MINIREVIEW

Helminths and their implication in sepsis – a new branch of their immunomodulatory behaviour?

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This well written review gives a comprehensive overview on the immunopathology of sepsis and the modulation of immune responses by helminths. It provides evidence that helminths or components thereof may improve the outcome of severe infections. This will allow the development of therapeutic strategies to fight infections and sepsis.

Keywords
helminth; sepsis; hygiene hypothesis; immunomodulation; CARS; SIRS.

Abstract

The prevalence of autoimmune and allergic disorders has dramatically increased in developed countries, and it is believed that our ‘cleaner living’ reduces exposure to certain microorganisms and leads to deviated and/or reduced regulation of the immune system. In substantiation of this health hygiene hypothesis, multiple epidemiological studies and animal models have characterized the protective immune responses induced by helminths during auto-inflammatory disorders. The beneficial effects of such helminths, like schistosomes and filariae, are thought to lie in their immunomodulatory capacity, which can be induced by different life-cycle stages or components thereof. In addition to suppressing autoimmunity recent evidence indicates that concurrent helminth infections also counterbalance exacerbated pro-inflammatory immune responses that occur during sepsis, improving survival. As with allergy, epidemiological studies have observed a steady rise in severe sepsis cases and although this may have resulted from several factors (immunosuppressive drugs, chemotherapy, transplantation, increased awareness and increased surgical procedures), it is tempting to hypothesize that the lack of helminth infections in Western countries may have contributed to this phenomenon. This review summarizes how helminths modulate host immunity during sepsis, such as manipulating macrophage activation and provides an overview about the possible implications that may arise during overwhelming bacterial co-infections.

Immunologically distinct windows during sepsis

Sepsis remains one of the leading causes of mortality in surgical patients or individuals in intensive care units. In 2009, Beale et al. performed a global study comparing the mortality rates of severe sepsis cases in hospitals throughout the world. They reported that the mortality rate of severe septic patients ranged from 33% to 67% with Australia having the least cases. India, the USA and Germany had a mortality rate around 40%, Canada and Argentina with 50% and 57%, respectively, and Malaysia and Brazil with 66–67% (Beale et al., 2009). Moreover, sepsis accounts for 9.3% of all deaths in the USA (Angus et al., 2001), and although mortality due to septic shock has declined since 1979 in the USA, the frequency of severe sepsis has almost tripled from 1979 to 2000 (Martin et al., 2003). Such changes have been associated with the major causative agent for sepsis. From 1979 to 1987, Gram-negative bacteria were the predominant cause for sepsis in the United States, whereas in 2000, more than 50% of the cases were due to infections with Gram-positive bacteria and only 38% caused by Gram-negative bacteria (Martin et al., 2003). Interestingly, the rate of fungal-induced sepsis has also steadily risen since 1979 (Martin et al., 2003).

The term ‘sepsis’ refers to when the body can no longer contain a local infection and results in a complex dysregulation of the immune system. This dissemination of the infection via the bloodstream develops a so-called systemic inflammatory response syndrome (SIRS). Accompanying symptoms may include fever, hypothermia, tachypnea, tachycardia, leucocytosis and hypotension. Two or more of these symptoms in response to an infection indicate the onset of sepsis. During severe sepsis, the patient
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additionaly suffers from organ hypoperfusion or dysfunction. A further drop in systemic mean blood pressure below 60 mm Hg despite fluid resuscitation or the need for vasopressors defines septic shock (Morrell et al., 2009). Following the SIRS phase, a compansatory, anti-inflammatory response syndrome (CARS) develops that leads to immunosuppression and may facilitate superinfections or reactivate dormant infections (Hotchkiss et al., 2009).

As mentioned above, cases of sepsis can be divided into two stages, SIRS and CARS, and interestingly, these phases can be further distinguished by the observed immunological responses. The primary SIRS phase is characterized by an excessive production of pro-inflammatory molecules (cytokines, chemokines, metabolic factors) in response to the infection. The constituents of such responses depend on the location of the ensuing sepsis. For example, Kupffer cells, the macrophages of the liver, are a major cell population of the hepatic nonparenchymal cell fraction and have a pivotal role in removing bacteria, bacterial components, and toxins from the blood stream (Van Amersfoort et al., 2003). Similarly, peritoneal macrophages are essential for the detection of changes in the microenvironment of the peritoneal cavity, which may occur due to damage of intestinal organs. Thus, resident peritoneal macrophages are essential for recognizing bacterial infections and recruiting additional phagocytes to the site of infection (Calhier et al., 2005). During initial microbial infections, host immune reactions are driven by innate-mediated responses. These immediate effects are communicated through the recognition of pattern recognition receptors (PRRs) on the surface of innate cells such as macrophages and dendritic cells (DC). Two distinct families have become focal research points over the last years: Toll-like receptors (TLR) and C-type lectin receptors (CTL). TLR4 and 2 are respectively associated with the recognition of bacterial cell wall components lipopolysaccharide (LPS) in Gram-negative bacteria and lipoteichoic acid from Gram-positive bacteria. In addition, LPS can be sensed by scavenger receptors on macrophages and bound by the primary granule protein BPI (bactericidal permeability-increasing protein) on neutrophils (Van Amersfoort et al., 2003). CTL responses are initiated after contact with agents and receptors such as fungi with Dectin 1 or 2 receptors (Hardison & Brown, 2012), and both innate pathways result in the immediate release of pro-inflammatory mediators. Murine models of SIRS can be induced using a variety of microbial stimuli ranging from whole bacteria to defined antigens such as LPS and CpG. Although much research has focused on the LPS TLR2/4 signalling dynamic, all responses are mediated through the Myd88 central adaptor molecules whose activation triggers the production of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin-6 (IL-6) and IL-12. Another rapidly secreted cytokine is IL-1β, but its release requires the additional activation of the inflammasome pathway to cleave pro-IL-1β into its bioactive form (Martinon et al., 2009). In the case of a nonconfined infection, the continuous output of inflammatory cytokines, due to constantly increasing bacterial loads, leads to the activation of additional phagocytes such as neutrophils, and their excessive stimulation creates feedback loops that further trigger inflammation. Moreover, excessive concentrations of chemokines and cytokines in the circulation activate endothelial cells and neutrophils in the blood vessels thus impairing chemotaxis and recruitment of neutrophils to the site of infection (Phillipson & Kubes, 2011). Although neutrophils are essential for bacterial clearance, excessive numbers and activation may hereby damage tissue integrity by the release of proteases and oxygen radicals (Cohen, 2002; Phillipson & Kubes, 2011). Furthermore, pro-inflammatory cytokines trigger coagulation by inducing the expression of tissue factors on endothelial cells that generate thrombin and fibrin, leading to fibrin clots in blood vessels (Cohen, 2002). Anticoagulant proteins that prevent clot generation, including antithrombin, activated protein C, tissue factor pathway inhibitor (TFPI), are further downregulated during sepsis (Cohen, 2002; Stearns-Kurosawa et al., 2011). These effects take several days but without intervention eventually lead to hypoperfusion of organs, organ failure and ultimately death.

Can blocking of the initial pro-inflammatory immune response during SIRS improve survival?

Animal studies have shown that a reduction in pro-inflammatory immune responses during SIRS improves survival of endotoxiaemia or bacteria-induced sepsis. Interestingly, such protection was dependent on the release of anti-inflammatory cytokines because depletion of IL-10 resulted in increased mortality in an endotoxemia model (Berg et al., 1995), whereas addition of exogenous IL-10 mediated protection (Howard et al., 1993). Regulatory T-cells (Treg) that are renowned for their ability to prevent autoimmune responses to ‘self-antigens’ and balance host responses to infections may also be implicated in the modulation of sepsis. They exert their function through cell-cell contact or through regulatory cytokines such as IL-10 and TGF-β. Accordingly, depletion of CD4^+CD25^+ regulatory T-cells or studies using CD25-deficient mice turned a nonlethal E. coli challenge fatal (Okeke et al., 2013). Inhibition of the primary pro-inflammatory immune response to reduce sepsis-associated pathology was successful using antibodies against TLR4 in a murine E. coli sepsis model (Roger et al., 2009) and antibodies against the TLR4/MD2 complex in the colon ascendens stent peritonitis (CASP) mouse model (Daubeuf et al., 2007). In addition, antagonizing TLR2-mediated activation with a TLR2-specific antibody protected mice against lethal lipopeptide and Bacillus subtilis challenge (Meng et al., 2004). Similarly, mice that are deficient for MyD88 were reported to have an improved survival of CASP-induced SIRS without impairment of antibacterial defences (Weighardt et al., 2002), although another study showed a higher susceptibility to a wide range of bacterial infections in these mice (von Bernuth et al., 2008). However, so far it was not possible to transfer the observed protective effects from animal studies into clinical practice. Interestingly, it has been observed that signalling via MyD88 seems to be redundant, and lack of MyD88 results only in
susceptibility to some pyrogenic bacteria species (von Bernuth et al., 2008), indicating the complexity of sepsis aetiology. Clinical studies using an IL-1 receptor antagonist (rhIL-1Ra), which blocks the binding sites for IL-1β (Fisher et al., 1994), TLR4 antagonists (eritoran) (Kalil et al., 2011; Opal et al., 2013), or TNFsr 55 (lenercept) (Abraham et al., 2001b) have only benefited a minor patient cohort (~3%) who presented with a high degree of sepsis severity (Phillip Dellinger & Parrillo, 2004; Kalil et al., 2011). Possible explanations as to why such treatments cannot be reproduced in a clinical setting may depend upon the timing of the treatments and that patients are at a greater risk for superinfections and reactivation of dormant infections (Sprung et al., 2008).

Maintaining T-cell responses improves sepsis survival

With regard to the aforesaid, sepsis is generally referred to as an excessive inflammatory immune response. However, most patients do not succumb to the infection during the SIRS phase, but die days or weeks later due to multiple organ failure in a phase of sepsis that is referred to as CARS (Hotchkiss & Opal, 2010). Thus, researchers try to develop therapies that are applicable for the different phases of infection. The CARS phase of sepsis includes anti-inflammatory mediators and cell apoptosis, which leads to impaired T-cell immune responses (Hotchkiss & Opal, 2010). Furthermore, Treg numbers are increased in sepsis patients and may contribute to the suppressive phenotype observed during CARS (Venet et al., 2009). It is suggested that the impaired immune responses during CARS lead to an increased susceptibility of patients to secondary infections (Hotchkiss & Opal, 2010; Schwandt et al., 2012). Over the last years, several studies have investigated whether the prevention of immune suppression following sepsis rather than efforts to reduce pro-inflammatory immune responses during SIRS increased the chance of survival. As noted in the SIRS phase, a recent series of in vivo animal experiments demonstrated that a reduction in the immune features associated with CARS improved mortality rates. Here, however, it is the neutralization of anti-inflammatory cytokines like IL-10 or TGF-β that improves sepsis survival of mice after caecal ligation and puncture (CLP) because such treatment reduces Treg numbers and immune suppression (Hiraki et al., 2012). Similarly, efforts to prevent immunosuppression by sustainment of T-cell and macrophage/monocyte responses were shown to improve survival of CLP by experiments using PD-L1 (programmed death 1–ligand 1)-blocking antibodies and PD1 (programmed death 1)-deficient mice (Huang et al., 2009; Zhang et al., 2010). PD1-PD-L1 interactions have been shown to impair immunity by inducing apoptosis and increasing the production of IL-10, which prevented T-cell proliferation and responsiveness and have therefore been implicated in the immunosuppression observed in sepsis patients. Accordingly, septic shock patients have an increased PD1-PD-L1 expression on monocytes and CD4+ T-cells, reduced lymphocyte proliferation, and increased peripheral IL-10 levels, and expression levels of PD1-PD-L1 correlated positively with the occurrence of secondary nosocomial infections and sepsis mortality (Guignant et al., 2011). Similarly, in vivo administrations of IL-7 (Unsinger et al., 2010) and IL-15 (Inoue et al., 2010) prevented apoptosis of CD8+ T-cells, natural killer (NK), and DC preventing immunosuppression and improving survival after CLP in mice. Both cytokines are anti-apoptotic, and whereas IL-7 implements T-cell survival and expansion, IL-15 is important for effector T-cell differentiation and priming of NK cells (Inoue et al., 2010; Unsinger et al., 2010). Innate-mediated mechanisms contribute to the development of an impaired adaptive T-cell response during CARS (Schwandt et al., 2012). Thus, following E. coli-induced sepsis in mice, splenic macrophages release type 1 interferons in a TLR4-dependent manner, which impairs antigen presentation and pro-inflammatory cytokine production by DC and resulted in T-cell immune paralysis (Schwandt et al., 2012). First hints that indicated that the treatment of CARS-induced immunosuppression might improve sepsis survival in humans came from a study that restored HLA-DR expression and TNFα release from peripheral macrophages by interferon gamma (IFNγ) treatment in human sepsis patients with low monocytic HLA-DR, which strengthened the antimicrobial defence and resulted in sepsis clearance in eight of nine patients (Docke et al., 1997). Similarly, treatment of human patients with severe sepsis and septic shock with GM-CSF restored HLA-DR expression on monocytes and production of TNFα, thus reducing the APACHE-II score as well as intrahospital and intensive care unit stay (Meisel et al., 2009). Thus, sustainment of innate and adaptive immune responses can benefit sepsis patients by reducing immunosuppression and the risk of opportunistic infections or reactivation of dormant infections. The obvious difficulty in efficiently treating human sepsis cases may therefore be due to the two opposing phases of sepsis compromising of an initial excessive pro-inflammatory immune response and the subsequent development of immunosuppression. To date, no immunomodulatory treatments have been proved to be beneficial in clinical trials. Therefore, the standard treatment for severe sepsis and septic shock remains limited to immediate initiation of empiric antibiotic treatment, central venous pressure guided fluid resuscitation to prevent organ failure and maintenance of adequate oxygenation and arterial blood pressure. Antibiotic treatment is usually adapted following results from antimicrobial culture (Morrell et al., 2009). Sepsis survival is hereby essentially improved by early appropriate administration of antibacterial treatment (Kolle et al., 1999; Morrell et al., 2005, 2009; Gaieski et al., 2010). Accordingly, Gaieski et al. reported a significantly reduced mortality risk from 33% to 19.5% when appropriate antibiotics were given within one hour post-trauma (Gaieski et al., 2010), whereas inappropriate antibiotic treatment significantly increased in hospital mortality from 12% to 52% (Kolle et al., 1999). This may be due to the fact that early reduction in the bacterial burden reduces excessive pro-inflammatory immune responses during SIRS and therefore reduces coagulation and the developing compensatory immunosuppressive response, thus improving sepsis survival.
survival. Dependent on the current stage of sepsis, additional treatment to reduce pro-inflammatory immune responses during SIRS or recapitulation of innate and adaptive immune responses during CARs may further improve sepsis survival. In line with this, clinical trials blocking pro-inflammatory cytokine function or TLR4 signaling benefited only those patients with a high sepsis severity (Phillip Dellinger & Parrillo, 2004; Kalil et al., 2011).

**Helminths are potent regulators of the host’s immune system**

Helminth infections have developed multiple ways to modulate the host’s immune system and ensure their survival. In chronic cases, such as filariasis and schistosomiasis, this requires long-term survival strategies bringing forth the speculation that co-evolution with helminths was necessary for the development of a balanced immune system. Thus, a multitude of human and animal studies have demonstrated that helminth infections ameliorate or prevent autoimmune diseases and allergy (Elliott et al., 2007; Dittrich et al., 2008; Hübner et al., 2009; Lehuen et al., 2010; Matsiz et al., 2011; Elliott & Weinstock, 2012; Hübner et al., 2012b; Larson et al., 2012a, b; van der Vlugt et al., 2012). Such studies have helped incorporate helminths into the ‘Expanded Hygiene Hypothesis’. Originally, this hypothesis stated that due to well-established sanitation and vaccination procedures, there was an overall reduction in Th1-inducing (bacterial and viral) infections, which has resulted in a decreased ability to immunologically counterbalance Th2-driven diseases (Rook, 2009). With regard to helminths, this initially created a conundrum because they are strong inducers of Th2 immunity and also elicit eosinophilia and IgE: hallmarks of allergy. Nevertheless, after consolidating the findings of 30 independent epidemiological surveys, studying the influence of geohelminth infections on allergy prevalence, the ‘Parasites in Asthma Study Group’ concluded that protective effects were dependent on the worm species, age, state of infection (chronic vs. acute) and parasite burden (Leonardi-Bee et al., 2006).

Currently, it is estimated that one-third of the world’s population carry at least one helminth infection (Savioli et al., 2002), and although the majority of infected individuals adjust to the helminth’s presence in some cases, it can lead to a debilitating capacity (Semnani & Nutman, 2004; Bethony et al., 2006; Taylor et al., 2010). Individuals infected with filarial nematodes (Wuchereria bancrofti and Onchocerca volvulus) or the trematode family of schistosomes (e.g. Schistosoma mansoni, S. japonicum) pass through an early Th1 phase and then develop strong type 2 responses that are characterized by Th2 cells and related cytokines, elevated levels of IgE, IgG1 and the activation of additional cell types such as eosinophils (Allen & Maizels, 2011). Eventually, helminths establish a regulatory, anti-inflammatory milieu in their hosts and can produce immunomodulatory molecules like TGF-β homologues that can bind and function on host receptors (Gomez-Escobar et al., 2000). In association, excretory/secretory (E/S) antigens from helminths, such as Heligmosomoides polygyrus, have been found to signal through host TGF-β pathways and induce de novo Foxp3+ T-cells (Grainger et al., 2010). With regard to schistosomiasis, Foxp3+ T-cells ensure a balanced immune response because their depletion prevents exacerbated granulomatous pathology and schistosome-specific T-cell responses (Layland et al., 2007). Interestingly, in CBA/J mice, the ratio of Treg to activated T-cells was significantly higher when comparing mice with moderate splenomegaly to those with hyper-splenomegaly (Watanabe et al., 2009). Moreover, different helminth infections induce Treg with distinct genetic signatures (Layland et al., 2010), and these markers, such as ICOS, GITR, CD103 or CTLA-4, have essential functions during helminths infections (Maizels et al., 2004; Satoguina et al., 2008; Reynolds & Maizels, 2012). The first indication that Treg played a role in filarial infections stemmed from the elucidation of Tr1 cells in O. volvulus (Satoguina et al., 2002). Subsequently, these cells have been associated with high levels of IgG4, high worm burden and pathology containing Foxp3+ T-cells and TGF-β (Korten et al., 2008, 2011). This constellation is typical for hyposensitive individuals but patients with severe pathology (hyperor sensitive or Sowda) are prone to elevated IgE and IL-4 but have reduced numbers of Treg and interestingly parasite burden (Adjibiyem & Hoerauf, 2010). It has long been assumed that the elevated levels of IgG4 counter-regulate IgE because they bind to the same receptor (Hussain & Ottesen, 1988), but it remains a puzzle why two individuals, infected with the same agent, could develop opposing disease symptoms. Recently, it was shown that human Treg suppress all IgG and IgE production by activated B-cells except IgG4 (Adjibiyem et al., 2013). Moreover, following TLR4 or TLR9 but not TLR2 stimuli, this Treg control is lost, and further, Treg upregulate RORC2 and produce pro-inflammatory IL-17, contributing to the accumulating knowledge about the dynamic nature of Treg (Burgler et al., 2010). Interestingly, with TLR2 activation, IgG4 production was actually enhanced as was the production of IL-10 (Adjibiyem et al., 2013). Thus, these data indicate that under conditions like bacterial or viral infections, B-cells can escape Treg control and provide an explanation as to why patients suffering from allergy or helminth infections display polar immunopathological symptoms despite being exposed to the same agent (Adjibiyem & Hoerauf, 2010; Ludwig-Portugall & Layland, 2012).

Many Th responses are dictated by innate reactions; therefore, researchers have intensively studied the effects of helminths and antigens thereof on innate systems. For example, resistin-like molecule α (RELMα) and arginase 1 have anti-inflammatory properties and are produced by a whole host of cells including alternatively activated macrophages (AAM), eosinophils, basophils, mast cells and neutrophils (Allen & Maizels, 2011). Arginase 1, released from AAM, results in the production of proline that is involved in wound healing, leads to a reduced nitric oxide (NO) production by competing for its substrate L-arginine with the nitrite oxide synthase (Allen & Maizels, 2011) and impairs T-cell activation by the removal of L-arginine (Choi et al., 2009). RELMα on the other hand binds macrophages...
and effector Th2 cells and reduces Th2 immune responses. Its deficiency leads to aggravated pathology in schistosome infection models and *Nippostrongylus brasiliensis* infection and accelerates the expansion of the latter (Nair et al., 2009; Pesce et al., 2009). With regards to other antigen-presenting cells, *Brugia malayi* microfilaria (Mf), the offspring of filarial parasites, induce *in vitro* apoptosis of human-derived DCs, inhibit their ability to release IL-12 or IL-10 (Semnani et al., 2003) and reduce MyD88-triggered responses (Semnani et al., 2008). In addition, exposure of human monocytes to these Mf increases the expression of alternative activation markers (CCL17, CCL18, PDL-1, PDL-2) and decreases their ability to phagocytose (Semnani et al., 2011). Similarly, monocytes from filarial-infected patients have a reduced TLR-mediated activation (Babu et al., 2005) and produce less pro-inflammatory chemokines like CXCL-8, MIP-1α, MIP-1β after bacterial stimulation (Semnani et al., 2006). All of these pieces of data fit to a recent study on patients with lymphatic filariasis (*W. bancrofti*) (Arndts et al., 2012) that compared Mf⁺ individuals with Mf⁻ patients (that did not have severe pathology). This latter cohort is of particular interest because these hosts are a ‘dead end’ for the parasites transmission. Upon comparison, it was observed that the presence of Mf dampened all filarial-specific and bystander responses (Arndts et al., 2012). Such data highlight that the helminths continually modulate the host’s immune responses and that either subtle or dramatic changes can be dependent on the current exposed life-stage. Of course in this situation, down-regulating responses are ideal for the helminth because it allows Mf to circulate within the host without creating overt immune responses and thus increases the chance for vector-mediated uptake. With regard to schistosomes, it is also the helminths offspring that drives modulated responses and this is partly due to the fact that schistosome eggs induce CD4⁺ T-cell dependent granulomas in the host’s tissue and instigate Th2 immunity. Interestingly, when cultured with DC *in vitro*, no pro-inflammatory cytokines are released, but the presence of eggs or soluble egg antigen (SEA) can suppress TLR-triggered responses (Kane et al., 2004). However, in a similar setting, SEA was shown to activate the NLRP3 inflammasome by triggering Dectin-2, causing the release of pro-inflammatory IL-1β (Ritter et al., 2010). SEA is a complex mix of proteins, lipids and glyco-components thereof, and when heat inactivated, the ability to drive inflammasome activation was lost, whereas the dampening of TLR responses remained, indicating that various components within the SEA makeup are responsible for the different reactions observed *in vitro*. Schistosome infections in mice lacking ASC or NLRP3 components of the inflammasome also influenced the outcome of infection because both skewed adaptive immune responses and reduced pathology were observed (Ritter et al., 2010). These data correlated to earlier studies in Myd88-deficient animals, indicating that IL-1 signalling is a crucial factor for host responses (Layland et al., 2005).

Several helminth-derived components have been shown to possess immunomodulatory properties. For example, cysteine protease inhibitors (cystatins) from *B. malayi* interfere with antigen processing and presentation (Manoury et al., 2001), whereas those from *O. volvulus* modulate PBMCs and induce initial pro-inflammatory (TNF-α), then anti-inflammatory (IL-10) cytokines (Schonemeyer et al., 2001; Schierack et al., 2003). The phosphorylcholine containing glycoprotein ES-62 from the filarial nematode *Acanthocheilonema viteae* is probably the best described filarial E/S product, and its ability to modulate macrophages, DCs, B-cells, mast cells and T-cells has been reported to protect against allergies and autoimmune diseases (Al-Riyami & Harrett, 2012). ES-62 inhibits FcεRI-mediated mast cell activity (Melendez et al., 2007) and by triggering TLR4 reduces IL-12 production from LPS-stimulated macrophages and DCs, probably via modulation of intracellular signalling (Goodridge et al., 2005). Other E/S products from various helminths have been shown to induce Th2 immune responses IL-10- and Foxp3⁺-producing regulatory T-cells, inhibit T-cell proliferation and macrophage NO production (Hewitson et al., 2009; Grainger et al., 2010). As mentioned above, different effects on host immunity arise with different life-cycle stages of the parasite. For example, *B. malayi* Mf release serine protease inhibitors that induce Th1 immune responses, whereas adult worms drive Th2 immune responses (Hewitson et al., 2009). Similarly, E/S products from *Litomosoides sigmodontis* Mf, a murine model of filariasis, reduce basophil responsiveness, whereas adult worm E/S products do not (Larson et al., 2012b). In addition, effects may vary in the quality and quantity of released proteins, factors which need to be taken into consideration when studying their immunomodulatory potential (Hewitson et al., 2009).

**Emerging hints that helminths induce bacterial translocation**

Due to advances in microbiome technology, researchers are beginning to investigate the relationship between host, macrofauna and a possible third partner, microbial communities. Recent studies using *Trichuris muris* showed that a successful infection in the large intestine was dependent on bacterial microbial communities (Hayes et al., 2010; Hoerauf, 2010). Current studies have shown, however, that chronic infectious enteric diseases do not dramatically alter the composition of gut flora. *Toxoplasma gondii* infection induces elevations in Gram-negative bacteria, which led to aggravated intestinal Th1 immunopathology (Heimesaat et al., 2006), whereas in experimental *Angiostrongylus cantonensis* infection, there was only an insignificant increase in these bacteria (Nobre et al., 2004). Intestinal-dwelling helminths cause tissue disruptions that allow the entrance of bacteria and bacterial products into the blood stream. For example, patients infected with hookworms were recently reported to display microbial translocation (George et al., 2012). Similarly, research using *Fasciola hepatica*-infected rats showed that levels of bacterial infection in the bile duct correlated with infection duration and parasite burden (Valero et al., 2006). Interestingly, bacterial translocation has also been reported with other trematodes such as *S. mansoni*. Adult worm pairs reside in the portal vein where...
females release eggs, these have to penetrate into the intestinal lumen so that they can be excreted with the stool (Pearce & MacDonald, 2002). However, it remains unclear how eggs penetrate the epithelia, but there are indications that a certain level of pro-inflammatory stimuli, such as TNFα, is required for the eggs to squeeze through (Amiri et al., 1992). This raises the question as to where the TNFα stems from, especially in light of evidence that indicates that eggs and SEA do not elicit such responses from innate cells (Kane et al., 2004; Ritter et al., 2010). Thus, hypothetically, the source of pro-inflammatory cytokines could stem from leakages of host microbial communities, whilst eggs are penetrating, which is enough to instigate innate responses but which in turn are regulated by the parasite itself. Nevertheless, these actions require a fine balance, and if they become dysregulated, then responses are skewed and may lead to bacterial translocation. Elevated levels of endotoxins have been reported in humans that have been hyperexposed to S. mansoni, and surprisingly, the amount of measured endotoxin was 10 times higher than those normally reported in patients with lethal septic shock (Onguru et al., 2011). In association, infections with the murine gastrointestinal nematodes N. brasiliensis and Strongyloides venezuelensis also increase levels of portal LPS in mice after intragastric LPS injection (Farid et al., 2008). This endotoxin translocation was thought to be due to helminth-induced intestinal mastocytosis that reduced the expression of tight junction molecules, thus increasing intestinal permeability (Farid et al., 2008). Therefore, one could assume that a helminth infection might cause patients to be more prone to septic infections, especially those in postoperative conditions, as was recently shown for surgical treatment for Schistosoma-induced portal hypertension (Ferraz et al., 2005).

However, helminth-induced sepsis cases are not common, which argues that potent immunomodulatory effects by the helminths prevent such developments. In association, hookworm-infected patients with bacterial translocation had increased plasma levels of IL-10, whereas peripheral levels of acute phase proteins and pro-inflammatory cytokines like TNFα, IL-12 and IFN-γ did not differ (George et al., 2012). Prime candidates for mediating anti-inflammatory responses are AAM. The suppressive function of these cells is dependent on IL-4 (Loke et al., 2004; Jenkins & Allen, 2010), and AAM can be induced by both IL-4 and IL-13 that share the same IL-4Rα receptor. These cells have already been shown to prevent the development of Schistosoma induced granulomas because mice lacking the IL-4Rα on macrophages or neutrophils develop severe pathology (Herbert et al., 2004). This finding also correlated with increased levels of aspartate transaminase and endotoxin, suggesting hepatic and intestinal damage. Moreover, during the acute phase of S. mansoni infection, IL-4Rα-deficient mice succumbed to the infection due to sepsis (Herbert et al., 2004). In addition, AAM display a similar phenotype as LPS-tolerized macrophages (Porta et al., 2009; Pena et al., 2011), suggesting that bacterial translocation may instigate the induction of regulating AAM during helminth infections. However, it could be speculated that exposure of macrophages to helminths may also hamper the protective immune response to a bacterial infection due to a reduced production of antimicrobial NO and a reduced production of pro-inflammatory cytokines, which impairs the recruitment of additional phagocytes to clear infections. AAM have also been shown to locally expand in filarial infections (Jenkins et al., 2011) expressing arginase 1. In this scenario, arginase 1 competes with iNOS for L-Arginine, and because the latter is required for NO production, there is an overall reduction in NO production by AAM when compared to classically activated macrophages (Munder et al., 1998). Impaired phagocytic capacity was further revealed in AAM that were generated from human monocytes either by cultivation with IL-4 or Mφ exposure (Semnani et al., 2011). It is further thought that helminth-induced AAM can be reprogrammed to improve their antimicrobial response (Mylonas et al., 2009), suggesting a plasticity similar to that observed with T-cells. The entire repertoire of AAM function is not yet fully revealed but they may be considered to be beneficial during acute pro-inflammatory responses due to their known functions in tissue repair and resolution of inflammatory immune responses that may limit excessive inflammation and the development of severe pathology during sepsis.

The effects of helminths on host responses to bacteria and bacterial toxins

Although the ability of helminths to suppress allergy or autoimmunity is well-established, in some circumstances like bacterial infections, a residing helminth infection may be actually harmful to the host. In essence, the strong regulatory reactions induced by the helminth are thought to impair host protective Th1 responses that are essential for controlling bacterial infections such as Mycobacterium tuberculosis (Salgame, 2005; Elias et al., 2007; van Riet et al., 2007). Individuals with chronic filariasis and latent M. tuberculosis infections for example present reduced purified protein derivate (PPD)-specific IFN-γ and IL-17 responses and have a reduced TLR2 and TLR9 activation in response to M. tuberculosis antigens (Babu et al., 2009a, b). Moreover, epidemiological studies have revealed an increased frequency of helminth disease in acutely infected M. tuberculosis patients compared with M. tuberculosis negative controls living in the same household (Elias et al., 2006). Similarly, animal studies showed a dramatic reduction in protective immune responses to M. bovis infection when animals were in an acute phase of S. venezuelensis or chronically co-infected with S. mansoni (Elias et al., 2005; Dias et al., 2011). Furthermore, Potian et al. (2011) showed an impaired control of M. tuberculosis during an acute infection with N. brasiliensis in mice. However, a recent report did not reveal an increased susceptibility to M. tuberculosis when animals were chronically infected with the rodent filaria L. sigmodontis (Hübner et al., 2012a). In those experiments, cotton rats were used, as they are the natural host for L. sigmodontis and develop M. tuberculosis pathology, which is similar to that observed in M. tuberculosis-infected humans. Chronic L. sigmodontis infection in
cotton rats did not impair protective immune responses to *M. tuberculosis* and led to reduced *M. tuberculosis* burdens in the lungs compared with *M. tuberculosis*-only challenged controls (Hübner et al., 2012a). In correlation, studies using co-infections of *N. brasiliensis* and *Toxocara canis* with *M. bovis* or *M. tuberculosis*, respectively, did not find impaired protective immune responses either (Erb et al., 2002; Frantz et al., 2007).

Besides their impact on Mycobacteria infections, a series of studies investigated the impact helminths and their products have on endotoxemia and challenge with other bacterial species (summarized in Table 1). Possible mechanisms by which helminths and their products modulate immune responses to bacterial infections are shown in Fig. 1. Experimental infections of mice with *Ascaris suum* underscore the importance of the state of helminth infection on the outcome of bacterial co-infections, as aerosol exposure to *Pasteurella multocida*, whilst *A. suum* larvae were migrating through the lung resulted in septicemia and severe pneumonia leading to increased death (Tjornehoj et al., 1992). Similarly, pre-existing *S. mansoni* infections impaired protective immune responses to bacterial infections, as *S. mansoni*-infected hamsters had a delayed clearance of Salmonella Paratyphi A from the peripheral blood compared with bacteria-only challenged hamsters (Mikhail et al., 1982). Six-week *S. mansoni*-infected BALB/c mice displayed a significantly higher mortality after *S. Typhimurium* challenge compared with *S. Typhimurium*-only challenged controls (Tuazon et al., 1985). Interestingly, pretreatment of mice with praziquantel, an anti-helmintic drug against schistosomes, before the bacterial challenge improved survival of the *S. Typhimurium* challenge (Tuazon et al., 1985). However, *Schistosoma* infection, determined by *Schistosoma*-specific circulating

**Table 1** Helminth infection and helminth antigens in their implication in sepsis models

| Helminth                          | Model                      | Outcome                                                                 | Refs.       |
|-----------------------------------|-----------------------------|-------------------------------------------------------------------------|-------------|
| *L. sigmodontis* microfilaria     | Endotoxin challenge in mice | Increased pro-inflammatory cytokine production and mortality            | Hübner et al. (2008) |
| injection and patent female adult worm implantation | Endotoxin challenge in mice | Reduced pro-inflammatory cytokine production                            | Hübner et al. (2008) |
| *L. sigmodontis* prepatent female worm implantation | Endotoxin challenge in mice | Reduced thrombin generation                                              | Moons et al. (2002) |
| *A. caninum* tNAPc2              | Endotoxin challenge in chimpanzees | Reduced thrombin generation and IL-10 levels, but no impact on pro-inflammatory cytokines | de Pont et al. (2004) |
| *B. malayi* antigen              | Endotoxin challenge in mice | Reduced pro-inflammatory cytokine production via macrophage tolerization by endosymbiotic *Wolbachia* bacteria | Turner et al. (2006) |
| *F. hepatica* FhDM-1             | Endotoxin challenge in mice | FhDM-1 binds LPS and prevents the interaction with LBP thus reducing pro-inflammatory cytokine production | Robinson et al. (2011) |
| *F. hepatica* tegument antigen   | Endotoxin challenge in mice | Reduces DC maturation and function thus reducing pro-inflammatory cytokine production | Hamilton et al. (2009) |
| Chtiohexoase (originally from *S. digitata*) | Endotoxin challenge in mice | Binding to TLR4 and induction of AAM. Increased sepsis survival | Panda et al. (2012) |
| *A. suum*                        | Aerosol exposure to *P. multocida* in mice | Increased death, severe pneumonia and septicaemia during the migratory phase of *A. suum* | Tjornehoj et al. (1992) |
| *H. polygyrus*                   | Enteric *C. rodentium* orally in mice | Bacterial translocation to spleen and mesenteric lymph nodes. Increased mortality due to an impaired IFNγ response, increased AAM and IL-10-producing DCs | Chen et al. (2005, 2006), Weng et al. (2007) and Su et al. (2012) |
| *N. brasiliensis*                | *K. pneumonia* in mice      | Improved survival of peritoneal sepsis. Improved bacterial clearance in a mast cell dependent manner | Sutherland et al. (2011) |
| *S. mansoni*                     | Salmonella Paratyphi i.c.ardially in hamsters | Prolonged bacteraemia after intracardial injection | Mikhail et al. (1982) |
| *S. mansoni*                     | *S. Typhimurium* i.v. in mice | Increased mortality                                                      | Tuazon et al. (1985) |
| *A. caninum* tNAPc2              | *E. coli* i.p. in mice      | No effect on pro-inflammatory immune response and bacterial burden       | Weijer et al. (2004) |
| Mice expressing *A. caninum* NIF on pulmonary vascular epithelial cells | *E. coli* i.p. in mice | Reversed PMN recruitment to the lung and vascular damage and delayed sepsis mortality | Xu et al. (2002) |

Bold script is used for studies that demonstrated a protective effect.
anodic antigen (CAA) positivity in HIV-infected humans, is not correlated with a higher risk for nontyphoid Salmonella bacteraemia and death (Gordon et al., 2003), and the presence of intestinal helminths including A. lumbricoides or Strongyloides stercoralis does not seem to increase the risk of nontyphoid Salmonella infection in HIV-infected individuals (Dowling et al., 2002). In contrast, corticosteroid therapy or administration of chemotherapy in lymphoma or transplant patients can lead to hyperinfection if individuals have a concomitant S. stercoralis infection and commonly results in respiratory stress and sepsis (Newberry et al., 2005; Gorman & Craven, 2008; Huston et al., 2009; Abdelrahman et al., 2012). In mice, infections with the intestinal helminth H. polygyrus increased the intestinal injury caused by the enteric bacterium Citrobacter rodentium in a STAT 6 (signal transducers and activators of transcription 6)-dependent manner, and this effect was lethal (Chen et al., 2005). In association, H. polygyrus infections provoked enhanced mucosal and systemic Th2 immune responses whilst reducing protective IFN-γ production in response to C. rodentium challenge. Consequently, there was increased bacterial burden and bacterial systemic translocation and delayed bacterial clearance in co-infected animals. Hypothetically, delayed bacterial clearance may be due to the observed increased influx of AAM to the colonic lamina propria of co-infected mice, as those macrophages showed a reduced killing of internalized bacteria by an impaired autophagy, but an increased TNFα production (Weng et al., 2007; Su et al., 2012). This significantly increased colonic TNFα secretion in co-infected
animals correlated with an aggravated colonic pathology in co-infected mice (Chen et al., 2005). The deleterious effect of *H. polygyrus* infection on *C. rodentium*-induced colitis was shown in a follow-up study to be dependent on IL-10-producing dendritic cells (Chen et al., 2006). Nevertheless, Sutherland et al. (2011) showed that co-infections with *N. brasiliensis* reduced bacteriaemia and improved survival of septic peritonitis caused by *Klebsiella pneumoniae*. This protection was mediated through IL-4-conditioned mast cells, which led to an increased production of IL-6 and improved neutrophil recruitment after *K. pneumoniae* infection (Sutherland et al., 2011). Accordingly, recent studies have revealed that an *E. coli* challenge in chronically *L. sigmodontis*-infected BALB/c mice resulted in a reduced inflammation, milder hypothermia and improved bacterial clearance independent of the Mf status (F Gondorf, A Hoerauf and MP Hübner unpublished findings). The improved bacterial clearance in chronically *L. sigmodontis*-infected mice was dependent on macrophages and correlated with increased peritoneal macrophage numbers after the *E. coli* challenge, whereas the phagocytic capacity was not altered (F Gondorf, A Hoerauf and MP Hübner unpublished observation). Interestingly, the frequency of peritoneal AAM was increased after *E. coli* challenge in *L. sigmodontis*-infected animals, whereas in the absence of *E. coli*, peritoneal macrophages did not show an alternatively activated phenotype (F Gondorf, A Hoerauf and MP Hübner unpublished findings). These data correlate with recent epidemiological findings from Panda et al. (2013) which show that human filarial infection may indeed prevent the development of clinical sepsis because there was a reduced prevalence of sepsis in individuals that are positive for circulating filarial antigen.

The dissimilar reports that are found in such animal models may be explained by the different experimental designs, but are more likely to lie in the type of helminth and bacteria species. Variations in the location of the helminth within the host, adaptation, induction of pathology, immunomodulation and duration of infection may further determine the impact on bacterial co-infections. For example, protective immune responses against bacterial co-infections are likely to be affected by the location of the employed helminth species within the host, as helminth-induced immunomodulation is usually most prominent at the site of infection, which elicits an overall change in the immunological milieu. Local as well as systemic immunomodulation may further differ between helminth species. In addition, larval stages of helminths often vary in their location within the host from their adult stage and the E/S products released, suggesting that duration of infection is another important factor that affects immune responses to co-infections. These factors may play a role in how phagocytes are recruited to the site of a bacterial infection and the overall ensuing immune response. The adaption of the helminth to the host is another important point, which may result in an increased susceptibility to pathology or co-infections. Therefore, it can be assumed that similar to the findings of the ‘Parasite in Asthma Study Group’ (Leonardi-Bee et al., 2006), the effect on concomitant bacterial infections is dependent on the status of the helminth species, state of infection and parasite burden, and additional studies with different helminth species are necessary to identify protective mechanisms and helminth-derived products.

Although it is possible to observe the overall picture using full helminth infections, it is difficult to pinpoint which life-stage or helminth-derived molecule is mediating the responses and moreover which immunological pathways are required. An additional problem is the complexity of bacteria-induced immune responses and the pathogenesis of sepsis. Thus, several studies employ the murine LPS shock model because this experimental system can be well controlled and LPS contributes to sepsis pathology (Fink & Heard, 1990). Using this model, previous studies have shown that the presence of Mf, either by i.v injection or implantation of patent adult *L. sigmodontis* female worms, worsens LPS-induced endotoxemia, resulting in increased levels of circulating pro-inflammatory cytokines, an exacerbated hypothermia and a fatal outcome (Hübner et al., 2008). Accordingly, Mf injection has been shown to increase peripheral IFN-γ, IL-12p40 and CXCL9/MIG levels on their own in naive mice (Hübner et al., 2008). However, the implantation of prepatent female adult *L. sigmodontis* worms reduced the LPS-induced release of pro-inflammatory cytokines *in vivo*, strongly indicating that it is the Mf developmental stage that may induce the immune response to bystander antigens, whereas molecules from female helminths, particularly shortly before and at fecundity, induce immunoregulation.

Several helminth-derived molecules have recently been shown to interfere with LPS-induced inflammation. Secreted *F. hepatica* helminth defence molecules (FhDM-1) bind directly to the surface of macrophages and to LPS, reducing its interaction with LPS-binding protein, thus protecting mice against LPS-induced inflammation (Robinson et al., 2011). FhDM-1 appears therefore to be biochemically and functionally similar to human defence peptides (Robinson et al., 2011) that have antimicrobial functions and promote phagocytosis but also modulate innate immune responses by reducing inflammatory mediators released by macrophages (Auvynet & Rosenstein, 2009; Miles et al., 2009). These characteristics suggest that human defence peptides are potential candidates for antisepsis therapies (Hancock & Sahl, 2006). *F. hepatica* also posses tegument antigens that have immunomodulatory properties because their administration during a model of LPS-induced septic shock reduced DC maturation and serum IL-12p70 and IFN-γ levels (Hamilton et al., 2009). Interestingly, direct blocking of LPS signalling via TLR4 can be achieved using chitohexaose, the active component of a filarial glycoprotein derived from *Setaria digitata* (Panda et al., 2012). In this study, specific binding of TLR4 was also described for a number of helminth extracts stemming from *N. brasiliensis*, *H. polygyrus* and the free-living nematode *Caenorhabditis elegans*, suggesting a conserved innate mechanism (Panda et al., 2012). Moreover, administration of chitohexaose in mice increased their survival in an endotoxemia model up to 48 h after LPS administration and reduced the production of pro-inflammatory cytokines *in vivo* (Panda et al., 2012). In
vitro studies further showed that chitohexaose treatment triggers a TLR4-dependent alternative activation phenotype in macrophages (Panda et al., 2012). Whether other known filarial products signalling via TLR4, for example A. vitae-derived ES-62, have a similar protective effect against endotoxia should be the focus of future studies. A direct modulation of LPS responses in humans with active filarial disease is also thought to occur because PBMCs, derived from filarial patients, produce less pro-inflammatory cytokines after in vitro LPS stimulation compared with PBMCs from uninfected controls (Panda et al., 2012). Moreover, in W. bancrofti-infected individuals, this effect was shown to be dependent on the presence of Mf (Arndts et al., 2012), and monocytes from such patients show reduced IL-1β production following LPS stimulation (Sasisekhar et al., 2005).

The ensuing immune and pathological responses that occur in models using a bolus endotoxin challenge represent only a part of the complexity that occurs during bacterial-induced sepsis (Buras et al., 2005). Helminth-induced anti-inflammatory immune responses may improve survival after an endotoxin challenge by reducing inflammatory immune responses, whereas challenge with viable bacteria may result in an impaired bacterial control, triggering the pro-inflammatory immune response during SIRS and the following anti-inflammatory CARS phase thus increasing mortality. However, in cases where helminth infections do not impair bacterial confinement and clearance, helminth-induced anti-inflammatory immune responses may be beneficial and reduce the bacteria-induced pro-inflammatory immune response, dampen the following CARS phase and improve sepsis survival (Fig. 2). Thus, it is important that studies trying to test the feasibility of helminths or components thereof use models with relevant viable pathogens. In such settings, NIF, the neutrophil inhibitory factor isolated from Ancylostoma hook worms appeared to have a positive impact on bacterial infections because during E. coli sepsis, its conditional expression reversed PMN recruitment to the lung, reduced vascular damage and delayed death (Xu et al., 2002). In the case of the recombinant nematode anticoagulant protein c2 (rNAPc2), derived from the hookworm A. caninum, possible protective mechanisms have been observed and even tested in human trials. rNAPc2 is a potent inhibitor of the tissue factor VIIa complex that initiates blood coagulation (Stassens et al., 1996) and inhibition of this tissue factor pathway by the administration of tissue factor pathway inhibitor (TFPI) dampened E. coli-induced IL-6 levels and prevented mortality in baboons (Creasey et al., 1993). In a follow-up study using mice, however, rNAPc2 did not reduce E. coli-elicited pro-inflammatory immune responses and had no antibacterial impact (Weijer et al., 2004). Continuing the research in primates, rNAPc2 reduced low-dose endotoxin-induced thrombin generation in chimpanzees, suggesting it may inhibit coagulation activation in sepsis patients (Moons et al., 2002). Accordingly, treatment of humans with rNAPc2 blocked, in a low-dose endotoxin challenge, thrombin generation and reduced IL-10 levels, but failed to reduce peripheral IL-6, CXCL8/IL-8 or TNFα (de Pont et al., 2004). A following phase II clinical trial using recombinant TFPI in patients with severe sepsis observed an accelerated drop of IL-6 levels (Abraham et al., 2001a); however, the following phase III trial OPTIMIST did not reveal an improved severe sepsis survival (Abraham et al., 2003).

Overall, there is a growing body of evidence suggesting that helminths or molecules thereof may improve the outcome of bacterial co-infections and bacterial-induced sepsis. This extends upon their already established role in preventing allergy and autoimmunity but as with that line of research, prevention appears to be dependent on the combination of helminth and bacteria. Although a few potential candidates for therapy have been revealed, more work is required to decipher the immunological mechanisms.
behind such protective modulation and their implication on the two distinct phases of sepsis – SIRS and CARS.

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