



Review Article

Interleukin 4 (IL-4) in Urinary Schistosomiasis as a Diagnostic Biomarker During Its Reinfection- A Review

Aigbogun Edwin Ighodaro¹, Mohammed Sani Sambo Datsugwai¹, Umar Nabeela Bello¹, Afangide Christopher Stephen²

¹Department of Microbiology, Faculty of Science, Kaduna State University, Kaduna, Nigeria

²Zamani College, Kaduna, Nigeria

Email address:

aigbogunighodaro@gmail.com (A. E. Ighodaro)

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Abstract: Urinary schistosomiasis is caused by *Schistosoma haematobium* worm and it is most common source of haematuria (blood in urine) worldwide. This disease has long been recognized as serious public health to man especially in countries like Nigeria, Egypt, with currently more than 790 million people at risk. Since IL-4 stimulates IgE production, the hypothesis that Helper T cell 2 (Th2) associated with cell immunity participate in protection to reinfection in an anti-inflammatory dichotomy manner. IL-4 confers proliferation of T cells, induction of class switching immunoglobulins and also serve as a biomarker in co association with IL-5 for (Th2). The aim of this review paper is to simplify the immunological mechanism that happens when Schistosome worm elicit strong humoral and cellular response in definite host.

Keywords: Helper T Cell, Schistosomiasis, Interleukin 4, Immunoglobulin

1. Introduction

Schistosomiasis or bilharzia is a disease condition caused by a trematode schistosome, which was discovered by Theodor Bilharz in 1852. Species of the worm that prevalently infect man are *Schistosoma haematobium*, *S. mansoni* and *S. japonicum*. This condition is characterized by inflammation mainly in the bladder, intestine and liver [1, 2]. Schistosomiasis can be acute which is characterized by feverish syndrome (Katayama fever), systemic hypersensitivity reaction within few weeks to months after primary infection [3] and chronic; abdominal pain, inflamed liver, blood in the stool or blood in the urine, and problems passing urine [4].

Epidemiologically, about 200-300 million people are infected worldwide and more than 790 million people are at risk [4, 5]. Immunopathologically, schistosome eggs trapped in the tissue for years leading to obstruction of the urinary bladder, urogenital inflammation and scarring by *S. haematobium* or intestine or liver leading to inflammation and

fibrosis by *S. mansoni* and *S. japonicum* respectively [3] and the chronic stage of this infection is characterized by the release of IL-4 [4].

IL-4 was discovered by Maureen Howard and William Paul and Ellen Vitella and her research group in 1982. They are cytokines produced by leukocyte in the blood. IL-4 has compact, globular fold, stabilized by three disulphide bonds.

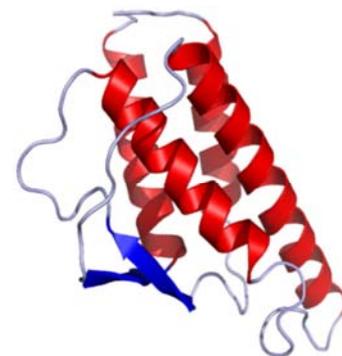


Figure 1. Interleukin 4 cytokine protein [6].

One half of the structure is dominated by a 4-alpha helix bundle with a left handed twist [7]. IL-4 was once said to be produced only by Th1/Th2 but recent studies have revealed that it can be produced by Natural Killer (NK) T cells basophils, mast cells, eosinophils, Type II innate lymphoid cells (ILC2 cells) [7-9].

IL-4 orchestrates the stimulation of activated B-cell to elicit the production of antibodies which can further undergo class switching in order to produce immunoglobulin E (IgE) necessary for reinfection of schistosome worm which serve as

diagnostic biomarker [10], elicit differentiation and proliferation of Helper T cell, cell metastasis, induces differentiation of naive helper T cells Th0 cells to Th2 cells. Upon activation by IL-4, Th2 cells subsequently produce additional IL-4 in a positive feedback loop [11] and has recently be found to initiate a regeneration cascade through phosphorylation of its intracellular effector STAT6 in an experimental Alzheimer's disease model in adult zebra fish brain [12].

2. Overview Roles of Interleukin 4 in Urinary Schistosomiasis

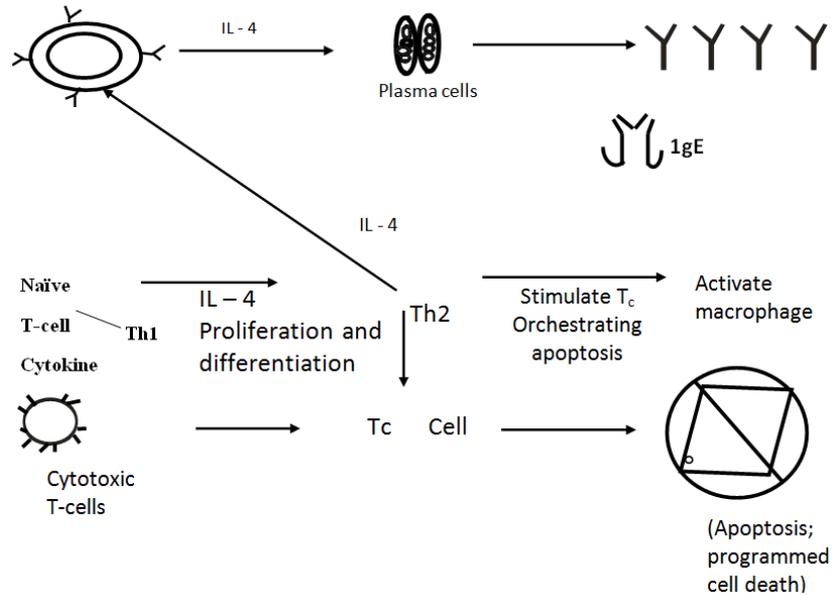


Figure 2. Diagram of interleukin-4 role in urinary schistosomiasis.

When granulomatous reaction occur following infection by *S. heamatobium*, the Antigen Presenting Cells (APC) process the exogenous antigen of the adult worm into antigen peptides and present it on the receptor referred to as Major Histocompactability Complex (MHC II) of Helper T cells.

The latter delivers cytokine that further activates the APC [13]. The IL-4 released by the Th0 in higher concentration further orchestrate the proliferation and differentiation of Th 2 cells and inhibit Th1 cells [14].

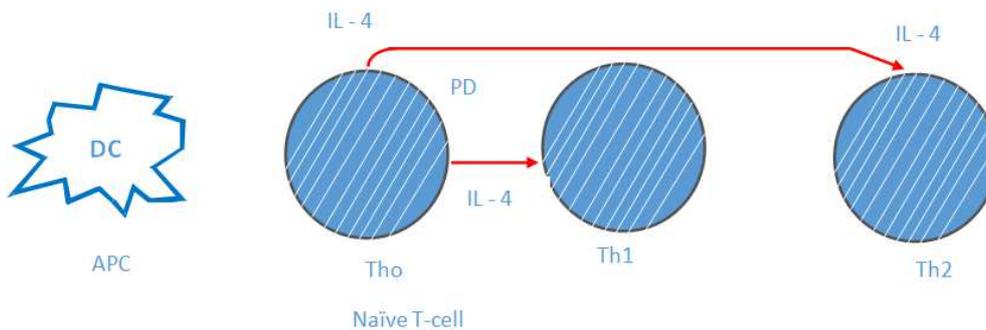


Figure 3. The proliferation and differentiation of Tho to Th2 after activation by APC.

- KEY:
 Tho- Naïve T cell
 Th- Helper T cell
 Th1-Helper T cell 1
 Th2-Helper T cell 2
 DC – Dentrtric cell
 APC –Antigen presenting cell

2.1. Stimulation of Activated B Cells

IL-4 induces the stimulation of activated B cells against the worm antigen. The differentiated Th2 cells further releases IL-4 towards B cells which causes cytochange of B cells, thereby differentiating it to plasma cells which further produces immunoglobulin (Ig) and memory B cell against

further reinfection of the exogenous antigen of the worm [13]. One condition for this to happen is that, MHC of Th2 must recognize B cell receptor, adhere, synthesize IL-4 and CD4 ligand which orchestrates cytoskeletal changes in activated B cells [15].

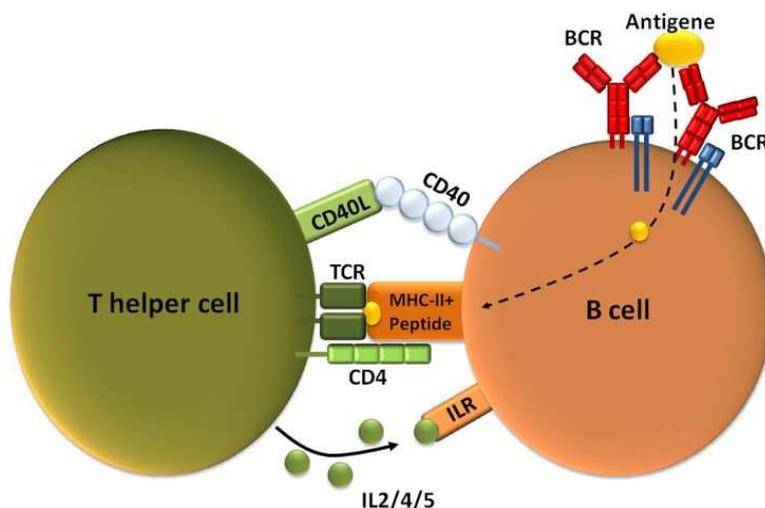


Figure 4. Diagram indicating adherence of B cell to Th2. [16].

The production of antibodies against the antigen of the worm lead to protective outcome such as precipitation, agglutination and complement system activation [17].

It is important to understand that infected individuals of all ages have varying immunoglobulin class and subclass. IgE for example, is associated with resistance to reinfection after treatment with praziquantel, whereas, IgM, IgG 4 and IgG2 are associated with susceptibility to reinfection after treatment while IgA has been implicated with eosinophil mediated killing of the parasite, this is to confirm that IL-4 induce class switching that makes other immunoglobulin to have some specificity but different biological characteristics [18]. In 2007, [19] showed relationship between age and intensity of infection as connected to immunoglobulin profile in cohort group. The result showed that IgM and IgE are extremely high in serum of infected population compared to uninfected population. It synoptically means that without the help of or release of IL-4, there will be no protection to fighting parasitic reinfection, and 2016 result of [20] arrived at the same conclusion with Nmorsi. Hence, measurement of immunoglobulin concentration can be used as indicators of heavy and acute infection of *S. haematobium* in our endemic localities. Reports exits where IgE has been indicated as diagnostic biomarker of infections as it correlates positively with the intensity of infection. Serologically, these levels of Ig can be used as markers of chronic schistosomiasis in clinical and laboratory practice, especially where clinical presentations of the infection are covert and sub clinical [21].

2.2. Allergies or Hypersensitivity

Allergy or hypersensitivity is allergen which is a substance

that causes allergic reaction in susceptible individuals [22].

Researches had been done and facts have been concluded that IgE have protective outcome against parasitic worm and also cause immediate (type 1) hypersensitivity characterized by a reaction in a sensitized individual within minutes of exposure to antigen [23].

Upon exposure, the allergen readily combines with the cell fixed IgE. At least two cell bound IgE molecules for reaction to occur. Within milliseconds, the IgE-antigen attachment and cross linkage of IgE in the cell membrane cause the mast cell or eosinophil to release histamine, leukotrienes, postagladins and cytokines in the process called degradation. These mediators are direct causes of hives, hay, fever, asthma and anaphylactic shock [24].

2.3. Diagnostic Biomarker

Parasitological techniques (stool examination and/or urine filtration/microscopy) are still the diagnosis of choice in national schistosomiasis control programmes around the globe. However it comes with its cost of labour and time wallowing procedures. There is an undying need for a more sensitive approach especially in endemic area and persons with prolong cases of Schistosomiasis [10]. The presence of IL-4 can be measured by the amount or concentration of CD4 using flow cytometry or ELISPOT kit [25].

3. Conclusion

Minute amount of IL-4 against urinary schistosomiasis does not produce significant reactions in the living system except in increased concentration or co association with IL-5. However,

it is a key player in in dealing with parasitic infection caused by *S. haematobium* because of its multi facet dynamics in function as part of the immune system to actualizing its primary aim to protect infected individuals against reinfection and regulate proliferation, differentiation, and apoptosis in multiple cell types of haematopoietic and non-haematopoietic source.

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