Role of Parasitic Helminths in Protection Against Inflammatory Bowel Diseases

Doaa A. Yones

Department of Medical Parasitology, Faculty of Medicine, Assiut University, Egypt

ABSTRACT: Helminth parasites are of considerable medical and economic importance. Studies of the immune response against helminths are of great interest in understanding interactions between the host immune system and parasites. The lack of exposure to helminth infections, as a result of improved living standards and medical conditions, may have contributed to the increased incidence of inflammatory bowel diseases (IBDs) in the developed world. Epidemiological, experimental, and clinical data sustain the idea that helminths could provide protection against IBD. Studies investigating the underlying mechanisms by which helminths might induce such protection have revealed the importance of regulatory pathways, for example, regulatory T-cells. Further investigation on how helminths influence both innate and adaptive immune reactions will shed more light on the complex pathways used by helminths to regulate the hosts immune system. Although therapy with living helminths appears to be effective in several immunological diseases, the disadvantages of a treatment based on living parasites are explicit. Therefore, the identification and characterization of helminth-derived immunomodulatory molecules that contribute to the protective effect could lead to new therapeutic approaches in IBD and other immune diseases.

[Doaa A. Yones. **Role of Parasitic Helminths in Protection Against Inflammatory Bowel Diseases Doaa A. Yones.** Journal of American Science 2011; 7(12):945-955]. (ISSN: 1545-1003).
http://www.americanscience.org.

KEYWORDS: Helminths, Inflammatory bowel diseases, Hygiene Hypothesis, Immunomodulation.

INTRODUCTION

More than two billion people are infected with parasitic helminths. Although infection by most of these pathogens are generally not fatal, they are associated with high rates of morbidity, with chronic infection often leading to anaemia and malnourishment.[1]

Developed countries have controlled these infections through primary health care programs and effective public sanitation, but helminth diseases are still widespread in developing nations and often drug treatment does not protect against rapid reinfection. The need for effective vaccines to control these infections is compelling and at least few clinical trials are currently underway. However, one impediment towards development of an effective vaccine is lack of understanding of the actual components of the immune response that mediate protection against helminthes.[2]

Helminths usually cause asymptomatic or subclinical chronic infection, although some parasitized individuals can suffer from severe disease which may be fatal. Indeed, worms tend to be aggregated in their distribution, with a large number of hosts harboring few parasites and few heavily infected hosts. [3]

This remarkable equilibrium between most hosts and parasites is the product of long term coevolution of the two partners and particularly of the immune defence of the host and the immune evasion of the parasite.[4]

For parasites, it is advantageous to trick the host into developing an ineffective immune response, to find a suitable niche for maturation and propagation, and to do so without killing or unduly harming the host. Conversely, the host has to ideally generate an effective immune response to expel the parasite, and minimize its harmful effects, while not sacrificing its ability to effectively respond to other pathogens.[5] The immune responses of the hosts to helminth infection are generally characterized by a skewed Th2-like response. Helminths have developed several means of escaping these immune responses. Recently, Maizels et al. called them "masters of immunomodulation". These immunomodulatory abilities enable the worm to persist in the host and can lead to interactions with inflammatory and immune mechanisms involved in other infections, to vaccines or in allergic and autoimmune diseases.[6]

IBDs, such as Crohn's disease (CD) and ulcerative colitis (UC), are chronic immune diseases of the gastrointestinal tract. Although the aetiologies of these diseases still remain unknown, probably results from an inappropriately vigorous immune response to the normal contents of the intestinal lumen.[7] Genetic factors and environmental factors both contribute to the damaging mucosal immune response.[8]

Environmental factors affect the risk for IBD.[9] Appendicitis followed by appendectomy lowers the incidence of UC,[10–12] whereas cigarette smoking enhances the chance for CD.[13] Some enteric infections can trigger IBD like cytomegalovirus and amebic (*Entamoeba histolytic*a) colitis. Moreover, the modern day absence of exposure to intestinal helminths is an important environmental factor contributing to IBD.[14]

A characteristic feature of helminth infection is a Th2-dominated immune response, but stimulation of immunoregulatory cell populations, such as regulatory T cells and alternatively activated macrophages, is equally common. Typically, Th1/17 immunity is blocked and productive effector responses are muted, allowing survival of the parasite in a "modified Th2" environment. Drug treatment to clear the worms reverses the immunoregulatory effects, indicating that a state of active suppression is maintained by the parasite.[15-19]

Considering classical Th1/Th2 paradigm, it is reasonable to speculate that helminth induced Th2-skewing with downregulation of Th1 immune responses results in an amelioration of Th1 diseases. As IL-4 is known to suppress Th17 development,[20] Th17 response could also be suppressed as well as Th1 response in helminth-infected or helminth antigen-treated animals.[21] Downregulation of both T helper responses may be beneficial for the amelioration of various kinds of autoimmunity.[22]

There have been several clinical trials using helminthes to treat IBD. Results from these trials suggest that infection with at least some human or animal helminths improves clinical outcome, which supports the premise that natural helminth infection is protective. There was clinical improvement in a double-blind clinical study in UC and an open-label study in CD. These studies used live ova from porcine whipworm (*Trichuris suis*) as an oral therapeutic intervention.[23–25] Another study in CD showed efficacy using live human hookworm administered via skin application.[26]

In the present review, some lights are thrown on recent findings regarding the mechanisms of protection in helminth infections and the advantage of these knowledge to identify and select individual helminth-derived molecules that may harbor therapeutic potential against inflammatory bowel diseases (IBDs).

INFLAMMATORY BOWEL DISEASES AND THE HYGINE HYPOTHESIS

The incidence of IBD has steadily increased in the developed world since 1950.[27,28] According to the hygiene hypothesis, this is directly related to the higher hygienic standards in these countries.[29, 30] It is suggested that the lack of exposure to infectious agents like helminths, as a result of improved living standards and medical conditions, modulates the development of the immune system and thereby increases the risk of immune diseases.[31, 32] The hygiene hypothesis was initially proposed by Strachan in 1989 for hay fever,[33] and additional epidemiological studies were performed to further investigate the link between this hygiene concept and the incidence of other immunological diseases. As a consequence, the hygiene hypothesis is now proposed for several immunological disorders such as asthma and allergic diseases,[34] cardiovascular diseases,[35] Type 1 diabetes mellitus,[36] multiple sclerosis,[37] and IBD.[38] The hygiene hypothesis for IBD is clearly supported by the geographical distribution of the disease. There is a well described north-south gradient for the incidence of IBD. Northern Europe and North America have the highest IBD incidence rates whereas Crohn's disease and ulcerative colitis remain scarce in South America, Africa, and Asia.[28, 39] However, the gap between high and low incidence areas in northern versus southern regions is narrowing. In Asia, for example, incidence rates still remain low as compared to Europe, but they are rapidly increasing.[18] Changing lifestyle is thought to be the major cause of the disease increase in low incidence areas.[40] The most important factor to explain these geographical differences is the socioeconomic level.[38] IBD is more frequently seen among patients with a higher socioeconomic status.[41, 42] Higher socioeconomic levels can be associated with better sanitation conditions, high quality water, and better medical standards.[43] Another factor supporting the hygiene hypothesis is the inverse relationship between infant mortality rates and the incidence of IBD. Infant mortality might be linked to worse hygiene and medical conditions. Countries with high infant mortality rates consequently have lower reported incidence of IBD.[44] As mentioned previously, better hygienic circumstances translate into diminished exposure to infectious agents like helminths. The absence of such parasitic infections during childhood renders the immune system more prone to allergic and immune diseases. Thus infections seem to activate an important protective factor against these disorders.[29] Identifying the nature of this protective effect and implementing this notion in therapeutic strategies against IBD and other immune diseases is now the challenge for basic research.

IMMUNE MECHANISMS AGAINST HELMINTHS AND THEIR REGULATION

Helminth infections are typically associated with hypereosinophilia, considerable IgE production, mucous mastocytosis, and goblet cells hyperplasia. These immune parameters are involved in different effector mechanisms highly depending on where the helminth is localized.[4]

IMMUNE MECHANISMS AGAINST TISSUE PARASITES AND ESCAPE MECHANISMS DEVELOPED BY THE PARASITE

Several mechanisms against tissue-dwelling parasites have been described. These parasites are mainly larval stages, for example, of trematodes (*Schistosoma spp.*, *Fasciola spp.*) or nematodes, which migrate through tissue.

Antibody Dependent Cellular Cytotoxicity (ADCC) is dependent on eosinophils, neutrophils,

macrophages, or platelets as effector cells and IgE, IgG, or IgA as antibodies. The parasitic structures covered by antibodies are destroyed by cells carrying receptors to the Fc fragment (fragment crystallizable) of the antibodies (Figure 1). When these cells are activated by fixation of the antibodies to the RFc, they (activated cells) release products that are toxic to the worm (major basic protein, eosinophil cationic protein, eosinophil-derived neurotoxin and reactive nitrogen intermediates). ADCCs are also able to immobilize nematode larval stages as they migrate through the gut mucosa.[45–48]

A granuloma can occur around the parasite in the tissue which stops the worm migration and development. This phenomenon has been well investigated for *Schistosoma mansoni*. The granuloma is composed of eosinophils, macrophages, and lymphocytes with an increasingly fibrotic extracellular matrix,[49] which surrounds and segregates the eggs from the hepatic tissue. In the long term, fibrosis may develop as the eggs die and the granuloma is resolved.[50]

Finally, nitric oxide (NO), toxic to the worm, is released by the macrophages classically activated by IFNγ and TNFα. This mechanism has been described mainly against trematodes (*Schistosoma sp., Fasciola sp.*) during acute infection, before egg production in *Schistosoma mansoni*.[51–53]

Tissue dwelling parasites have developed several mechanisms to escape the effector immune response of the host. For example, *Fasciola* sp. escapes from the immune responses by different means as follows:

(i) *Fasciola gigantica* produces superoxide dismutase which neutralizes superoxide radicals toxic for juveniles.[54, 55]

(ii) *F. hepatica* releases cathepsin L-protease which cleaves IgE and IgG involved in the ADCC.[56]

(iii) Juvenile flukes were found to be covered by IgM.[57] While eosinophils do not express Fcγ receptor, IgM deposition on fluke tegument could inhibit eosinophil adhesion. IgG produced during fasciolosis in susceptible has been also suspected to be a blocking immunoglobulin of the ADCC.[58]

Furthermore, *F. hepatica* secretes several molecules able to modulate the immune response. Excretory-secretory products of *F. hepatica* (ESPFh) can depress the sheep and rat lymphocytes stimulation[59, 60] and induce eosinophil apoptosis.[61] Milbourne and Howell (1990, 1993)[62, 63] have shown that there is an "IL5-like" substance in the excretory-secretory products (ESPs) probably responsible in part of the local and systemic eosinophilia observed during fasciolosis. Cathepsin L-proteases induce a decrease of lymphoproliferation and of the CD4 (cluster of differentiation or cluster of designation) expression on human and ovine T cells.[64] GST (glutathione S-transferase) from *F. hepatica* induces a significant inhibition of nitrite production by peritoneal macrophage.[59]

IMMUNE MECHANISMS AGAINST LUMINAL PARASITES AND ESCAPE MECHANI- SMS DEVELOPED BY THE PARASITE

Intestinal anaphylaxis, with IgE-induced mast cells degranulation, is responsible for changes in the intestinal physiology as well as architecture and chemistry of the gut epithelium, including stimulation of fluid, electrolyte and mucus secretion, smooth muscle contractility, increased vascular and epithelial permeability, and recruitment of immune cells such as eosinophil or mast cells [17] (Figure2). This can lead to rapid elimination of the gastrointestinal larvae, before they reach their tissue niche, and to expulsion of the adult.[65] Furthermore, IgA on the surface of the gut mucosa helps to neutralize the metabolic enzymes released by the worms and interfere with the worm's ability to feed.[66, 67]

As for tissue-dwelling parasites, parasites localized in the lumen of ducts are able to produce immunomodulatory substances to escape to the host immune responses. For example, *Necator americanus* secretes a metalloprotease which cleaves eotaxin, a chemotactic factor for eosinophils.[68] Gastrointestinal nematodes produce also superoxide dismutase and glutathione S-transferase which neutralize toxic oxide radicals.[21] A cystatin produced by *Haemonchus contortus* and *Nippostrongylus brasiliensis* modulates the antigen presentation to T cells by inhibiting cysteine proteases of antigen presenting cells, involved in the processing of the antigen.[69, 70]

REGULATION OF IMMUNE RESPONSES AGAINST HELMINTHS

All these mechanisms, except the classically activated macrophages, are regulated by Th2-like cytokines and immunomodulatory cell types (Figure 1). Interleukin-4 is involved in the IgE isotype-switched B-cell responses, IL-5 is involved in the production of eosinophils, and IL-13 has similar functions to IL-4 and is involved mainly in the effector phase of inflammation and the development of fibrosis.[50] T regulatory cells (T_{Reg} cell) produce the suppressive cytokines IL-10 and TGF-β (Transforming growth factor beta) which have anti-inflammatory effects and could be involved in the skewed Th2-like responses. Immune deviation may also be promoted by the development of a Th2-driving dendritic cell population induced by excretory-secretory antigens from *Nippostrongylus brasiliensis*[71] or soluble egg antigen from schistosome.[72]

Finally, IL-4 and IL-13 are able to alternatively activate macrophages (AAMps) which

have strong anti-inflammatory properties, enhance Th2 cell differentiation, contribute to fibrosis, and repair at the site of injury.[73] Thus, an environment, with downregulated pro-inflammatory responsiveness, activated damage-repair mechanisms, and a controlled development of Th2-like antiparasite effector responses is created during infection with helminthes.[18]

Several proteins produced by helminths were involved in the regulation of cytokine production.[15, 19] Schistosome soluble egg antigen contains molecules as alpha-1 or omega-1 that initiate a Th2-like response.[74–76]

ES-62, a leucine aminopeptidase secreted by *Acanthocheilonema vitae*, reduces CD4+ cell IL-4 and IFNγ production but promotes IL-10 production by peritoneal B1 cells.[77, 78] It also inhibits the antigen-presenting cells ability to produce IL-12p70 and drives Th2-like differentiation in vitro.[79, 80] Helminths could also secrete cytokine homologues as macrophage migration inhibitory factor (MIF) which induces, with IL-4, the development of alternatively activated macrophage.[16]

PROTECTIVE AND IMMUNOPATHOLOGICAL EFFECTS OF THE IMMUNE RESPONSE AGAINST HELMINTHS

Despite the Th2-like response induced against helminths, these parasites are often able to persist in the host for a long time, resulting in chronic infection. However 2 types of immunity evaluated from the partial elimination of settled parasites and from host resistance to reinfection have been described, namely, premune immunity and partial immunity.[4] Premune immunity against helminths is very common and particularly observed against gastrointestinal helminths. Premunition or concomitant immunity has been defined by MacDonald et al.[19] as a state wherein the host is protected from further infection with a given species by ongoing persistent infection with the same organism. Thus immune mechanisms existing concomitantly with parasites (adults and encysted larval stages) in animals infected by gastrointestinal nematodes prevent the establishment of new larvae. In contrast, the elimination of adult worms by the phenomenon of "self-cure" (spontaneous expulsion of adults by massive larval invasion during a short period of exposure) or by anthelminthic treatment results in the installation of new larvae until an equilibrium state is obtained. Premune immunity can also be expressed as a reduction in adult worm size and in female worm fertility. In contrast, the primary immune response against *Fasciola hepatica* limits the number of metacercariae which develops in adults and reduces the fertility of the females. However it is unable to prevent the establishment of new parasites, which is a great difference with the premune immunity. It also permits partial expulsion of adults in the bile ducts. So, immune responses against *Fasciola hepatica* partially protect the host against the infection.[20]

The protective role of Th1- and Th2-like responses during fluke infection is less clear: Th1-like responses might act on larvae migrating through the liver parenchyma whereas the chronic phase with *F. hepatica* might be due to Th2- like responses against which the fluke has developed several escape mechanisms. As described during infection with *Schistosoma mansoni*, Th2-like responses are predominant during infection by *F. hepatica* but early Th1-like responses seem to be involved in protection against this parasite.[20]

This suggests that protection against *Fasciola sp.* is linked with Th1-cytokine production.[81] Similarly, vaccinal trials with cathepsin L-protease from *F. hepatica* proved that protection induced by this antigen is mediated by a Th1-like response.[82] Although the host immune reaction against helminths may control the infection, it can also be responsible for tissue lesions and symptoms which are often the primary cause of disease during worm infection. Immunopathologic phenomena have been thoroughly investigated in infections with *Schistosoma spp.* As described above for *F. hepatica* infection, acute schistosomosis is associated with Th1-like responses against adult parasites. The Th2-like responses, induced as a result of egg antigens secretion, downregulate the production and effector functions of Th1-like mediators.[83, 84] When Th2-like responses against the eggs were blocked experimentally, an exacerbated granuloma driven by Th1 and Th17 cells resulted in hepatic damage and death.[85] Granulomatous responses evolve from an early Th1- to a sustained and dominant Th2-like response. Whereas tissue fibrosis stimulated by Th2-like cytokine (IL-13) promotes tissue healing, excessive fibrosis may become pathogenic with loss of hepatic functions and portal hypertension.[86, 87] It seems that during trematode infections Th1-like responses are more protective than Th2-like responses against which these parasites have developed many escape mechanisms. Although Th1-like responses are closely associated with immunopathogenesis, Th2-like responses may also contribute to inflammatory damage. Treg cells seem to regulate this detrimental immune response by suppressing the Th1-like response and by down regulating any excessive Th2-like response during granuloma formation.[88]

Protection against gastrointestinal nematodes and against tissue-dwelling trematodes is controlled by Th2- and Th1-like responses, respectively. The migration step in tissue is considered an immunoevasive strategy due to the predominant Th2-like response during helminth

infection whereas protection in tissue is mediated by the Th1-like response. However, the immune mechanisms, particularly those regulated by Th1-like cytokines, are responsible for considerable immunopathological damage and for the clinical signs observed during a helminthic disease.[89]

Even if the immune responses against most of helminths are orchestrated by Th2-like cytokines, the worms are still able to persist in the host for a long time. Indeed, the immune response during the chronic phase of infection was recently reported to be a modified Th2-like response, that is, a Th2-like response associated with Treg activity and the production of antiinflammatory cytokines such as IL-10 and TGFβ.[90]

The induction of immunomodulatory Th2/Treg responses would allow the survival of both partners, by downregulating the host's inflammatory response and the immunopathological lesions observed during helminths infection, and also the protective immune mechanisms directed against the parasite.[91, 92]

HELMINTHS AND COINFECTION

Some helminths are able to downregulate the Th1-like response because their high immunomodulator activity allows the induction of Th2/Treg-type responses.[93]

Helminths influence not only host resistance to another pathogen but also the gravity of the resulting disease. Cerebral malaria is associated with an overproduction of pro-inflam- matory cytokines. Helminth infections are able to decrease the production of these cytokines by secreting IL-10 and TGFβ and thereby diminish the risk of severe disease.[92] *Trichinella spiralis* infection limits pulmonary damage induced by influenza virus in mice.[94]

However, other pathogens can also influence the immune response against helminths. For example, Miller et al.[95] recently showed that the production of Th1-like cytokines and classic activation of macrophages were little altered when *F. hepatica* infection preceded or succeeded *T. gondii* infections, whereas the production of *F. hepatica*-specific Th2- like cytokines and recruitment of AAMp were suppressed by *T. gondii* infection. Similarly, neutrophil-activating protein from *Helicobacter pylori* downmodulated the Th2-like response to *Trichinella spiralis* infection.[96] The effects of helminths on infections with other pathogens are complex and dependent on many factors such as the helminth species, coinfecting pathogen, protective and pathological immune mechanisms of the host.

HELMINTHS AND VACCINATION

Several studies have shown that helminths can influence vaccine efficacy by modulating host immune response, in particular when Th1-like and cellular-dependent responses are required. *Schistosoma sp.* and *Onchocerca volvulus* infections decrease the efficacy of vaccine against tuberculosis or tetanus,[92] and *Ascaris suum* alters the efficacy of vaccine against *Mycoplasma hyopneumoniae.*[97] In mice, *Heligmosomoides polygyrus* was able to downregulate the strong immunity against *Plasmodium chabaudi* induced by blood stage antigens.[98] Effects of helminth infections on vaccine efficacy must be taken into account when using vaccines and also when developing new vaccines, in particular by choosing adapted adjuvants which are able to counterbalance the immunomodulatory activities of the helminths.

HELMINTHS AND ALLERGIC AND AUTOIMMUNE DISEASES

For several years, epidemiologic observations have shown that the prevalence of helminths infection is decreasing in westernized countries whereas the prevalence of diseases due to immune or inflammatory disorders such as allergic or autoimmune diseases is increasing. Epidemiologic and experimental data prove that chronic infection with helminths is protective against allergy. Humans infected with worms rarely develop allergic reactions.[50] Treatment against gastrointestinal nematodes increases cutaneous reactivity against house dust mites.[99] These results are paradoxical because allergy is linked to mastocyte degranulation by IgE; the production of which is stimulated by helminths. In fact, worms induce the production of large quantities of anti-inflammatory cytokines (IL-10, TGFβ) by the regulatory T cells which then inhibit allergic inflammation.

In the same way, helminths can protect the host against autoimmune disease or at least decrease the gravity of symptoms induced by autoimmune inflammation. For example, *S. mansoni* infection inhibits the development of type 1 diabetes in mice[100] or of experimental autoimmune encephalomyelitis in mice.[101] Helminth-specific Treg cells and their anti-inflammatory cytokines (IL-10, TGFβ) seem to be largely implicated in the inflammatory disorders associated with allergic diseases. Several studies are currently underway to investigate the possibility of treating allergic and inflammatory diseases with immunomodulatory molecules from helminths, with special focus on the molecules involved and the ways in which helminths manipulate the host response, particularly how they activate and induce the expansion of Treg cells.[4]

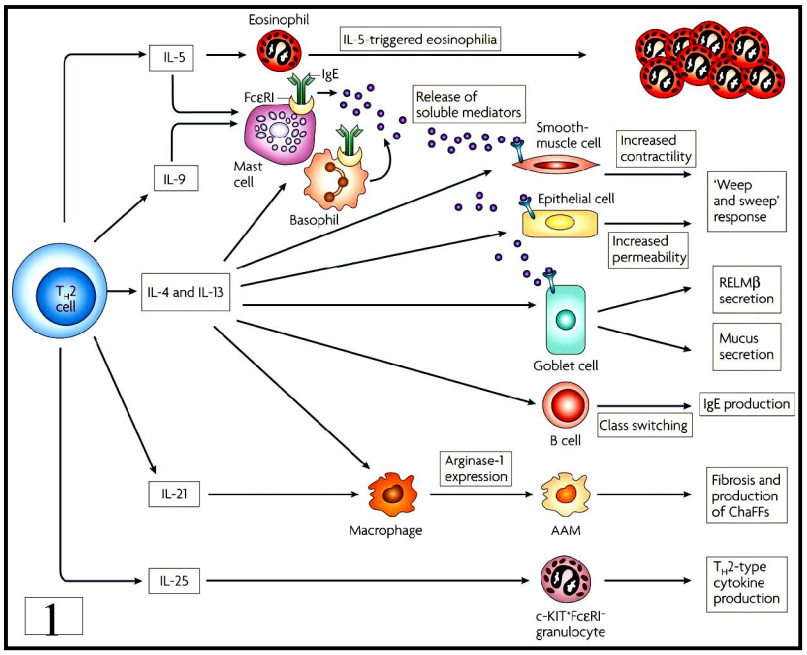

Figure 1: TH2-cell functions during tissue-dwelling parasites

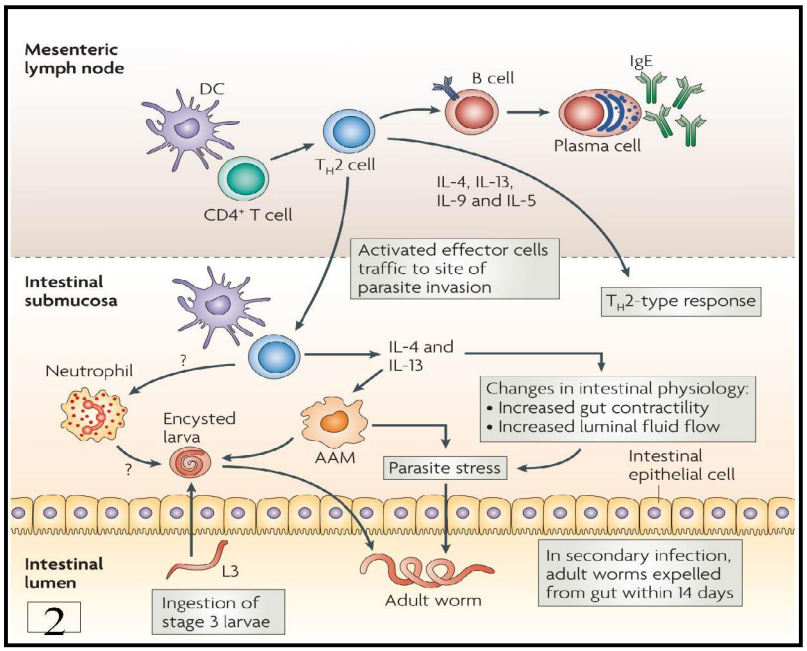

Figure 2: Protective TH2-type response during intestinal nematode

IMMUNOMODULATORY MOLECULES OF HELMINTHS AS NEW ANTI-INFLAMATORY THERAPY

The starting point for considering parasitic helminths as a therapeutic option in inflammatory bowel disease is the modulation of the Th1–Th2 cytokine balance.

Immunomodulatory function of helminths and their products could be used as anti-inflammatory drugs. *Trichuris suis* has been tested recently to treat patients with inflammatory bowel disease and Crohn's disease with success.[102, 103] An excretory-secretory protein of *Acanthocheilonema vitae,* E-S62, has been well

studied for its anti-inflammatory property. ES62 significantly decreases the severity of collagen-induced arthritis in mice[102] and of cutaneous hypersensitivity dependant on mast cells.[103] However, these immunomodulatory molecules could have side effects by increasing the risk of infections. Furthermore, they could be responsible for allergic reactions because they could be allergens or they could cross react with allergens derived from pollen or another source.[104] The 'therapeutic helminth' must be as innocuous as possible, and this precludes the use of many species such as filarial worms, schistosomes and auto-infective species. Weinstock and colleagues see significant anticolitic benefit with the nematode *T. suis* [105] and the intestinal cestodes (i.e. hymenolepids) are interesting candidates as therapeutic helminthes.[106, 107]

SUMMARY

Helminth species have coevolved with their host for a long time. This has led to a strict adaptation which enables them to settle and persist in the host. The hygiene hypothesis suggests an inverse relationship between parasitic infections and the incidence of IBD. Epidemiological, experimental, and clinical data sustain the idea that helminths could provide protection against IBD. The importance of regulatory pathways such as regulatory T-cells, by which helminths induce such protection have been described. Helminths are strong immunomodulators able to interfere with immune and inflammatory mechanisms induced by themselves and by coinfecting pathogens, inflammatory disorders, or vaccine. Immunomodulatory products from helminths are probably the anti-inflammatory molecules of the future. Helminths influence innate as well as adaptive immune responses and this knowledge can contribute to new therapeutic approaches of helminth-induced protection. Therapy with living helminths appears to be effective in several immunological diseases. A logical next step, to avoid the possible disadvantages of a treatment with living parasites, is the identification and characterization of helminth derived immunosuppressive molecules that contribute to the protective effect infection.

REFERENCES

[1] **WHO.** World Health Report. World Health Organization; Geneva, Switzerland: 1999.

[2] **Capron A, Riveau G, Capron M, Trottein F.** Schistosomes. The road from host-parasite interactions to vaccines in clinical trials. Trends Parasitol 2005;21:143–149.

[3] **Hall A, Horton S, and De Silva N.** The costs and cost-effectiveness of mass treatment for intestinal nematode worm infections using deferent treatment thresholds. PLoS Neglected Tropical Diseases, 2009; 3(3):article 402.

[4] **Moreau E, and Chauvin A.** Immunity against Helminths: Interactions with the Host and the Intercurrent Infections. Journal of Biomedicine and Biotechnology 2010, Article ID 428593, 9 pages doi:10.1155/2010/428593

[5] **Anthony R, Laura I, Joseph F, Miguel J, and William C.** Protective immune mechanisms in helminth infection. Nat Rev Immunol. 2007 Author manuscript; available in PMC 2008 February 28.

[6] **Maizels RM, Balic A, Gomez-Escobar N, Nair M, Taylor MD, and Allen JE.** Helminth parasites masters of regulation. Immunological Reviews 2004;201: 89–116.

[7] **Moreels TG and Pelckmans PA**. The hygiene hypothesis and inflammatory bowel diseases: role of helminthes. Acta Gastro-Enterologica Belgica. 2006;69(4):413–417.

[8] **Fiocchi C.** The multiple components of inflammatory bowel disease pathogenesis: should we invest in all of them or should we pick and choose?. Current Opinion in Gastroenterology. 2005;21?(4):399–400.

[9] **Loftus EV, Sandborn WJ.** Epidemiology of inflammatory bowel disease [Review]. Gastroenterol Clin North Am. 2002;31:1–20.

[10] **Andersson RE, Olaison G, Tysk C.** Appendectomy and protection against ulcerative colitis. N Engl J Med. 2001;344:808–814.

[11] **Derby LE, Jick H.** Appendectomy protects against ulcerative colitis. Epidemiology. 1998;9:205–207.

[12] **Russel MG, Dorant E, Brummer RJ.** Appendectomy and the risk of developing ulcerative colitis or Crohn's disease: results of a large case-control study. South Limburg Inflammatory Bowel Disease Study Group. Gastroenterol 1997;113:377–382.

[13] **Calkins BM.** A meta-analysis of the role of smoking in inflammatory bowel disease. Dig Dis Sci. 1989;34:1841–1854.

[14] **Joel V. Weinstock MD, and David E. Elliott MD.** Helminths and the IBD Hygiene Hypothesis. Inflamm Bowel Dis 2009;15:128 –133.

[15] **Hewitson JP, Grainger JR, and Maizels RM.** Helminth immunoregulation: the role of parasite secreted proteins in modulating host immunity. Molecular and Biochemical Parasitology, 2009;167(1):1–11.

[16] **Prieto-Lafuente L, Gregory WF, Allen JE, and Maizels RM.** MIF homologues from a filarial nematode parasite synergize with IL-4 to induce alternative activation of host macrophages. Journal of Leukocyte Biology, 2009; 85(5): 844–854.

[17] **Farthing MJ.** Immune response-mediated pathology in human intestinal parasitic infection. Parasite Immunology, 2003,(25):5, pp. 247–257.

[18] **Jackson JA, Friberg IM, Little S, and Bradley JE.** Review series on helminths, immune modulation and the hygiene hypothesis: immunity against helminths and immunological phenomena in modern human populations: coevolutionary legacies. Immunology, 2009;126(1):18–27.

[19] **McDonald J, Harn DA, Atochina O, and Da'dara AA.** Modulation of host immune responses by helminth glycans Immunological Reviews, 2009;230(1): 247–257.

[20] **Chauvin A, Zhang W, and Moreau E.** Fasciolosis of ruminants: immunity, immunomodulation and control strategies," Bulletin de l'Academie Veterinaire de France, 2007;160: 85–92.

[21] **Liddell M, and Knox DP.** Extracellular and cytoplasmic Cu/Zn superoxide dismutases from *Haemonchus contortus*. Parasitology,1998;116(4):383–394.

[22] **Terefe G, Lacroux C, Andreoletti O.** Immune response to *Haemonchus contortus* infection in susceptible (INRA 401) and resistant (Barbados Black Belly) breeds of lambs. Parasite Immunology, 2007; 29(8):415–424.

[23] **Summers RW, Elliott DE, Urban JF Jr.** *Trichuris suis* therapy in Crohn's disease. *Gut.* 2005;54:87–90.

[24] **Summers RW, Elliott DE, Urban JF Jr.** Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. Gastroenterol, 2005;128:825– 832.

[25] **Summers RW, Elliott DE and Weinstock JV.** Is there a role for helminths in the therapy of inflammatory bowel disease?. Nat Clin Pract Gastroenterol Hepatol. 2005;2:62– 63.

[26] **Croese J, O'Neil J, Masson J.** A proof of concept study establishing *Necator americanus* in Crohn's patients and reservoir donors. Gut. 2006;55:136 –137.

[27] **Russel MG.** Changes in the incidence of inflammatory bowel disease: what does it mean? European Journal of Internal Medicine,2000;11(4):191–196.

[28] **Lakatos PL.** Recent trends in the epidemiology of inflammatory bowel diseases: up or down? World Journal of Gastroenterol,2006;12(38):6102–6108.

[29] **Strachan DP.** Family site, infection and atopy: the first decade of the 'hygiene hypothesis. Thorax,2000;55(1):2–10.

[30] **Bresciani M, Parisi C, Manghi G, and Bonini S.** The hygiene hypothesis: does it function worldwide? Current Opinion in Allergy and Clinical Immunology ,2005; 5(2):147–151.

[31] **Vercelli D.** Mechanisms of the hygiene hypothesis— molecular and otherwise. Current Opinion in Immunology,2006;18(6):733–737.

[32] **Garn H and Renz H.** Epidemiological and immunological evidence for the hygiene hypothesis. Immunobiology,2007;212(6):441–452.

[33] **Strachan DP.** Hay fever, hygiene, and household size. British Medical Journal, 1989;299(6710):1259–1260.

[34] **Bach JF.** The effect of infections on susceptibility to autoimmune and allergic diseases. The New England Journal of Medicine,2002;347(12):911–920.

[35] **Magen E, Borkow G, Bentwich Z, Mishal J and Scharf S.** Can worms defend our hearts? Chronic helminthic infections may attenuate the development of cardiovascular diseases. Medical Hypotheses,2005;64(5):904–909.

[36] **Cooke A, Zaccone P, Raine T, Phillips JM and Dunne DW.** Infection and autoimmunity: are we winning the war, only to lose the peace? Trends in Parasitology, 2004;20(7):316–321.

[37] **Fleming JO and Cook TD.** Multiple sclerosis and the hygiene hypothesis," Neurology,2006;67(11):2085–2086.

[38] **Feillet H and Bach JF.** Increased incidence of inflammatory bowel disease: the price of the decline of infectious burden? Current Opinion in Gastroenterology ,2004;20(6):560– 564.

[39] **Weinstock JV.** Helminths and mucosal immune modulation Annals of the New York Academy of Sciences,2006;1072:356–364.

[40] **Loftus EV and Sandborn WJ.** Epidemiology of inflammatory bowel disease. Gastroenterology Clinics of North America, 2002;31(1):1–20.

[41] **Alic M.** Inflammatory bowel diseases are diseases of higher socioeconomic status: dogma or reality? The American Journal of Gastroenterology, 2000;95(11):3332–3333.

[42] **Green C, Elliott L, Beaudoin C and Bernstein CN.** A population-based ecologic study of inflammatory bowel disease: searching for etiologic clues," American Journal of Epidemiology, 2006; 164(7):615–623.

[43] **Moreels TG and Pelckmans PA.** The hygiene hypothesis and inflammatory bowel diseases: role of helminthes. Acta Gastro-Enterologica Belgica,2006;69 (4):413–417.

[44] **Montgomery SM, Pounder RE and Wakefield AJ**. Infant mortality and the incidence of inflammatory bowel disease. The Lancet,1997;349(9050):472–473.

[45] **Capron M and Capron A.** Effector functions of eosinophils in schistosomiasis," Memorias do Instituto Oswaldo Cruz,1992; 87(4):167–170.

[46] **Meeusen EN, Balic A and Bowles V.** Cells, cytokines and other molecules associated with rejection of gastrointestinal nematode parasites. Veterinary Immunology and Immunopathology,2005;108(1):121–125.

[47] **Piedrafita D, Parsons JC, Sandeman RM.** Antibody- dependent cell-mediated cytotoxicity to newly excysted juvenile *Fasciola hepatica* in vitro is mediated by reactive nitrogen intermediates. Parasite Immunology,2001;23(9) 473–482.

[48] **Weller PF.** Eosinophils: structure and functions. Current Opinion in Immunology ,1994;6(1):85–90.

[49] **Anthony RM, Rutitzky LI, Urban JF, Stadecker MJ and GauseWC.** Protective immune mechanisms in helminth infection. Nature Reviews Immunology,2007;7(2):975–987.

[50] **MacDonald AS, Araujo MI, and Pearce EJ.** Immunology of parasitic helminth infections. Infection and Immunity,2002;70(2):427–433.

[51] **Cervi L, Rossi G, Cejas H and Masih DT.** *Fasciola hepatica*-induced immune suppression of spleen mononuclear cell proliferation: role of nitric oxide," Clinical Immunology and Immunopathology,1998;87(2):145–154.

[52] **Gazzinelli RT, Oswald IP, James SL and Sher A.** IL-10 inhibits parasite killing and nitrogen oxide production by IFN-γ- activated macrophages. Journal of Immunology ,1992;148(6):1792–1796.

[53] **Sibille P, Tliba O, and Boulard O.** Early and transient cytotoxic response of peritoneal cells from *Fasciola hepatica* infected rats. Veterinary Research,2004;35(5): 573–584.

[54] **Ganga G, Varshney JP and Patra RC.** Activity of antioxidant enzymes in excretory-secretory fluid and somatic extracts of *Fasciola gigantica*. Journal of Veterinary Parasitology, 2007;21(1):51–52.

[55] **Piedrafita D, Estuningsih E, Pleasance J.** Peritoneal lavage cells of Indonesian thin-tail sheep mediate antibody-dependent superoxide radical cytotoxicity in vitro against newly excysted juvenile *Fasciola gigantica* but not juvenile *Fasciola hepatica*. Infection and Immunity,2007;75(4):1954–1963.

[56] **Smith AM, Dowd AJ, Heffernan M, Robertson CD and Dalton JP.** *Fasciola hepatica*: a secreted cathepsin L- like proteinase cleaves host immunoglobulin. International Journal for Parasitology, 1993;23(8):977–983.

[57] **Chauvin A and Boulard C.** Local immune response to experimental *Fasciola hepatica* infection in sheep. *Parasite*,1996; 3(3):209–215.

[58] **Hansen DS, Clery DG, Estuningsih SE, Widjajanti S, Partoutomo S and Spithill TW.** Immune responses in Indonesian thin tail and Merino sheep during a primary infection with *Fasciola gigantica*: lack of a specific IgG_2 antibody response is associated with increased resistance to infection in Indonesian sheep. International Journal for Parasitology,1999;29(7):1027–1035.

[59] **Cervi L, Rossi G and Masih DT**. Potential role for excretory-secretory forms of glutathione-S-transferase (GST) in *Fasciola hepatica*. Parasitology, 1999;119(6):627–633.

[60] **Moreau E, Hervé S , Yu ZW and Alain C.** Modulation of sheep lymphocyte responses by *Fasciola hepatica* excretory- secretory products. Veterinary Parasitology, 2002;108 (3):207–215.

[61] **Serradell MC, Guasconi L, Cervi L, Chiapello LS, and Masih LS.** Excretory-secretory products from *Fasciola hepatica* induce eosinophil apoptosis by a caspase-dependent mechanism. Veterinary Immunology and Immunopathology,2007;117(3):197–208.

[62] **Milbourne EA and Howell MJ.** Eosinophil responses to *Fasciola hepatica* in rodents. International Journal for Parasitology,1990;20(5):705–708.

[63] **Milbourne EA and Howell MJ.** Eosinophil di□erentiation in response to Fasciola hepatica and its excretory/secretory antigens. International Journal for Parasitology ,1993;23(8):1005–1009.

[64] **Prowse RK, Chaplin P, Robinson HC and Spithill TW.** *Fasciola hepatica* cathepsin L suppresses sheep lymphocyte proliferationin vitro and modulates surface CD4 expression on human and ovine T cells. Parasite Immunology,2002 ;24(2):57–66.

[65] **Balic A, Bowles VM, and Meeusen ENT.** Mechanisms of immunity to *Haem-onchus contortus* infection in sheep. Parasite Immunology,2002;24(1):39–46.

[66] **Gill HS, Gray GD, Watson GL and Husband AJ.** Isotype-specific antibody responses to *Haemonchus contortus* in genetically resistant sheep. Parasite Immunology,1993 ;15(2):61–67.

[67] **Smith G.** The population biology of the parasitic stages of *Haemonchus contortus*. Parasitology, 1988;96(1):185– 195.

[68] **Culley FJ, Brown A, Conroy M, Sabroe I, Pritchard DI and Williams TJ.** Eotaxin is specifically cleaved by hookworm metalloproteases preventing its action in vitro and in vivo. Journal of Immunology,2000;165(11):6447–6453.

[69] **Newlands GF, Skuce PJ, Knox DP and Smith WD.** Cloning and expression of cystatin, a potent cysteine protease inhibitor from the

gut of *Haemonchus contortus*. Parasitology,2001;122(3):371–378.

[70] **Dainichi T, Maekawa Y, Ishii K.** Nippocystatin, a cysteine protease inhibitor from *Nippostrongylus brasiliensis*, inhibits antigen processing and modulates antigen-specific immune response. Infection and Immunity,2001;69(2) :7380–7386.

[71] **Else KJ.** Have gastrointestinal nematodes outwitted the immune system? Parasite Immunology,2005; 27(10):407–415.

[72] **Thomas PG, Carter MR, Atochina O.** Maturation of dendritic cell 2 phenotype by a helminth glycan uses a Toll-like receptor 4-dependent mechanism. Journal of Immunology,2003;171(11):5837–5841.

[73] **Kreider T, Anthony RM, Urban JF and Gause WC.** Alternatively activated macrophages in helminth infections. Current Opinion in Immunology,2007;19(4) :448–453.

[74] **Grzych JM, Pearce E, Cheever A.** Egg deposition is the major stimulus for the production of Th2 cytokines in murine *Schistomiasis mansoni*. Journal of Immunology, 1991;146(4):1322–1327.

[75] **Schramm G, Falcone FH, Gronow A.** Molecular characterization of an interleukin-4-inducing factor from *Schistosoma mansoni* eggs. Journal of Biological Chemistry,2003;278(20):18384–18392.

[76] **Everts B, Perona-Wright G, Smits HH.** Omega-1, a glycoprotein secreted by *Schistosoma mansoni* eggs, drives Th2 responses. Journal of Experimental Medicine, 2009;206(8):1673–1680.

[77] **Wilson EH, Katz E, Goodridge HS, Harnett MM and Harnett W.** In vivo activation of murine peritoneal B1 cells by the filarial nematode phosphorylch- oline containing glycoprotein ES-62. Parasite Immunology,2003;25(8):463–466.

[78] **Marshall FA, Grierson AM, Garside P, Harnett W and Harnett MM.** ES-62, an immunomodulator secreted by filarial nematodes, suppresses clonal expansion and modifies effector function of heterologous antigen-specific T cells in vivo. Journal of Immunology,2005;175(9):5817–5826,2005.

[79] **Goodridge HS, Harnett W, Liew FY and Harnett MM.** Differential regulation of interleukin-12 p40 and p35 induction via Erk mitogen-activated protein kinase-dependent and independent mechanisms and the implications for bioactive IL-12 and IL-23 responses. Immunology,2003;109(3):415–425.

[80] **Whelan M, Harnett MM, Houston KM, Patel V, Harnett W and Rigley KP.** A filarial nematode secreted product signals dendritic cells to acquire a phenotype that drives development of Th2 cells. Journal of Immunology,2000; 164(12):6453–6460.

[81] **Zhang WY, Moreau E, Hope JC, Howard CJ, Huang W and Chauvin A.** *Fasciola hepatica* and *Fasciola gigantica*: comparison of cellular response to experimental infection in sheep. Experimental Parasitology,2005;111(3):154–159.

[82] **Mulcahy G and Dalton LP.** Cathepsin L proteinases as vaccines against infection with *Fasciola hepatica* (liver fluke) in ruminants. Research in Veterinary Science,2001;70(1):83–86.

[83] **Kaplan MH, Whitfield JR, Boros DL and Grusby MJ.** Th2 cells are required for the *Schistosoma mansoni* egg- induced granulomatous response. Journal of Immunology, 1998;160(4):1850–1856.

[84] **Pearce EJ, Kane CM, Sun J, Taylor JJ, McKee AS and Cervi L.** Th2 response polarization during infection with die helminth parasite *Schistosoma mansoni*. Immunological Reviews,2004;201:117–126.

[85] **Stadecker MJ, Asahi H, Finger E, Hernandez HJ, Rutitzky LI and Sun J.** The immunobiology of Th1 polarization in high pathology schistosomiasis. Immunological Reviews, 2004; 201:168–179.

[86] **Wynn TA, Thompson RW, Cheever AW and Mentink-Kane MM.** Immunopathogenesis of schistosomiasis. Immunological Reviews,2004;201:156–167.

[87] **Pearce EJ and MacDonald AS.** The immunobiology of schistosomiasis. Nature Reviews Immunology,2002;2(7):499–511.

[88] **Burke ML, Jones MK, Gobert GN, Li YS, Ellis MK and McManus DP.** Immunopathogenesis of human schistosomiasis. Parasite Immunology, 2009; 31(4):163– 176.

[89] **Mulcahy G, O'Neill S, Fanning J, McCarthy E and Sekiya M.** Tissue migration by parasitic helminthes an immunoevasive strategy. Trends in Parasitology,2005 ;21(6):273–277.

[90] **Maizels RM.** Infections and allergy—helminths, hygiene and host immune regulation. Current Opinion in Immunology,2005;17(6):656–661.

[91] **Maizels RM and Yazdanbakhsh M.** Immune regulation by helminth parasites: cellular and molecular mechanisms. Nature Reviews Immunology,2003; 3(9): 733–744.

[92] **Van Riet E, Hartgers FC and Yazdanbakhsh M.** Chronic helminth infections induce immunomodulation: conesquences and mechanisms. Immunobiology,2007; 212(6):475–490.

[93] **Pesce JT, Ramalingam TR, Wilson MS.** Retnla (Relmα/Fizz1) suppresses helminth-

induced Th2- type immunity . PLoS Pathogens, 2009;5(4):ArticleID e1000393.

[94] **Furze RC, Hussell T and Selkirk ME.** Amelioration of influenza-induced pathology in mice by coinfection with *Trichinella spiralis*. Infection and Immunity,2006;74(3):1924–1932.

[95] **Miller CMD, Smith NC, Ikin RL, Boulter NR, Dalton JP and Donnelly S.** Immunological interactions between 2 common pathogens, Th1-inducing protozoan *Toxoplasma gondii* and the Th2-inducing helminth *Fasciola hepatica*. PLoS ONE,2009; 4(5): article e5692.

[96] **Del Prete G, Chiumiento L, Amedei A.** Immunosuppression of TH2 responses in *Trichinella spiralis* infection by *Helicobacter pylori* neutrophil activating protein. Journal of Allergy and Clinical Immunology,2008;122(5):908–913.

[97] Urban JF, Steenhard NR, Solano-Aguilar GI et al. Infection with parasitic nematodes confounds vaccination efficacy. Veterinary Parasitology,2007;148 (1):14–20.

[98] **Su Z, Segura M and Stevenson MM.** Reduced protective efficacy of a blood stage malaria vaccine by concurrent nematode infection. Infection and Immunity,2006; 74(4):2138–2144.

[99] **Biggelaar AHJ, Rodrigues LC , Van Ree R.** Long-term treatment of intestinal helminths increases mite skin test reactivity in Gabonese schoolchildren. Journal of Infectious Diseases,2004;189(5):892–900.

[100] **Cooke A, Tonks P, Jones FM.** Infection with *Schistosoma mansoni* prevents insulin dependent diabetes mellitus in non-obese diabetic mice. Parasite Immunology, 1999; 21(4):169–176.

[101] **Sewell D, Qing Z, Reinke E.** Immunomodulation of experimental autoimmune encephalomyelitis by helminth ova immunization. International Immunology,2003;15 (1):59–69.

[102] **Summers RW, Elliott DE, Qadir K, Urban JF, Thompson R and Weinstock JV.** *Trichuris suis* seems to be safe and possibly effective in the treatment of inflammatory bowel disease. American Journal of Gastroenterology, 2003; 98(9):2034–2041.

[103] **Summers RW, Elliott DE, Qadir K, Urban JF, Thompson R and Weinstock JV.** *Trichuris suis* therapy in Crohn's disease. Gut,2005;54(1):87–90.

[104] **Harnett W, McInnes IB and Harnett MM.** ES-62, a filarial nematode derived immunomodulator with anti-inflammatory potential. Immunology Letters,2004;94(2) :27–33.

[105] **Weinstock JV, Summers RW, Elliott DE, Qadir K, Urban JF, Thompson R.** The possible link between de-worming and the emergence of immunological disease. J Labor Clin Med 2002;139: 334–338.

[106] **Reardon C, Sanchez A, Hogaboam CM, McKay DM.** Tapeworm infection reduces the ion transport abnormalities induced by dextran sulphate sodium (DSS) colitis. Infect Immunity, 2001; 69: 4417–4423.

[107] **Hunter MM, Wang A, Webb RA, McKay DM.** Tapeworm infection reduces inflammation in a murine model of colitis. Can J Gastroenterol, 2003; 17: A54.

2011/12/12