Role of IL-4Rα during acute schistosomiasis in mice

H. NDLOVU & F. BROMBACHER

Division of Immunology, International Center for Genetic Engineering and Biotechnology (ICGEB), Cape Town Component and Institute of Infectious Diseases and Molecular Medicine (IIDMM), University of Cape Town, Cape Town, South Africa

SUMMARY

Schistosomiasis is an important parasitic disease that causes major host morbidity and mortality in endemic areas. Research conducted in mouse models of schistosomiasis has provided great insights and understanding of how host protective immunity is orchestrated and key cellular populations involved in this process. Earlier studies using cytokine-deficient mice demonstrated the importance of IL-4 and IL-10 in mediating host survival during acute schistosomiasis. Subsequent studies employing transgenic mice carrying cell-specific deletion of IL-4Rα generated using the Cre/LoxP recombination system have been instrumental in providing more in-depth understanding of the mechanisms conferring host resistance to Schistosoma mansoni infection. In this review, we will summarize the contributions of IL-4/IL-13-responsive cellular populations in host resistance during acute schistosomiasis and their role in limiting tissue pathology.

Keywords IL-4Rα, immunity, mice, schistosomiasis

INTRODUCTION

Schistosomiasis is a chronic parasitic disease caused by blood-dwelling trematode flatworms (flukes) of the genus Schistosoma. The disease is endemic in over 74 developing countries where it is estimated to infect approximately 200 million people (1–3). Schistosomiasis is a major cause of host morbidity and mortality in endemic areas, and 280 000 deaths per annum are attributed to the disease in sub-Saharan Africa alone; hence, the World Health Organization (WHO) has placed it amongst the top ten infectious diseases of global importance (4). The emergence of HIV/AIDS in areas where schistosomiasis is endemic has raised serious concerns about the control of schistosome infection. There is already evidence suggesting that schistosome infection affects the aetiology and transmission of HIV (5–9), tuberculosis (6, 10, 11) and malaria (12–14). Although schistosomiasis can effectively be treated with praziquantel, the drug does not prevent re-infection of individuals, a common occurrence in endemic areas. Thus, studying the immune biology of schistosomiasis is crucial for broadening our understanding of the disease and assisting in rational design and development of a vaccine candidate.

Schistosoma mansoni (S. mansoni) eggs lodged in the host liver and intestines provoke a dominant CD4+ T cell-dependent Th2 immune response, extensive tissue fibrosis and granulomatous inflammatory responses (15–18). Infection of gene-deficient mice with S. mansoni demonstrated an essential host protective role for Th2 cytokines such as IL-4, IL-13 and IL-10 during acute schistosomiasis (19–21). IL-4 and IL-13 signalling is mediated by heterodimeric receptor complex containing a common IL-4 receptor α (IL-4Rα) subunit (22, 23). IL-4 uniquely binds and signals through the type I receptor consisting of IL-4Rα subunit and the common gamma chain (γc), while IL-13 signals through the type II receptor composed of IL-4Rα subunit and the common gamma chain (γc). IL-4 uniquely binds and signals through the type I receptor consisting of IL-4Rα subunit and the common gamma chain (γc), while IL-13 signals through the type II receptor composed of IL-4Rα subunit and IL-13Rα1 chain (22). Furthermore, IL-13 binds to the homodimeric IL-13Rα2 receptor with high affinity (24). Initially, the IL-13Rα2 receptor was thought to act as a decoy receptor possessing no signalling abilities, but recent studies have shown that IL-13 signalling via the IL-13Rα2 induces TGF-β production and mediates fibrosis in chronic TNBS colitis (25, 26). The contribution of IL-4/IL-13 signalling via IL-4Rα in mediating immune responses conferring host resistance to acute schistosomiasis has been investigated using transgenic mouse models lacking IL-4Rα expression on all haematopoietic cells.

Correspondence: Frank Brombacher, International Center for Genetic Engineering and Biotechnology (ICGEB), University Campus, Wernher Beit South Building, Anzio Road, Observatory 7925, Cape Town, South Africa (e-mail: brombacherfrank@gmail.com).

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In this review, we discuss the role played by IL-4/IL-13 signalling via the IL-4Rα in certain cellular populations during acute schistosomiasis and how it mediates host resistance or susceptibility to infection. We further discuss recent data on how cell-specific IL-4Rα expression controls granuloma formation and maintains the fine balance between a Th1/Th2 immune response, crucial for limiting the deleterious effects on the host.

ACUTE VS. CHRONIC SCHISTOSOMIASIS

Schistosomiasis is characterized by two main clinical conditions – acute and chronic schistosomiasis – depending on the maturation of the parasites and their eggs. In humans, acute schistosomiasis is a debilitating febrile illness (Katayama fever) that usually occurs before the appearance of eggs in the stool and peaks 6–8 weeks after infection (27–29). Although less studied, acute illness has been associated with a predominantly T helper 1 (Th1) immune response characterized by high levels of tumour necrosis factor (TNF) in the plasma, and peripheral blood mononuclear cells (PBMCs) have been shown to produce large quantities of TNF, IL-1 and IL-6 (28, 30). Interestingly, the symptoms associated with acute disease seem to be uncommon in individuals living in areas where schistosomiasis is endemic compared to individuals with no previous history of exposure to infection. Chronic schistosomiasis is a more clinically relevant disease that is potentially life-threatening in individuals that develop hepatoportal disease in response to eggs trapped in various tissues (27, 28, 31). This severe form of the disease is accompanied by hepatic and periportal fibrosis, portal hypertension, ascites and portosystemic shunting of venous blood (31).

The focus of this review is on murine models of schistosomiasis, which have been crucial in expanding our understanding of the host–parasite interactions and the hosts immune response to *S. mansoni* infection. Like in humans, *S. mansoni* infection in mice progresses through two main stages: acute schistosomiasis and chronic schistosomiasis that are characterized by different immune response profiles. During the acute stage of infection (0–8 weeks post-infection), the immune response alters between Th1 and Th2 depending on the eliciting antigens. Immature parasite antigens elicit a moderate Th1 immune response early during infection (3–5 week post-infection), while egg antigens induce a robust Th2 immune response that peaks at 8 weeks post-infection (28). The dominant Th2 immune response and the associated pathologies are down-modulated during the chronic stages of infection (10 weeks post-infection onwards) in immunocompetent wild-type mice through a mechanism involving IL-10 (32–34). It is important to mention that *S. mansoni* infection of mice does not evoke all aspects associated with human schistosomiasis such as portal tract fibrosis (35).

IL-4Rα-MEDIATED SIGNALLING IS CRUCIAL FOR HOST SURVIVAL DURING ACUTE SCHISTOSOMIASIS

Earlier studies elucidated immunological factors involved in coordinating the mechanisms conferring host resistance or susceptibility to acute schistosomiasis using gene-deficient mice. Mice lacking IL-4 production by all haematopoietic cells (IL-4^−/−^) suffered from severe disease characterized by rapid cachexia coinciding with the onset of egg deposition by adult worms and eventually succumbed to *S. mansoni* infection by 8–10 weeks post-infection compared to wild-type control mice (19). Mortality in infected IL-4^−/−^ mice was associated with increased production of pro-inflammatory cytokines IFN-γ and TNF-α, uncontrolled liver granuloma formation and increased intestinal inflammation that resulted in endotoxemia (19, 20). In contrast, IL-13^−/−^ mice infected with *S. mansoni* developed a sufficient Th2 immune response and displayed enhanced survival due to reduced hepatic fibrosis (20). Mice deficient of IL-4 and IL-13 (IL-4^−/−^/IL-13^−/−^) were found to be extremely susceptible to acute schistosomiasis, even more so than IL-4^−/−^ mice (20). Therefore, these studies were crucial in demonstrating that IL-4 and IL-13 play distinct and contrasting pathogenic roles during *S. mansoni* infection in mice.

More studies were conducted using gene-deficient mice to uncover more cytokines involved in the pathogenesis of schistosomiasis. IL-4/IL-10 double-deficient mice quickly succumbed to *S. mansoni* infection due to increased weight loss, augmented hepatocellular damage indicated by serum aspartate transaminase (AST) levels and increased production of pro-inflammatory mediators IFN-γ, TNF-α and nitric oxide (NO), suggesting that IL-10 might be an essential immunomodulatory cytokine during acute schistosomiasis in mice (21). Unexpectedly, mice deficient in IL-10/IL-12 developed a severe wasting disease that culminated in death during the chronic stages of *S. mansoni* infection despite the presence of a sufficient Th2 immune response (21). This study by Hoffmann and colleagues conclusively demonstrated that excessive Th1 or Th2 cytokine responses may lead to lethal disease during *S. mansoni* infection in mice. Thus, regulating the polarization of the Th1 and Th2 immune response triggered by *S. mansoni* egg antigens is essential for host survival.

Generation of transgenic mice lacking IL-4Rα expression on all haematopoietic cells (IL-4Rα^−/−^) was instru-
mental in dissecting the role of IL-4Rα signalling in the mechanism conferring host resistance or susceptibility to acute schistosomiasis. IL-4Rα<sup>−/−</sup> mice infected with *S. mansoni* quickly succumbed to infection by eight weeks post-infection due to exacerbated liver hepatotoxicity indicated by increased serum AST levels, impaired egg expulsion, abrogated granuloma formation and severe gut inflammation that ultimately resulted in the leakage of lipopolysaccharides (LPS) into the bloodstream, leading to endotoxemia and septic shock (36). Treatment of IL-4Rα<sup>−/−</sup> mice with antibiotics extended survival time during *S. mansoni* infection, providing a mechanism responsible for mortality in these mice (36). A recent study by Herbert and colleagues showed that IL-4Rα expression by bone marrow-derived cells is required for host survival against acute schistosomiasis by limiting liver hepatotoxicity and maintaining the integrity of the gut (37). Therefore, it can be concluded that IL-4/IL-13-mediated signalling via IL-4Rα is indispensable for host survival during acute schistosomiasis.

The cellular contributions of IL-4Rα to the mechanisms providing host resistance to *S. mansoni* infection have been determined using novel transgenic mouse models deficient in cell-specific IL-4Rα expression generated using the Cre/croloxP recombination system. Mice lacking IL-4Rα expression on macrophages and neutrophils (LysM<sup>cre</sup>IL-4Rα<sup>−/−</sup>) were found to be highly susceptible to *S. mansoni* infection despite the presence of a sufficient Th2 immune response (36). Mortality in LysM<sup>cre</sup>IL-4Rα<sup>−/−</sup> mice was caused by augmented liver damage and excessive gut inflammation which subsequently led to endotoxemia and septic shock (36). It was generally thought that the presence of classically activated macrophages that possess the ability to produce pro-inflammatory mediators is responsible for the extensive inflammation found in LysM<sup>cre</sup>IL-4Rα<sup>−/−</sup> mice infected with *S. mansoni*. However, a recent study by Rani and colleagues showed that mice deficient in both classically and alternatively activated macrophages, generated by crossing MIIG transgenic mice (mice that use CD68-IVS1 promoter to drive IFN-γ-dominant negative receptor) with IL-4Rα<sup>−/−</sup> mice (MIIG × IL-4Rα<sup>−/−</sup>), quickly succumbed to *S. mansoni* infection due to rapid weight loss, severe liver injury and failure to upregulate the expression of indoleamine 2,3 dioxygenase (IDO), a crucial immunosuppressive enzyme (38, 39). Therefore, maintaining a fine balance between IL-4Rα-responsive alternatively activated macrophages and IFN-γ-driven classically activated macrophages is crucial for prolonging host survival during acute schistosomiasis and down-modulating tissue inflammation.

Mice deficient in IL-4Rα expression specifically on CD4<sup>+</sup> T cells (Lck<sup>cre</sup>IL-4Rα<sup>−/−</sup>) survived acute schistosomiasis by controlling egg-induced intestinal inflammation even though they developed increased granulomatous liver pathology (40). A subsequent study by Dewals and colleagues utilizing iLck<sup>cre</sup>IL-4Rα<sup>lox/lox</sup> mice (pan-T cells IL-4Rα-deficient mice) showed the importance of IL-4/IL-13-responsive non-CD4<sup>+</sup> T cells in conferring host resistance to acute schistosomiasis and limiting liver pathology (41). The specific IL-4/IL-13-responsive non-CD4<sup>+</sup> T cell population contributing to the mechanism conferring resistance to acute schistosomiasis is yet to be determined. It has been postulated that IL-4/IL-13-responsive B cells and CD11c<sup>+</sup> dendritic cells may be involved in mediating host resistance to *S. mansoni* infection.

The host protective role of IL-4Rα to *S. mansoni* infection is not only limited to haematopoietic cells but has recently been demonstrated in non-haematopoietic target cells. Mice deficient in IL-4Rα expression on smooth muscle cells (SM-MHC<sup>cre</sup>IL-4Rα<sup>−/−</sup>) were found to be highly susceptible (succumbed to infection earlier than wild-type littermate control mice) to acute schistosomiasis despite developing sufficient Th2 immune responses and the absence of intestinal inflammation and sepsis (42). Increased susceptibility of SM-MHC<sup>cre</sup>IL-4Rα<sup>−/−</sup> mice to *S. mansoni* infection was associated with severe weight loss, impaired egg expulsion and decreased intestinal hypercontractility compared to wild-type littermate control mice (42). The contribution of different IL-4Rα-responsive cellular population in host survival during acute schistosomiasis is summarized in Table 1.

### Table 1

| IL-4/IL-13-Responsive Haematopoietic Cells Regulate Liver Granuloma Size in *S. Mansoni*-Infected Mice |
|---------------------------------------------------------------|
| *Schistosoma mansoni* eggs trapped in the host tissue induce a Th2-dependent granuloma formation that is characterized by the presence of T cells, eosinophils and macrophages (17, 20, 28, 43). The absence of IL-4Rα signalling in all haematopoietic cells impaired granuloma formation during *S. mansoni* infection despite the presence of a sufficient Th2 response in the liver (16). In-depth analysis of cytokine production by liver granuloma-associated single cells from infected IL-4Rα<sup>−/−</sup> or STAT6<sup>−/−</sup> mice revealed that granuloma-associated Th2 cells can develop independently of IL-4Rα/Stat6<sup>−/−</sup> signalling in vivo and in vitro (15, 18). Therefore, IL-4Rα is crucial for regulating granuloma formation in mice infected with *S. mansoni*. |
| A study by Herbert and colleagues found that mice lacking IL-4Rα expression on BM-derived cells had augmented liver granuloma size than wild-type mice, non-BM IL-4Rα<sup>−/−</sup> and IL-4Rα<sup>−/−</sup> mice (37). Specific IL-4Rα-responsive cellular populations involved in regulating liver |

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granuloma size during *S. mansoni* infection in mice have been elucidated. These cellular populations are alternatively activated macrophages (36) and CD4+ T cells (40, 41). Other IL-4/IL-13-responsive haematopoietic cells, such as B cells and dendritic cells, might be involved in regulating granuloma size in infected mice. However, IL-4/IL-13-responsive nonhaematopoietic cells seem to play little or no role in granuloma formation as infected *S. mansoni* infection indicated by similar quantities of Th1 and Th2 cytokines and IL-10 production (49). Importantly, a small subpopulation of granulomas expressing macropage mannose receptor (MMR) and chitinase-like molecule-1 (Ym1; MMR "Ym-1") was found in the periphery of granulomas of infected *S. mansoni* infection. However, a subsequent study by Cook and colleagues demonstrated that DCs expressing IL-4Rα-signalling specifically on CD4+ T cells failed to develop a sufficient Th2 immune response indicated by reduced production of IL-4 and IL-13 by splenocytes after stimulation with schistosome egg antigen (SEA) (40). In fact, these mice developed a highly polarized Th1 immune response characterized by increased production of IFN-γ by splenocytes from infected mice (40). Moreover, impairing IL-4Rα-signalling on pan-T cells abrogated Th2 cytokine production while augmenting Th1 cytokine production by total mesenteric lymph node cells and splenocytes stimulated with α-CD3 in vitro (41). Therefore, these studies demonstrated the importance of IL-4/IL-13-responsive T cells in driving optimal Th2 immunity during *S. mansoni* infection.

Mice deficient of alternatively activated macrophages developed a mixed Th1/Th2 cytokine responses characterized by increased production of IL-4Rα-responsive cellular populations that are involved in coordinating the development of Th2 immunity during acute schistosomiasis. Mice deficient of IL-4Rα signalling specifically on CD4+ T cells failed to develop a sufficient Th2 immune response indicated by reduced production of IL-4 and IL-13 by splenocytes after stimulation with schistosome egg antigen (SEA) (40). In fact, these mice developed a highly polarized Th1 immune response characterized by increased production of IFN-γ by splenocytes from infected mice (40). Moreover, impairing IL-4Rα-signalling on pan-T cells abrogated Th2 cytokine production while augmenting Th1 cytokine production by total mesenteric lymph node cells and splenocytes stimulated with α-CD3 in vitro (41). Therefore, these studies demonstrated the importance of IL-4/IL-13-responsive T cells in driving optimal Th2 immunity during *S. mansoni* infection.

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### Table 1 Schistosoma mansoni-induced pathological outcomes in cell-specific IL-4Rα-deficient mice

| Mouse strain         | IL-4Rα cell specificity | Mortality | AST level | Fibrosis | LPS level | Reference |
|----------------------|-------------------------|-----------|-----------|----------|-----------|-----------|
| IL-4Rα−/−            | All cells               | +         | +         | −        | +         | (36)      |
| LysMCreIL-4Rαlox     | Macrophages and         | +         | +         | ±        | +         | (36)      |
| CD4+IL-4Rαlox        | CD4+ T cells            | −         | +         | ±        | −         | (40)      |
| iLckCreIL-4Rαlox     | Pan-T cells             | +         | ±         | ±        | ±         | (41)      |
| SM-MHCCreIL-4Rαlox   | Smooth muscle cells     | +         | NM        | ±        | ±         | (42)      |

AST, aspartate transaminase (indicator of hepatocellular damage); LPS, lipopolysaccharides (indicator of gut destruction); +, increased compared to littermate control mice; −, decreased compared to littermate control mice; ±, equivalent to littermate control mice; NM, not measured.
IL-4Rα SIGNALLING DOWN-MODULATES LIVER FIBROSIS DURING ACUTE SCHISTOSOMIASIS

Studies have demonstrated that interfering with IL-4Rα signalling on haematopoietic cells impairs tissue fibrosis during *S. mansoni* infection (16, 36, 37, 41). IL-13 was identified as a main profibrotic factor driving collagen production during *S. mansoni* infection (20, 51). It was postulated that IL-4/IL-13-responsive alternatively activated macrophages are an important source of proline, a key ingredient in collagen formation (52). However, mice deficient of alternatively activated macrophages had similar concentrations of hydroxyproline as wild-type littermate control mice infected with *S. mansoni* (36). Another marker for alternatively activated macrophages is Arginase-1, a key enzyme involved in the synthesis of collagen and fibrosis (53, 54). A recent study by Pesce and colleagues found that mice deficient of Arginase-1-expressing macrophages were resistant to *S. mansoni* infection compared to wild-type control mice (37). This was accompanied by enlargement of the liver and increased shunting of the eggs into the lungs, the key pathological features associated with hepatosplenic form of schistosomiasis (54–56). Therefore, these studies have demonstrated that IL-4/IL-13 signalling to macrophages via IL-4Rα or macrophage-derived Arginase-1 do not mediate collagen deposition during schistosomiasis in mice.

Infection of Lck^−/−^IL-4Rα^−/−^ mice with *S. mansoni* resulted in unaltered liver hydroxyproline content compared to littermate control mice (40). Furthermore, collagen deposition was similar between pan-T cells IL-4Rα-deficient mice and littermate control mice (41). These findings were further supported by a study by Herbert and colleagues that showed that chimeric mice lacking IL-4Rα expression on bone marrow cells (BM IL-4Rα^−/−^) had equivalent concentration of hydroxyproline as wild-type control mice (37). In contrast, non-BM IL-4Rα^−/−^ mice had reduced concentration of hydroxyproline compared to wild-type mice (37). Therefore, these studies demonstrated that IL-4/IL-13-responsive nonbone marrow-derived cells are a cellular source of collagen during *S. mansoni* infection.

CONCLUSION

Cell-specific IL-4Rα expression is crucial for elucidating mechanisms responsible for conferring host resistance or susceptibility to acute schistosomiasis in mice. Furthermore, cell-specific IL-4Rα expression influences the development of Th1/Th2 immune responses and regulated liver granuloma size and cellular composition. Therefore, more efforts are required to generate more cell-specific IL-4Rα-deficient transgenic mice strains to improve our insights and understanding of the immunobiology of schistosomiasis and factors contributing to host resistance.

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