Inflamm. Res. 54, 17–21. https://doi.org/10.1007/s00011-004-1316-7.

Palmer, D.R., Bradley, M., Bundy, D.A., 1996. IgG4 responses to antigens of adult Necator americanus: potential for use in large-scale epidemiological studies. Bull. World Health Organ. 74, 381–386.

Pellati, D., Mylonakis, I., Bertoloni, G., Fiore, C., Andrisani, A., Ambrosini, G., Armanini, D., 2008. Genital tract infections and infertility. Eur. J. Obstet. Gynecol. Reprod. Biol. 140, 3–11. https://doi.org/10.1016/j.ejogrb.2008.03.009.

Pérez-Villar, J.J., Melero, I., Navarro, F., Carretero, M., Bellón, T., Llano, M., Colonna, M., Geraghty, D.E., López-Botet, M., 1997. The CD94/NKG2-A inhibitory receptor complex is involved in natural killer cell-mediated recognition of cells expressing HLA-G1. J. Immunol. 158, 5736–5743.

Persson, G., Melsted, W.N., Nilsson, L.L., Hviid, T.V.F., 2017. HLA class Ib in pregnancy and pregnancy-related disorders. Immunogenetics 69, 581–595. https://doi.org/10.1007/s00251-017-0988-4.

Piccinni, M.P., Beloni, L., Livi, C., Maggi, E., Scarselli, G., Romagnani, S., 1998. Defective production of both leukemia inhibitory factor and type 2 T- helper cytokines by decidual T cells in unexplained recurrent abortions. Nat. Med. 4, 1020–1024. https://doi.org/10.1038/2006.

Poli, A., Michel, T., Thérésine, M., Andrès, E., Hentges, F., Zimmer, J., 2009. CD56bright natural killer (NK) cells: an important NK cell subset. Immunology 126, 458–465. https://doi.org/10.1111/j.1365-2567.2008.03027.x.

Pritchard, D.I., 1995. The survival strategies of hookworms. Parasitol. Today 11, 255–259.

Quinnell, R.J., Bethony, J., Pritchard, D.I., 2004. The immunoepidemiology of human hookworm infection. Parasite Immunol. 26, 443–454. https://doi.org/10.1111/j.0141-9838.2004.00727.x.

Rani, R., Jordan, M.B., Divanovic, S., Herbert, B.R., 2012. IFN-γ–Driven IDO production from macrophages protects IL-4Rα–Deficient mice against lethality during Schistosoma mansoni infection. AJPA 180, 2001–2008. https://doi.org/10.1016/j.ajpath.2012.01.013.

Redman, C., Sargent, I., 2005. Latest advances in understanding preeclampsia. Science 308 (80-), 1592–1594.

Redman, C.W.G., McMichael, A.J., Stirrat, G.M., Sunderland, C.A., Ting, A., 1984. Class 1 major histocompatibility complex antigens on human extra-villous trophoblast. Immunology 52, 457–468.

Reinhard, G., Noll, A., Schlebusch, H., Mallmann, P., Ruecker, A.V., 1998. Shifts in the TH1/TH2 balance during human pregnancy correlate with apoptotic changes. Biochem. Biophys. Res. Commun. 245, 933–938. https://doi.org/10.1006/bbrc.1998.8549.

Rolle, L., Memarzadeh Tehran, M., Morell-García, A., Raeva, Y., Schumacher, A., Hartig, R., Costa, S.D., Jensen, F., Zenclussen, A.C., 2013. Cutting edge: IL-10-Producing regulatory B cells in early human pregnancy. Am. J. Reprod. Immunol. 70, 448–453. https://doi.org/10.1111/aji.12157.

Rook, G.A.W., Martinelli, R., Brunet, L.R., 2003. Innate immune responses to myco-bacteria and the downregulation of atopic responses. Curr. Opin. Allergy Clin. Immunol. 3, 337–342. https://doi.org/10.1097/01.all.0000092602.76804.ad.

Rowe, J.H., Ertelt, J.M., Xin, L., Way, S.S., 2012. Pregnancy imprints regulatory memory that sustains anergy to fetal antigen. Nature 490, 102–106. https://doi.org/10.1038/nature11462.

Sabbagh, A., Sonon, P., Sadissou, I., Mendes-Junior, C.T., Garcia, A., Donadi, E.A., Courtin, D., 2018. The role of HLA-G in parasitic diseases. HLA 91, 255–270. https://doi.org/10.1111/tan.13196.

Saito, S., Nakashima, A., Shima, T., Ito, M., 2010. Th1/Th2/Th17 and regulatory T-Cell paradigm in pregnancy. Am. J. Reprod. Immunol. 63, 601–610. https://doi.org/10.1111/j.1600-0897.2010.00852.x.

Sakaguchi, S., 2005. Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells

in immunological tolerance to self and non-self. Nat. Immunol. 6, 345–352. https://doi.org/10.1038/ni1178.

Santner-Nanan, B., Peek, M.J., Khanam, R., Richarts, L., Zhu, E., Fazekas de St Groth, B., Nanan, R., 2009. Systemic increase in the ratio between Foxp3+ and IL-17-Producing CD4+ t cells in healthy pregnancy but not in Preeclampsia. J. Immunol. https://doi.org/10.1111/j.1096-3642.1945.tb00854.x.

Sasaki, Y., Darmochwal-Kolarz, D., Suzuki, D., Sakai, M., Ito, M., Shima, T., Shiozaki, A., Rolinski, J., Saito, S., 2007. Proportion of peripheral blood and decidual CD4+ CD25bright regulatory T cells in pre-eclampsia. Clin. Exp. Immunol. 149, 139–145. https://doi.org/10.1111/j.1365-2249.2007.03397.x.

Sasaki, Y., Sakai, M., Miyazaki, S., Higuma, S., Shiozaki, A., Saito, S., 2004. Decidual and peripheral blood CD4+CD25+ regulatory T cells in early pregnancy subjects and spontaneous abortion cases. Mol. Hum. Reprod. 10, 347–353. https://doi.org/10.1093/molehr/gah044.

Sobotková, K., Parker, W., Levá, J., Růžková, J., Lukeš, J., Jirků Pomajbíková, K., 2019. Helminth therapy – from the parasite perspective. Trends Parasitol. https://doi.org/10.1016/j.pt.2019.04.009.

Straubinger, K., Paul, S., Prazeres Da Costa, O., Ritter, M., Buch, T., Busch, D.H., Layland, L.E., Prazeres Da Costa, C.U., 2014. Maternal immune response to helminth infection during pregnancy determines offspring susceptibility to allergic airway inflammation. J. Allergy Clin. Immunol. 134, 1271–1279. https://doi.org/10.1016/j.jaci.2014.05.034. e10.

Svendsen, S.G., Søberg Udsen, M., Daouya, M., Funck, T., Wu, C.-L., Carosella, E.D., Lemaoult, J., Vauvert, T., Hviid, F., Faber, C., Holst Nissen, M., 2017a. Expression and differential regulation of HLA-G isoforms in the retinal pigment epithelial cell line, ARPE-19. Hum. Immunol. 78, 414–420. https://doi.org/10.1016/j.humimm.2017.04.007.

Svendsen, S.G., Udsen, M.S., Daouya, M., Funck, T., Wu, C.L., Carosella, E.D., LeMaoult, J., Hviid, T.V.F., Faber, C., Nissen, M.H., 2017b. Expression and differential regulation of HLA-G isoforms in the retinal pigment epithelial cell line, ARPE-19. Hum. Immunol. 78, 414–420. https://doi.org/10.1016/j.humimm.2017.04.007.

Tang, Y.T., Gao, X., Rosa, B.A., Abubucker, S., Hallsworth-Pepin, K., Martin, J., Tyagi, R., Heizer, E., Zhang, X., Bhonagiri-Palsikar, V., Minx, P., Warren, W.C., Wang, Q., Zhan, B., Hotez, P.J., Sternberg, P.W., Dougall, A., Gaze, S.T., Mulvenna, J., Sotillo, J., Ranganathan, S., Rabelo, E.M., Wilson, R.K., Felgner, P.L., Bethony, J., Hawdon, J.M., Gasser, R.B., Loukas, A., Mitreva, M., 2014. Genome of the human hookworm Necator americanus. Nat. Genet. 46, 261–269. https://doi.org/10.1038/ng.2875.

Tedder, T.F., Matsushita, T., Horikawa, M., Iwata, Y., 2018. Immunopathogenesis en-cephalomyelitis initiation and late-phase in controlling experimental autoimmune regulatory t cells have independent roles regulatory B cells (B10 cells) and. J. Immunol. https://doi.org/10.4049/jimmunol.1001307.

Terrazas, L.I., Bojalil, R., Govezensky, T., Larralde, C., 1998. Shift from an early protective TH1-type immune response to a late permissive TH2-type response in murine cysti-cercosis (Taenia crassiceps). J. Parasitol. 84, 74–81. https://doi.org/10.2307/3284533.

Tilburgs, T., Evans, J.H., Crespo, Â.C., Strominger, J.L., 2015. The HLA-G cycle provides for both NK tolerance and immunity at the maternal–fetal interface. Proc. Natl. Acad. Sci. 112, 13312–13317. https://doi.org/10.1073/pnas.1517724112.

Titz, T., de, O., de Araújo, C.A.A., Enobe, C.S., Rigato, P.O., Oshiro, T.M., de Macedo-Soares, M.F., 2017. Ascaris suum infection modulates inflammation: implication of CD4+ CD25high Foxp3+ t cells and IL-10. Parasite Immunol. 39, 12453. https://doi.org/10.1111/pim.12453.

Tsuda, H., Michimata, T., Sakai, M., Nagata, K., Nakamura, M., Saito, S., 2001. A novel surface molecule of Th2- and Tc2-type cells, CRTH2 expression on human peripheral and decidual CD4 1 and CD8 1 T cells during the early stage of pregnancy. Clin. Exp. Immunol. 123, 105–111.

Urban, J.F., Fayer, R., Sullivan, C., Goldhill, J., Shea-Donohue, T., Madden, K., Morris, S.C., Katona, I., Gause, W., Ruff, M., Mansfield, L.S., Finkelman, F.D., 1996. Local TH1 and TH2 responses to parasitic infection in the intestine: regulation by IFN-gamma and IL-4. Vet. Immunol. Immunopathol. 337–344. https://doi.org/10.1016/S0165-2427(96)05708-X.

Vacca, P., Cantoni, C., Vitale, M., Prato, C., Canegallo, F., Fenoglio, D., Ragni, N., Moretta, L., Mingari, M.C., 2010. Crosstalk between decidual NK and CD14+ myelomonocytic cells results in induction of Tregs and immunosuppression. Proc. Natl. Acad. Sci. U. S. A. 107, 11918–11923. https://doi.org/10.1073/pnas.1001749107.

van der Vlugt, L.E.P.M., Labuda, L.A., Ozir-Fazalalikhan, A., Lievers, E., Gloudemans, A.K., Liu, K.Y., Barr, T.A., Sparwasser, T., Boon, L., Ngoa, U.A., Feugap, E.N., Adegnika, A.A., Kremsner, P.G., Gray, D., Yazdanbakhsh, M., Smits, H.H., 2012. Schistosomes induce regulatory features in human and mouse CD1dhiB cells: in-hibition of allergic inflammation by IL-10 and regulatory T cells. PLoS One 7. https://doi.org/10.1371/journal.pone.0030883.

van Riet, E., Hartgers, F.C., Yazdanbakhsh, M., 2007. Chronic helminth infections induce immunomodulation: consequences and mechanisms. Immunobiology 212, 475–490. https://doi.org/10.1016/j.imbio.2007.03.009.

Wakkach, A., Fournier, N., Brun, V., Breittmayer, J.P., Cottrez, F., Groux, H., 2003. Characterization of dendritic cells that induce tolerance and T regulatory 1 cell dif-ferentiation in vivo. Immunity 18, 605–617 https://doi.org/S1074761303001134 [pii].

Wang, T., Van Steendam, K., Dhaenens, M., Vlaminck, J., Deforce, D., Jex, A.R., Gasser, R.B., Geldhof, P., 2013. Proteomic analysis of the excretory-secretory products from larval stages of Ascaris suum reveals high abundance of glycosyl hydrolases. PLoS Negl. Trop. Dis. 7. https://doi.org/10.1371/journal.pntd.0002467.

Wegmann, T.G., Lin, H., Mosmann, T.R., 1993. Bidirectional cytokine interactions in the maternal-fetal relationshi : is successful pregnancy a Th 2 phenomenon? Immunol. Today 14, 353–356.

White, C.J., Maxwell, C.J., Gallin, J.I., 1986. Changes in the Structural and Functional

Properties of Human Eosinophils During Experimental Hookworm Infection. J. Infect. Dis. 154, 778–783. https://doi.org/10.1520/JTE12271J.

WHO, 2018. Soil-transmitted Helminth Infections [WWW Document]. WHOhttps://doi. org/10.1016/S0140-6736(17)31930-X.

WHO, 2016. WHO | Disease Burden and Mortality Estimates [WWW Document]. WHO. URL http://www.who.int/healthinfo/global_burden_disease/estimates/en/ (accessed 6.20.18).

Wilczyński, J.R., 2006. Cancer and pregnancy share similar mechanisms of im- munological escape. Chemotherapy 52, 107–110. https://doi.org/10.1159/

000092537.

Xia, Y., Spence, H.J., Moore, J., Heaney, N., McDermott, L., Cooper, A., Watson, D.G., Mei, B., Komuniecki, R., Kennedy, M.W., 2000. The ABA-1 allergen of Ascaris lum- bricoides: sequence polymorphism, stage and tissue-specific expression, lipid binding function, and protein biophysical properties. Parasitology 120, 211–224. https://doi. org/10.1017/S0031182099005363.

Zenclussen, A.C., 2013. Adaptive immune responses during pregnancy. Am. J. Reprod. Immunol. 69, 291–303. https://doi.org/10.1111/aji.12097.