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ROLE OF ARGINASE ON THE PROGRESS OF SCHISTOSOMIASIS CAUSED BY *SCHISTOSOMA MANSONI*

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Abstract

Schistosomiasis is a parasitic disease caused by trematode flat worms of the genus *Schistosoma.* Most of the helminthic infections generally associated with the development of T-helper 2 (Th2) cell response. However, the acute stage of the infection induces Th1 response and the chronic stage induces the Th2 response. These Th2 cells produce cytokines that can alternatively activate macrophages and result in production of arginase. Arginase catalyzes the conversion of arginine in to L-ornithine and urea. L-ornithine is a necessary metabolite for the production of polyamines and prolines, which control cell proliferation and collagen production respectively. Parasite antigen-specific host immune responses which are expressed as inflammatory reaction are mostly the cause of host morbidity in Schistosomiasis. Therefore, this review was aimed to describe the role of arginase on the progression of Schistosomiasis. The acute stage of the disease that is characterized by increased Th1 cytokine production, and elevated activity of inducible nitric oxide synthase (NOS) which will result immunopathology are antagonized by the activity of arginase through reduction of cell differentiation and reduced production of nitric oxide by computing to arginine respectively. The immune-suppressive ability of arginase functions as an inhibitor of inflammation and fibrosis following chronic Schistosomiasis. On the other hand schistosomula killing ability of arginase was also suggested. In contrast, inhibition of NOS activity, synthesis of prolines and polyamines favor pathological importance of arginase. Therefore arginase has both inhibitory and pathologic role on the progression of Schistosomiasis. For this purpose, attention should be given on arginase effect study on human Schistosomiasis.

Keywords: Arginase, Schistosomiasis, Progression.

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Introduction

Schistosomiasis

Schistosomiasis is a chronic disease of human caused by blood fluke parasite called *Schistosoma*. *Schistosoma haematobium, S. mansoni, S. japonicum, S. mekongi*and *S. intercalatum* are among the different species of *Schistosoma.* It was estimated that about 207 million people in the world were affected by schistosomiasis[1]. In 2004 the annual global estimated death due to schistosomiasis was 41,000[2]. The estimated mortality owing to *Schistosoma mansoni*and *Schistosoma haematobium*in sub-Saharan Africa was 280,000 per year[3]. Both *S.mansoni*and *S.haematobium*are endemic in Ethiopia where about 4 million people are estimated to be infected and 30-35 million people are at risk of infection[4, 5].Health problems associated with schistosomiasis include sever organ pathology, anemia, malnutrition, stunted growth, impaired cognitive development and reduced capacity to work[6].

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As with most helminthic infections, schistosomiasis is associated with the development of a T helper 2 cell response[7]. In the course of an infection, the immune response progresses through at least three phases. In the first 3–5 weeks, during which the host is exposed to migrating immature parasites, the dominant response is Th1. As the parasites mature, mate and begin to produce eggs at weeks 5–6, the response alters markedly; the Th1 component decreases and this is associated with the emergence of a strong Th2 response. This response is induced primarily by egg antigens[8]. The chronic Th2 response is highly pathogenic resulting in hepatic fibrosis, portal hypertension and variceal bleeding which are the primary causes of morbidity and mortality in human schistosomiasis[9].

The survival of the host depend on the ability to make an appropriately balanced Th response that is able to prevent debilitating acute disease, and minimize fibrosis and severe morbidity during chronic infection[7]. The central role of immune response to schistosomiasis is played by Th2 cytokines recent works on pathogenesis of schistosomiasis was focused on mechanisms that initiate, maintain and suppress type-2 immunity[10].

Nature of arginase enzyme

Arginase is a hydrolase present in many tissues and organs that catalyzes arginine in to ornithine and urea[11]. It is expressed predominantly in the liver, and to lesser amount in breast, kidney, testes, salivary glands, epidermis and erythrocytes[12]. It exists in 2 isoforms, liver-type arginase I and non-hepatic type arginase II[13]. The cytosolic arginase (arginase 1) plays an important role in the urea cycle while arginase 2 is expressed in low amount and its function is less studied[14].

As it is shown on figure 1 arginine which is a substrate for both arginase and inducible Nitrogen Oxide Synthetase (iNOS) is a precursor for the synthesis of urea, polyamines, prolines, and Nitric Oxide[13]. In addition, the fundamental role in the hepatic urea cycle arginase is also expressed in the immune system. It is induced by Th2 cytokines and inflammatory agents. Macrophages and polymorphonuclear neutrophils can express it during inflammation[15]. In immunity arginase is an important enzyme that acts as double edged sword[16].

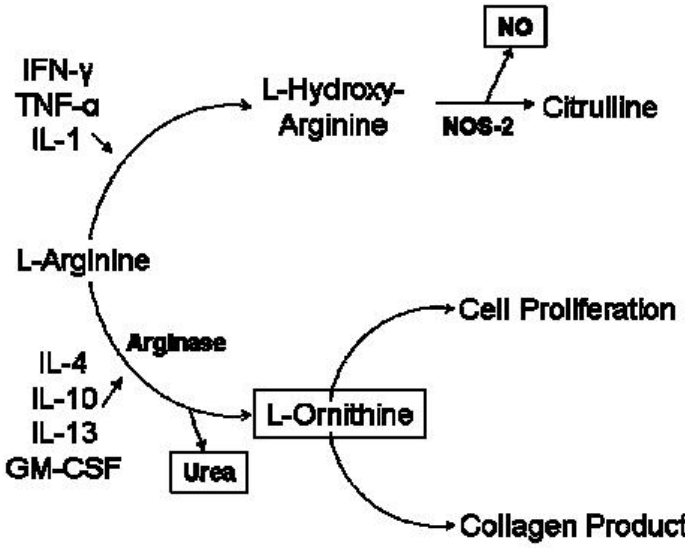

Fig. No. 01: Th1 and Th2 stimulant response pathway in macrophage cells[17].

L-ornithine, a product of arginase activity, is a necessary metabolite for the production of polyamines and prolines, which control cell proliferation and collagen production, respectively. Both of these activities are key parameters in the pathogenesis of inflammatory responses[18]. The protective activity of the Th2 response in schistosomiasis is directly linked to its role in promoting the differentiation of Alternatively Activated Macrophages (AAMs) that provide arginase[19]. Therefore,arginase activity by alternatively activated macrophages is an essential component of the mammalian host response in schistosomiasis[20]. Different mechanisms help arginase to play its role in the progression of schistosomiasis in the acute and chronic stage of

the disease[13, 15]. Therefore, this review was aimed to describe the progression of schistosomiasis and role of arginase during schistosomiasis.

Role of arginase on the progression of schistosomiasis

Progression of Schistosomiasis

Penetration of the skin by the cercariae is the first step in the invasion process of schistosomiasis. The cercariae will be changed into schistosomula which migrate to hepatic portal system via lungs and differentiation in to male and female, pairing and relocation to mesenteric venous plexus follows. Viable, active and highly antigenic eggs are deposited and these eggs can attach to the endothelium of mesenteric blood vessels, and cause inflammatory response in order to find their way into the intestine to be excreted in the faeces[21].

Parasite ova cause the recruitment of lymphocytes, eosinophil, and macrophages to the local microenvironment and this inflammatory response may damage the entire organ[22]. Therefore, few eggs may get trapped into liver, intestine or elsewhere and induce granuloma formation. This granulomatous inflammation is the cause of most pathological features and mortality due to *S. mansoni*[21]. Granulomatous reaction is composed of lymphocytes, macrophages and a large number of eosinophils; around eggs deposited in the tissuesand it progress to fibrosis, leading to portal hypertension[23]. Cell mediated immunity is promoted by secretion of Th1 interferon and interleukins ((IFN)-γ and interleukin (IL)-2) while antibody production is mediated by Th2 cytokines (IL-4, 5, and 10) in which both responses cross-regulate each other[24, 25].The major role of antibodies in protective immunity is to induce cytotoxic destruction of schistosomula targets, and antibody-cell mediated cytotoxicity appears to be the main mechanism for destruction of parasites both in rat and human schistosomiasis[26].

Two main clinical conditions recognized in *S.mansoni* infected individuals are acute schistosomiasis and chronic schistosomiasis[7]. Acute schistosomiasis in humans is a debilitating febrile illness that can occur before the appearance of eggs in the stool and which is thought generally to peak between 6 and 8 weeks after infection[27]. Peripheral-blood mononuclear cells (PBMCs) produce large quantities of Tumor Necrosis Factor (TNF), Interleukin-1 (IL-1) and IL-6. Cytokine production by PBMCs after stimulation with parasite antigen reflects a dominant Th1, rather than Th2, response[28].

When the parasite is sexually mature and starts to produce eggs the Th2 response becomes dominant on the former[29]. Antigen-specific host immune response which is expressed as inflammatory reaction is mostly the cause of host morbidity in schistosomiasis[30]. Generally, death during acute schistosomiasis was associated with increased Th1 cytokine production, hepatic and intestinal histopathology, increased NOS2 activity, inability to develop a Th2 response to regulate the initial pro-inflammatory response[19, 31].

Chronic disease is graded according to severity. The most serious form is a life-threatening hepatosplenic disease, which is usually accompanied by severe hepatic and periportal fibrosis[32]. Even though fibrosis is a normal means of wound healing responses, excessive accumulation of those substances could lead to the destruction of normal tissue architecture and loss of function[33]. Although a Th2 response is the dominant immune response during chronic schistosomiasis, prolonged Th2 responses contribute to the development of hepatic fibrosis and chronic morbidity[9].

Mechanism and Effect of arginase on the progression of schistosomiasis

T-helper 2 response in schistosomiasis plays an important role in promoting the differentiation of AAMs that give rise to arginase[19]. Arginase-I expressing alternatively activated macrophages are critical for host survival in acute *S. mansoni* infection and it protects the host during acute schistosomiasis by reducing massive Th1-mediated immunopathology and iNOS activity[34]. Arginase compute with the activity of iNOS activity and result in the reduction of NO production where over production of this substance can induce tissue damage and may contribute to mortality during schistosomiasis infection[30].

In contrast to arginase role of NOS inhibition, because arginase mediate production of proline that will result in fibrosis as it is a substrate for collagen synthesis, inhibition of iNOS activity leads to granulomas. Study using NOS-2-deficient mice

demonstrated that, the anti-inflammatory and anti-fibrotic effects of the type-1 response are completely NOS dependent. NOS-deficient mice developed granulomas 8 times larger than wild type mice did[35]. Similarly, investigation of the NO synthase and arginase pathways in resident peritoneal macrophages of mice infected with *S.mansoni* revealed opposite effect of the two enzymes; NO involved in the killing of the parasite whereas arginase stimulate parasite growth via polyamine synthesis. They found that, in infected mice, arginase expression in macrophages was associated with a tenfold increase in the concentration of circulating ornithine-derived polyamines. Therefore, arginase was suggested to have pathological importance, since parasitic helminthes are thought to be dependent on their hosts for the uptake and interconversion of polyamines[36].

IL-4 and IL-13 stimulate AAM differentiation and arginase I production, which in turn promotes Transforming Growth Factor-β (TGF-β) secretion but suppresses production of IL-6, IL-12, and IL-23 in study conducted on *S.mansoni* infected mice. This reduces Th1 and Th17 differentiation and increases the T regulatory response that promotes increased IL-10 and TGF-β. These later cytokines limit intestinal neutrophilic inflammation caused by the passage of worm ova through host intestinal tissue and may promote tissue repair as worm ova are passed out of the intestine and into the fecal stream throughout the course of disease and antagonizing Th1- and Th17-associated immunopathology[37]. IL-10 and TGF-*β* promote host survival by suppressing pro-inflammatory cytokine production and liver injury during acute schistosomiasis[38]. Thus, arginase contributes to the resolution of schistosomiasis by inhibiting Cluster of Differentiation (CD4+) T cell effector function[19]. The destructive potential of *S. mansoni*egg induced inflammation is counter balanced by alternative macrophage activation. This allows preservation of intestinal and liver functions during acute schistosomiasis[34].

Arginase-I is commonly believed to promote inflammation, fibrosis, and wound healing by enhancing L-proline, polyamine, and Th2 cytokine production. However, it was shown that it functions as an inhibitor of inflammation and fibrosis following chronic *S. mansoni* infection. Immunosuppressive role of arginase was demonstrated through the restoration of T cell proliferation by the provision of L-arginine, suggesting that arginase-I expressing macrophages depleted arginine, which is required to sustain CD4+ T cell responses. Thus these data suggested that, arginase-I expressing macrophages function as suppressor by depleting the available stores of arginine, which is required for T cells to proliferate when stimulated with soluble egg antigens[19].

Host protective role of arginase in schistosomiasis is mostly limiting parasite mediated tissue damage rather than killing[39]. This is because it does have a high role of inhibiting the host immunity, including the Th2 response itself[40, 41] or arginase-I negatively regulates Th2 responses and suppresses Th2-mediated fibrosis[11]. Therefore, the ability of arginase 1 to inhibit the cellular proliferation resulted in to play a critical regulatory role[42]. The major function of arginase 1 is to down modulate granulomatous inflammation in the liver and intestine and to slow the progression of Th2-dependent fibrosis in chronically infected mice[19]. In contrast to the inhibitory role, arginase 1 has a direct role in the biosynthetic pathway of collagen production and is thought to promote fibrosis during schistosomiasis[18].

In other way schistosomula killing ability of arginase was shown by an in vitro study. In this study, adherent peritoneal cell monolayers from *Corynebacteriumparvum* treated C57BL/6J mice killed an increased proportion of schistosomula in 24 h and suggested that arginase is a critical mediator of in vitro killing of this multicellular organism by activated macrophages[43, 44].Even though the mechanism is not clear, it was suggested that arginase may interfere with the parasites metabolism by arginine depletion because the parasite take up arginine or accumulation of toxic products such as urea or ammonia may result in such cytotoxicity[44].

Conclusion and recommendation

Schistosomiasis involved Th2 response, where the cytokines that are produced by these cells result in alternative activation of macrophages gives rise to arginase enzyme production. Involvement of arginase in certain mechanisms enabled arginase to play both inhibitory and pathologic role on the progression of schistosomiasis that is on both the

acute and chronic schistosomiasis. Even though mice are good animals to be used as experimental animal to observe role of arginase, efforts should be used to focus on effect of arginase on human schistosomiasis that will enable to develop the appropriate vaccine and/or treatment against schistosomiasis. The development of vaccine and treatment involving arginase for schistosomiasis should consider balancing of the inhibitory and pathologic effect of arginase on the progression of schistosomiasis.

References

1. WHO.Schistosomiasis: Media Centre 2013.
2. WHO. Schistosomiasis:The global burden of disease; 2008:110.
3. van der Werf MJ, de Vlas SJ, Brooker S, Looman CW, Nagelkerke NJ, Habbema JD. Quantification of clinical morbidity associated with schistosome infection in sub Saharan Africa. Acta Trop. 2003; 86(2-3):125-39.
4. Kassa L, Omer A, Tafesse W, Taye T, Kebebew F, Beker A. Schistosomiasis: Diploma program for the Ethiopian health center team: Ethiopia public health training initiative. 2005:8-18.
5. EHNRI. Proceding of the international stekholders consultative meeting on schistosomiasis and soli transmitted helminthes (STH) in Ethiopia. International workshop proceeding on schisto/STH; 2012:29-48.
6. WHO.working to overcome the global impact of neglected tropical disease: first WHO report on neglected tropical diseases. 2010:132.
7. Pearce EJ, MacDonald AS.Theimmunobiology of schistosomiasis. Nat Rev Immunol. 2002; 2:499-511.
8. Fallon PG. Immunopathology of schistosomiasis: a cautionary tale of mice and men. Immunol Today 2000;21(1):29-35.
9. Cheever AW, Hoffmann KF, Wynn TA. Immunopathology of S.mansoni in mice and men.Immunol Today 2000;21(9):465-6.
10. Wynn TA, Thompson RW, Cheever AW, Mentink-Kane MM. Immunopathogenesis of schistosomiasis. Immunol Rev. 2004;201 (1): 156-67.
11. Worthington Biochemical Corporation. Arginase; 2013.
12. DARG. Quantitative Colorimetric Arginase Determination.BioAssay Systems. 2012.
13. Mori M. Regulation of Nitric Oxide Synthesis and Apoptosis by Arginase and Arginine Recycling1–3.J Nutr 2007;137 1616–20.
14. Mori M., T. Gotoh. Regulation of nitric oxide production by arginine metabolic enzymes. BiochemBiophys Res Commun. 2000; 275: 715-9.
15. Munder M. Arginase: an emerging key player in the mammalian immune system. Br J Pharmacol. 2009; 158:638-51.
16. Das. P, Lahiri. A, Lahiri A, Chakravortty D. Modulation of the Arginase Pathway in the Context of Microbial Pathogenesis: A Metabolic Enzyme Moonlighting as an Immune Modulator. PLoS Pathogens.2010;6.
17. Scott VJ. The Role of Hemozoin in Disease: Oxidative Stress: Vanderbilt University; 2009.
18. Hesse M, Modolell M, Flamme ACL, Schito M, Fuentes JM, Cheever AW. Differential Regulation of Nitric Oxide Synthase-2 and Arginase-1 by Type 1/Type 2 Cytokines In Vivo: Granulomatous Pathology Is Shaped by the Pattern of L-Arginine Metabolism. JImmunol2001;167:6533-44.
19. Pesce JT, Ramalingam TR, Mentink-Kane MM, Wilson MS, Kasmi KCE, Smith AM. Arginase-1–Expressing Macrophages Suppress Th2 Cytokine–Driven Inflammation and Fibrosis.PLoS Pathogens.2009.
20. Fitzpatricka JM, Fuentes JM, Chalmersa IW, Wynn TA, Modolelld M, Hoffmanna KF. Schistosoma mansoniarginase shares functional similarities with human orthologs but depends upon disulphide bridges for enzymatic activity. Int J Parasitol 2009; 39(3): 267-279.
21. Nayak A, Kishore U. Pathogenic Persistence and Evasion mechanisms in Schistosomiasis Landes Bioscience and Springer; 2013.
22. Herbert DBR, Orekov T, Perkins C, Rothenberg ME, Finkelman FD. IL-4R Expression by Bone Marrow-Derived Cells Is Necessary and Sufficient for Host Protection against Acute Schistosomiasis.J Immunol 2008;180: 4948-4955.
23. Butterworth AE. Immunological aspects of human schistosomiasis.Br Med Bull 1998;54 (2):357-68.
24. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. Definition according to profiles of lymphokine activities

and secreted proteins.J Immunol.1986; 136: 2348-55.
25. Mosmann TR, Sad S. The expanding universe of T-cell subsets: Th1, Th2 and more. Immunol Today1996; 17:138-46.
26. Wu GY, Halim MH. Schistosomiasis: progress and problems.*World J. Gastroenterol.* 2000; 6(1):12-9.
27. Rabello A. Acute human schistosomiasis mansoni.MemInstOswaldo Cruz. 1995; 90:277-80.
28. De Jesus AR, Silva A, Santana LB, MagalhÃ£es A, de Jesus AA, de Almeida RP, et al. Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. *J Infect* 2002; 185(1):98-105.
29. Burke ML, Jones MK, Gobert GN, Li YS, Ellis MK, DP M. Immunopathogenesis of human schistosomiasis. Parasite Immunol.2009; 31(4):163-76.
30. Coutinho EM, Oliveira SAd, Barros AFd, Silva FL, Ramos RP. Manson's schistosomiasis in the undernourished mouse: some recent findings.MemInstOswaldo Cruz, Rio de Janeiro. 2010;105(4):359-66.
31. Brunet LR, Finkelman FD, Cheever AW, Kopf MA, Pearce EJ. IL-4 protects against TNF-alpha-mediated cachexia and death during acute schistosomiasis. J Immunol. 1997;159(2):777-85.
32. Dunne DW, Pearce EJ. Immunology of hepatosplenic schistosomiasis mansoni: a human perspective. Microbes Infect. 1999;1(7):553-60.
33. Kaviratne M, Hesse M, Leusink M, Cheever AW, Davies SJ, McKerrow JH. IL-13 Activates a Mechanism of Tissue Fibrosis That is Completely TGF- Independent. JImmunol. 2004;173:4020-9.
34. Herbert DBR, lscher CH, Mohrs M, Arendse B, Schwegmann A, Radwanska M. Alternative Macrophage Activation Is Essential for Survival during Schistosomiasis and Downmodulates T Helper 1 Responses and Immunopathology. Immunity.2004;20:623-35.
35. Hesse M, Cheever AW, Jankovic D, Wynn TA. NOS-2 Mediates the Protective Anti-Inflammatory and Antifibrotic Effects of the Th1-Inducing Adjuvant, IL-12, in a Th2 Model of Granulomatous Disease. Am J Pathol. 2000;157(3):945–55.
36. Abdallahi OM, Bensalem H, Augier R, Diagana M, De Reggi M, B. G. Arginase expression in peritoneal macrophages and increase in circulating polyamine levels in mice infected with Schistosoma mansoni. Cell Mol Life Sci. 2001;58(9):1350-7.
37. Herbert DBR, Orekov T, Roloson A, Ilies M, Perkins C, O'Brien W. Arginase I Suppresses IL-12/ IL-23p40–Driven Intestinal Inflammation during Acute Schistosomiasis. J Immunol.184:6438-46.
38. Herbert DBR, Orekov T, Perkins C, D.Finkelman F. IL-10 and TGF-β Redundantly Protect against Severe Liver Injury and Mortality during Acute Schistosomiasis. JImmunol. 2008;181(10):7214-20.
39. Herbert DR, Hölscher C, Mohrs M, Arendse B, Schwegmann A, Radwanska M. Alternative macrophage activation is essential for survival during schistosomiasis and downmodulates T helper 1 responses and immunopathology. Immunity2004; 20(5):623-35.
40. Pesce JT, Ramalingam TR, Wilson MS, Mentink-Kane MM, W.Thompson R, Cheever AW. Retnla (Relma/Fizz1) Suppresses Helminth- Induced Th2-Type Immunity.PLoS Pathogens. 2009;5(4).
41. Nair MG, Du Y, Perrigoue JG, Zaph C, Taylor JJ, Goldschmidt M, et al. Alternatively activated macrophage-derived RELM is a negative regulator of type 2 inflammation in the lung. J Exp Med. 2009;206 (4):937-52.
42. Jenkins SJ, Allen JE. Similarity and Diversity in Macrophage Activation byNematodes, Trematodes, and Cestodes. J Biomed Biotechnol. 2010.
43. Olds GR, Ellner JJ, Kearse LA Jr, Kazura JW, AA. M. Role of arginase in killing of schistosomula of Schistosoma mansoni. J Exp Med1980; 151(6):1557-62.
44. Peck CA, Carpenter MD, Mahmoud AAF. Species-related Innate Resistance to Schistosoma mansoni: Role of mononuclear phagocytes in schistosomula killing in vitro. J Clin Invest. 1983; 71:66-72.