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A Review on Ecosegregation and Parasitocoenosis of Helminthes: Perspective to Health and Sustainability

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Abstract

The parasitic helminthes are a group of invertebrates and including animals which have been adapted themselves to the parasitic mode of life. These are belonging to two important phyla namely, platyhelminthes and Aschelminthes. The parasites are those organism which lives at the expense of other organism, and in return causes injury or harm to the host. Thus it is an association in which one organism *i.e.* the parasite, is benefited while another one, the host, is harmed is called parasitism; however, behavior, occurrence, establishment and cuases of of parasitism known as parasitocoenosis. The parasitism has evolved accidently as a result of contact between different forms of animals, mainly for the purpose of obtaining nourishment and receiving shelter. An ideal parasite never causes too much harm to its host because if the host dies the parasite depending upon the host will also have to die. The parasitism and parasitocoenosis is a matter of conflict and ambiguity either it is structured association based on ecosegregation and microhabitat specificity or a stochastic assemblages and accidental contact due to utilization of common habitat and life style. The helminthes zoonotic infections are among the most common on erath and are responsible for major human infectious diseases. Some of the most important and well known human zoonoses are caused by parasitic helminthes including anisakiasis, trichinellosis, cysticercosis, echinococcosis, schistosomiasis, etc. However, along with social, epidemiological and environmental changes, together with improvements in our ability to diagnose helminth infections, several neglected parasite species are now fast-becoming recognized as important zoonotic diseases of humans, *e.g.*, anasakiasis, several fish-borne trematodiasis and fasciolosis. In the present review, we discuss the current status of the primary helminth zoonotic infections with particular emphasis on their ecosegregation and parasitocoenosis. Advances in molecular biology, proteomics and the release of helminth genome-sequencing project data are revolutionizing parasitology research. The authors wish to suppose and hupothesize

the application of these powerful experimental approaches, and their potential benefits to helminth biology and definitely these contrivances will be the mile stone to the future control of helminth infections of animals and humans.

Keywords: Ecosegregation, Parasitocoenosis, Parasitic helminthes, Zoonoses, Health and Sustainability.

1. INTRODUCTION

Parasitic helminths belong to two separate invertebrate phyla and mostly dangerous of over-generalization. There are various routes of anaerobic carbohydrate breakdown in parasitic helminths with different efficiencies and their power output as an adaptive feature of parasitism (Upadhyay, 2012). Additionally, anaerobic pathways must satisfy the redox requirements of the tissues and provide a source of intermediates for synthetic reactions. Other considerations include the metabolic cost of excretion and the effect of end-products on protein structure and function. The different end-products may fulfil additional functions such as pH control, nitrogenous excretion, osmotic regulation, intracellular signalling and the suppression of host responses (Jaiswal, 2006; Malhotra et al., 2009). A complicating factor in parasitic helminths is the existence of strains with different biochemical characteristics, including marked variation in end-product formation (Kumar, 2012). The various tissues of the same parasite can also produce different end-products and the pattern of end-product formation is influenced by a variety of extrinsic and intrinsic factors such as age, sex, length of incubation, partial pressure of oxygen and availability of substrates (Banerjee, 1991). The catabolic pathways of helminths thus show considerable functional adaptation. There is, as yet, no satisfactory explanation as to why helminths do not make the maximum use of any oxygen available to them; and the contribution of oxidative processes to the overall energy balance of parasites probably varies from species to species (Eberhart and Dubois, 1995; Jaiswal et al., 2013, 2014; Grencis, 2015).

According to Elton "the union of parasite and host is usually an elaboration compromise between extracting sufficient nourishment to maintain and propagate itself and not impairing too much the vitality or reducing the number of its host which is providing it with a home and free ride." To lead a parasitic mode of life, the parasites have adapted themselves in such a way as to survive and adjust itself with the body environment of their host. Adaptation is a dynamic process of adjustment with the new environment for establishment, self regulation, self preservation and race continuation (Gairola, 1989). The degree of adaptations exhibited by different types of parasites mainly depends upon their intimate relationship with their host (Jaiswal, 2006). Parasitic adaptations are responses to features in the parasite's environment and this environment is the body of another organism, the host. This seems to be a difficult environment to invade but those organisms that have done so have often been very successful both in terms of numbers of individuals and numbers of species. Blood and tissues seem to be harder to invade than the gut, as is shown by the smaller number of blood and tissue parasites. This is probably in part related to the difficulties of getting eggs to the outside from sites within the host (Gairola, 1989; Banerjee, 1991; Chaurasia, 2002).

2. PARASITOCOENOSIS OF ZOONOTIC HELMINTHES

Zoonotic infectious agents are among the most prevalent on earth and are thought to be responsible for major human infections and emerging human infectious diseases The success and widespread epidemiology of these infections can be attributed to a range of human factors including social and dietary changes as well as an increased mobility of the human population (Cunningham, 2005; Vorou et al., 2007). As the human population

continues to grow there is an ever increasing need to develop and maintain food products with a high protein content (particularly livestock and fish) under intensive farming situations, which is inevitably leading to a greater spread of animal diseases and their transmission to humans (Keiser and Utzinger, 2005). Improved diagnosis and/or recognition of neglected human infections can account for some diseases apparently emerging or re-emerging in recent times (e.g., human fasciolosis). Climate change has also been suggested as a cause for ecosegregation and disease spread i.e. parasitocoenosis, and is a concern for the future (McCarthy and Moore, 2000). The Zoonotic infections of humans are caused by a wide variety of agents including bacteria, viruses, parasites (e.g., leishmaniasis, schistosomiasis, anisakiasis, etc.) and other 'unconventional' agents such as prions (Mas-Coma et al., 2005). Human infections caused by parasitic helminthes are of particular importance given the relatively recent acknowledgement of a number of species as important human pathogens (Garcia et al., 2007). The major zoonotic and food-borne helminthes pathogens and their parasitocoenosis are the major neglected problem of the society based on aquaculture and animal products majorly. Therefore, authors suppose to aim and highlight their current disease status and show where advances in genomics, proteomics and molecular biology may lead to improved diagnosis and control of these important pathogens.

3. ECOSEGERGATION OF PARASITIC HELMINTHES

The parasitic helminthes of freshwater fish have long proved an attractive field for parasitologists, and have spawned an extensive and voluminous literature and the attention was directed primarily to their ecology (Dogiel et al., 1961; Malhotra, 1982; Malhotra et al., 2009; Jaiswal et al., 2013, 2014, Upadhyay et al., 2015; Upadhyay, 2017; Upadhyay and Singh, 2018). The Dogiel (1964) reviewed much of the existing literature in the light of ecological concepts, and examined the dependence of the parasite fauna as a whole, the parasitocoenosis, upon the environment as well as laying down general principles, to the influence of physical factors, such as water chemistry and habitat size, and biological factors, such as host age, diet and migration, upon the composition of the parasite fauna of a host population. The earlier researches based literature thus founded new discipline not only for the study of the ecology of fish parasites, but also for the new dimension of ecological parasitology in terms of eco-biology or ecosgregation (Anderson, 1988; Kennedy and Bush, 1992; Kennedy, 2009). Later on there was something of an explosion of publications on fish parasites and many investigators have continued to follow along the lines indicated by Dogiel (1964) and have concentrated on parasitocoenoses, but many others diversified into the field of population dynamics (Chubb, 1982; Anderson, 1988; Upadhyay et al., 2013; Jaiswal et al., 2013, 2014). Unfortunately, despite the numerous surveys and the large quantity of data available, few studies actually provide information suitable for analyses of community structure and determinant processes and fewer still have actually attempted such analyses. Many studies were undertaken for other purposes, and are often incomplete in respect of quantitative coverage of all parasites and/or specific determinations of all species. Above all, there is a dearth of information in the literature on individual hosts, i.e. the infracommunity level, as the great majority of published accounts present only sample summaries of infection parameters. At the compound community level, the difficulties of surveying the entire parasite community in a locality may be virtually insuperable. Most of the published data are descriptive and refer to the component community level. It is only in the last few years, following the development of a theoretical framework for parasite community studies have actually started to address the fundamental problems of organization, replicability and determinant processes of helminth communities of fish (Malhotra, 1982; Gairola, 1989; Kennedy and Bush, 1992; Kennedy, 2009). It was further identified that a number of factors as being essential to the production of a diverse helminth community, including complexity of the host alimentary canal, endothermy, host vagility and the breadth and selectivity of the host diet. Focusing on helminth colonization strategies, two categories of helminthes was recognized: autogenic species which matured in fish and allogenic species which matured in vertebrates other than fish and thus had a greater colonization potential and ability (Upadhyay, 2012). The recognition and appreciation of the different colonization strategies of autogenic and allogenic species in respect of host vagility and ability to cross land and sea barriers, thus breaking down habitat isolation, provided an understanding of, and explanation for, the patchy spatial distribution

and apparently stochastic nature of many freshwater fish helminth communities. Thus it was considered that colonization is a major determinant of helminth community structure.

4. HELMINTHES AND DISEASE TOLERANCE

Helminths are metazoan organisms many of which have evolved parasitic life styles dependent on sophisticated manipulation of the host environment. Most notably, they down-regulate host immune responses to ensure their own survival, by exporting a range of immuno-modulatory mediators that interact with host cells and tissues. While a number of secreted immunoregulatory parasite proteins have been defined, new work also points to the release of extracellular vesicles, or exosomes, that interact with and manipulate host gene expression (Malhotra et al., 2009; Kumar, 2012; Upadhyay, 2012). The physical characteristics of helminths, their general ability to induce a tissue-healing rather than tissue-destructive immune response and, in some cases, their long-lasting relationship to the host collectively indicate that mammals have evolved to tolerate these parasites. Tolerance to infection, also called disease tolerance, is a defense strategy by which the host activates intra- and inter-cellular networks to limit the damage incurred by the infectious agent or the immune response without affecting pathogen load (Medzhitov et al., 2012). Although appreciated in plant biology for decades, the concept of disease tolerance has only recently gained traction as an important mammalian host defense strategy against bacterial, viral and parasitic microorganisms that can occur in combination with or independent of resistance and derive from immune as well as non-immune pathways (Soares et al., 2017). Disease tolerance is also conceptually distinct from immunological tolerance which involves the unresponsiveness to self or foreign antigens (McCarville and Ayres, 2018). Here we provide a rationale for why disease tolerance is an important defense strategy against helminth infection and include recent data that adds complexity yet excitement to this rapidly evolving research field. Given the diversity of parasitic helminth species, life cycles and susceptible hosts as eloquently stated by Clark (1994).

Helminthes shared the IMD (Immune-mediatedare diseases) with the temporal and geographic prevalence patterns of multiple sclerosis (MS), type 1 diabetes (T1D), rheumatoid arthritis (RA), asthma, and many other autoimmune inflammatory diseases. This suggests that environmental factors which increase the risk for IBD, such as loss of helminth infections, also increase the risk for other immune-mediated illnesses (Correale and Farez, 2007). Furthermore, in a case report of four patients, pharmacological eradication of helminthic infections resulted in worsening MS activity. An open label trial of therapeutic *Trichuris suis* exposure in five patients with relapsing-remitting MS showed that helminth exposure resulted in fewer neurological symptoms and development of fewer CNS lesions, as measured by magnetic resonance imaging. Lesion development recurred after discontinuation of *T. suis*administration (Correale and Farez, 2011; Fleming et al., 2011).

Mice or rats immunized with myelin-associated peptides develop autoimmune encephalitis (EAE), which serves as a model of MS. Exposure of mice to *Schistosoma mansoni*, or even just to their dead eggs, protects mice from EAE. Schistosome exposure suppresses Th1-type cytokine (IL-12 p40, IFN-γ, and TNF-α) and augments regulatory and Th2-type cytokine (TGF-β, IL-10, and IL-4) production by splenocytes and CNS cells (La Flamme et al., 2003; Sewell et al., 2003). *Trichinella spiralis* infection also affords protection in the agouti rat EAE animal model of MS. Trichinosis suppresses lymph node cell IFN-γ and IL-17 secretion while promoting IL-10 and IL-4 production, and it increases the number of $CD4^+CD25^+Foxp3^+$ T cells in the spleen. Adoptive transfer of T cells from helminth-infected rats into helminth-naive rats protects these animals from developing EAE (Valadi, 2007; Chaiyadet, 2015). This shows that the process of protection is immunologically-mediated, and that T cells are sufficient to control the disease.

There are no published clinical trials of helminth exposure in patients with rheumatoid arthritis, but the effect of helminths on arthritis has been tested in animal models of this disease. Polyarticular arthritis develops spontaneously in MRL/lpr mice that have impaired Fas gene expression. Infection of these mice with bacteria aggravates arthritis, while infection with a helminth (*Nippostrongylus brasiliensis*) reduces the incidence of arthritis and the degree of synovial hyperplasia (Osada et al.,

2009). A more commonly used and well-described model of rheumatoid arthritis is collagen-induced arthritis. Mice infected with *Schistosoma mansoni* two weeks before sensitization with collagen in Freund's complete adjuvant (FCA) do not develop the expected polyarticular arthritis. The reduction in arthritic score correlates with the number of worms per mouse (Salinas-Carmona et al., 2009). *Schistosoma japonicum*, which is closely related to *S. mansoni*, also protects mice from collagen-induced arthritis (He et al., 2010).

5. PARASITE-HOST INTERCATION

Helminth parasites generally establish long-term infections in their host, reflecting their ability to drive a new physiological and immunological homeostasis that best accomodates the invader (Maizels, 2004). Over eons of evolutionary time, parasites have developed a remarkable suite of finely-tuned molecular adaptations that manipulate, inhibit or activate different host cells or pathways in order to maximise parasite success (Hewitson et al., 2009; Allen and Maizels, 2011). A wide variety of helminth species are able colonise an extraordinary array of niches and host organisms, in each case circumventing host defence and expulsion mechanisms. Interestingly, the strategy of helminths is not to outpace the immune system through rapid multiplication or antigenic variation, but to manipulate and modulate immunity in order to defuse immune defences, meaning the host fails to eliminate the parasites (Maizels et al., 2012). Helminths essentially take hold by stealth, first inactivating host detection systems that would otherwise raise the alarm, and then effectively tolerizing the immune system to parasite antigens, and in doing so, also dampening responses to bystander antigens in allergy or autoimmunity (Johnston et al., 2014). The softly–softly strategy of helminths has implications for how they communicate with their hosts and the immune system of their host, suggesting that there must be a continual dialogue to maintain the state of tolerance. Because infection comprises relatively stable populations of long-lived parasites, it is logical to deduce that the dialogue is conducted by products continuously released from live parasites that address different specific components of the immune system. This notion is supported by observations that most of the immunomodulatory effects of helminth infections are reversed following drug-mediated parasite clearance (Sartono, 1995; Grogan et al., 1996; Semnani et al., 2006). The first level of parasite communication with the host can be considered to be simple protein–protein interactions in the extracellular milieu, either with fluid phase host components, or exposed receptors on host cell surfaces. For example, *Heligmosomoides polygyrus* (formerly known as *Nematospiroides dubius*, and also referred to by some as *H. bakeri*) secretes a functional mimic of the immunomodulatory cytokine TGF-β, which ligates mammalian surface receptor and transduces a suppressive signal to T cells. Space precludes further discussion of the many individual proteins now found to be involved in host-helminth interactions, but perhaps the most intriguing are members of the CAP superfamily which are greatly expanded across all helminth parasite lineages (Chalmers and Hoffmann, 2012), and highly represented in the secreted protein compartments (Hewitson, 2011).

6. HOST RECOGNITION OF PARASITIC HELMINTHES

The first encounter between parasite and host generally entails breaching of a barrier surface (such as skin or intestinal epithelium) that provokes release of 'alarmins' (Oppenheim and Yang , 2005) and recognition of the invader by pattern recognition receptors (PRRs), such as the Toll-like receptors (TLRs) that drive inflammatory cytokine production. Alarmins, closely associated with helminth-mediated tissue damage, include IL-33 and TSLP (Ziegler and Artis, 2010; Cayrol and Girard, 2011), which both promote a Type 2 pro-allergic and anti-helminth mode of the immune response. However, helminths can partially or entirely circumvent this threat; for example, the response of dendritic cells (DCs) to TLR ligation is effectively negated by products from *Nippostrongylus brasiliensis* and other helminths, with IL-12 production being especially inhibited (Massacand, 2009; Donnelly, 2010) while epithelial cell release of IL-33 is directly blocked by products released by *Heligmosmoides polygyrus* (McSorley et al., 2014). Thus some of the molecular mediators responsible for blocking innate activation are now being defined. Innate mechanisms respond to tissue injury with release of alarmins (eg IL-33, TSLP) which can initiate a type 2 response; helminths can block alarmin release or receptors

for alarmins such as ST2 (the IL-33R). Pathogen associated molecular patterns may also be recognised eg by Toll Like Receptors (TLRs) or C-type lectin receptors (CLRs), and these molecular patterns may be directly presented by helminths, or indirectly through bacteria translocating through injured epithelium. In the latter case, the Th1 response driven by IL-12 is blocked by helminth secreted immune modulators (Fig. 1).

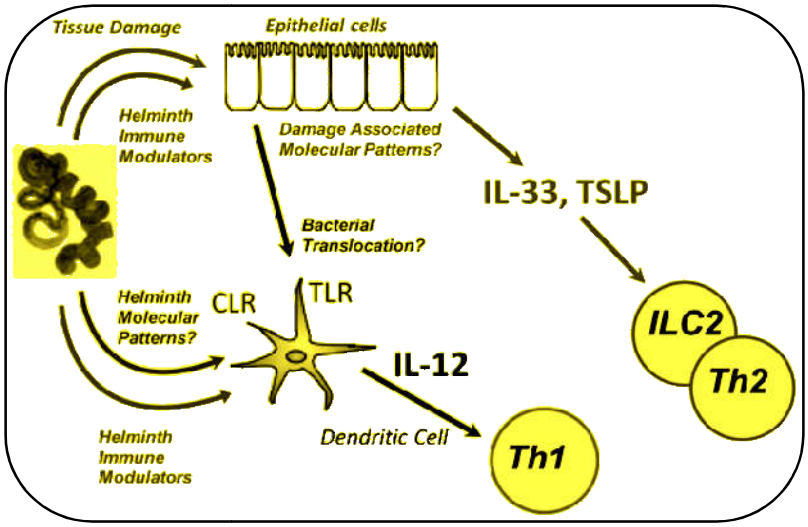

Figure 1: Host recognition system of parasite during helminthes infection. *Source: Coakley et al., 2016.*

The well-studied helminth glycoproteins are known to enter host cells and mediate profound biological effects. The *Schistosoma mansoni* egg-derived glycoprotein ω1 is a ribonuclease bearing Lewis X glycan side chains, that bind to surface lectin of dendritic cells, mediating uptake into the cell, resulting in the protein moiety acting to block protein synthesis (Steinfelder, 2009; Everts, 2012). A different mediator is the predominant secreted glycoprotein of the filarial nematode *Acanthocheilionema viteae*. A further example is the FheCL1 cysteine protease from *Fasciola hepatica,* which degrades TLR3 in host macrophages thereby inhibiting activation; although TLR3 is an intracellular pathogen sensor, FheCL1 is able to enter the endosome to degrade the receptor *in situ* (Donnelly, 2010). Human B cells exposed to CPI-2 from *Brugia malayi* (a human filarial parasite) are no longer able to process protein antigen for presentation to T cells, a pathway dependent on AEP activity in the endosome (Manoury et al., 2001). Further studies on a closely related cystatin from *A. viteae*show that this protein is taken up by mouse macrophages and activates ERK and p38 kinases, resulting in the production of immunoregulatory IL-10, in a manner linked to the phosphorylation of the CREB and STAT3 signalling factors (Klotz et al., 2011). Many other products have been shown to modulate intracellular signalling in host cells, although the mode of entry is not always understood. For example, the ALT-2 protein is derived from an abundant larval transcript of the filarial parasite *B. malayi*. The effect of this protein is seen when added to macrophages, or introduced into the macrophage via transfection of the intracellular protozoan *Leishmania mexicana*, in the induction of the signalling proteins GATA-3 and SOCS-1, which act to induce type 2 responses and dampen IFN-γ dependent inflammatory signals in the cell (Gomez-Escobar, 2005) (Fig. 2).

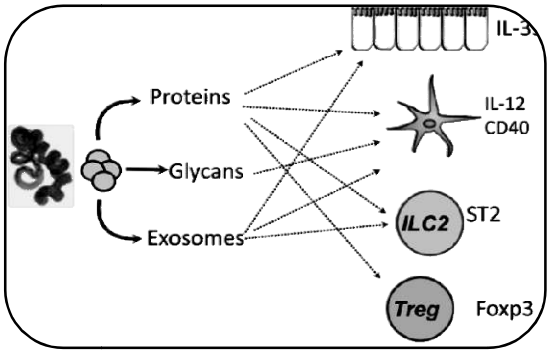

Figure 2: Helminths release diverse molecular species to communicate with host cells, including proteins, glycans and exosome components. *Source: Coakley et al., 2016.*

7. PARASITE-HOST INTERACTIVE INTERACTION: TWO WAY STREET

While the focus on how helminths deliver messages to the host immune system, there are some intriguing examples of how helminths also detect and respond to host immune status. The studies on *N. brasiliensis* found that the adult worms adapt to an immunised host by switching expression levels and isoforms of secreted acetylcholinesterase. More recently, detection of host cytokines has been found in schistosomes, which require the presence of host TNF to mature to egg laying and filarial parasites responding to high IL-5 levels *in vivo* by accelerating their maturation and production of offspring (Jones and Ogilvie, 1972; Amiri, 1992). An intriguing possibility that extracellular vesicles from the host provide a channel of communications that influence the helminth parasites, although as yet there are no reports of parasites being directly receptive to vesicle-mediated signals. However there is a growing literature demonstrating the use of host-derived extracellular vesicle impact on defence against pathogens. For example, exosomes derived from IFN-α stimulated cell were able to induce antiviral activity and limit viral replication in recipient infected cells (Giugliano, 2015).

8. PARASITIC COMMUNITIES CROSSTALK VS. IMMUNOREGULATORY RESPONSE

As intestinal helminths co-habitate with the most abundant and diverse microbial community in the host, important interactions occur between these organisms that reside in the same niche (Kumar, 2012; Upadhyay, 2012; Loke and Lim, 2015). Although commensal bacteria and multicellular helminths occupy very different taxonomic space, they have both responded to evolutionary forces by developing strategies of host immunomodulation. Moreover, it is apparent that these different kingdoms of life have developed a surprising degree of dialogue with a common agenda of establishing a new homeostasis in the host intestinal tract (Reynolds et al., 2015). For example, *Trichuris muris* migrates to the proximal colon, the site of greatest bacterial abundance in mammals, where they exploit commensal bacteria for egg hatching and adult worm development (Hayes, 2010; Hayes et al., 2010). In turn, *T. muris* infection alters the gut microbiota and promotes resistance against pathogenic bacteria, an effect dependent on the induction of a type-2 immune response (Ramanan et al., 2016). However, initial reports investigating the impact of human *T. trichiura* infection on the composition and function of the gut microbiota have provided mixed results (Cooper et al., 2013; Jenkins et al., 2017). Fricke et al. (2015) also reported that a type 2 immune response following *N. brasiliensis* infection in mice reduced abundance of segmented filamentous bacteria (SFB) in the small intestine compared to uninfected controls. SFB is a potent inducer of IL-17 production by murine T cells, an immune pathway shown to exacerbate tissue damage at the expense of limiting worm burden (Fricke et al., 2015). In complementary studies, Walk et al. found that *H. polygyrus* infection increased the abundance of Lactobacillaceae, a family of lactic-acid producing bacteria with established anti-inflammatory and immune suppressive effects (Walk et al., 2010).

Additionally, helminths could also mediate metabolic changes of the commensal bacteria that promote immunoregulatory functions. Indeed, Zaiss and Harris (2016) demonstrated that *H. polygyrus* infection enhanced the production of short chain fatty acids (SCFAs) by the intestinal bacteria that have potent ability to amplify Treg cell differentiation. Thus from the the cited literatures it has been cleared that the helminths and the microbiota influence each other's ability to persist in the mammalian intestinal tract and potentially dampen unwanted inflammatory responses in the intestine. Although studies are emerging that support an impact of helminth on the human gut microbiota, more studies are needed to provide a causal relationship and its impact on tolerance to homologous or heterologous co-infection.

9. CONCLUSIONS

Parasitic helminths are among the most pervasive pathogens of the animal kingdom. To complete their life cycle, these intestinal worms migrate through host tissues causing significant damage in their wake. As a result, infection can lead to malnutrition, anemia and increased susceptibility to co-infection. Despite repeated deworming treatment, individuals living in endemic regions remain highly susceptible to re-infection by helminths, but rarely succumb to excessive tissue damage. The chronicity of infection and inability to resist numerous species of parasitic helminths that have co-evolved with their hosts over millenia suggests that mammals have developed mechanisms to tolerate this infectious disease. Distinct from resistance where the goal is to destroy and eliminate the pathogen, disease tolerance is an active process whereby immune and structural cells restrict tissue damage to maintain host fitness without directly affecting pathogen burden. Although disease tolerance is evolutionary conserved and has been well-described in plant systems, only recently has this mode of host defense, in its strictest sense, begun to be explored in mammals. Thus helminths have accompanied a vast range of host species throughout evolution, developing sophisticated pathways of communication with, and even control of, the immune system of their hosts. The rapid discovery that many helminth species have the ability to release exosomes to mediate cross-phylum interactions speaks to the importance of this pathway in host-parasite biology. In this new light, we now see how the large extracellular parasites, classified as helminths, may be able to "reach in' to the intracellular machinery of host cells, modifying their behaviour in ever more remarkable ways.

Historically, parasitism has been thought to be solely detrimental: the parasite benefits at the expense of host health, with only one "winner" emerging from this interaction. Therefore, developing resistance to these invaders was the conceptual framework that led to great advances in understanding type-2 immunity and its relation to anti-helminth immunity. Tolerance to helminth infection also corresponds well with the "hygiene hypothesis" (and the expanded "old friend's hypothesis") suggesting that diminished exposure to infections or decreased diversity of commensal microorganisms has led to an increased prevalence of allergic (and potentially autoimmune) disease because of defective regulation of the immune system in early life. Going forward, a more complete picture of helminth–microbiota (communities) interactions and their effects on the host will certainly yield new approaches for the treatment of these "diseases of the developed world". It will also be important to identify the specific types of tissue damage and cell stress imposed by intestinal helminth infection to understand how the host limits tissue damage and initiates a repair process that is critical for tolerance. Moreover, further investigations will be required to understand the role of intestinal physiology on susceptibility to helminth invasion and its ability to simultaneously minimize immune-driven pathology in the context of tissue damage, a body of knowledge that could be applied to diverse settings of tissue infection and injury.

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REFERENCES

1. Allen, J.E. and Maizels, R.M. (2011). Diversity and dialogue in immunity to helminths. *Nat. Rev. Immunol.* 11: 375–388.
2. Amiri, P. (1992). Tumour necrosis factor a restores granulomas and induces parasite egg-laying in schistosome-infected SCID mice. *Nature* 356: 604–607.
3. Anderson, R.C. (1988). Nematode transmission patterns. *J. Parasitol*. 74: 30–45.
4. Banerjee, S.C.N. (1991). Populaion distribution and pathology of certain parasites in fishe of high altitude and Gangetic plains. Unpubl. D.Phil. Thesis, Univ. Allahabad, 551p.
5. Cayrol, C. and Girard, J.P. (2014). IL-33: An alarmin cytokine with crucial roles in innate immunity, inflammation and allergy. *Curr. Opin. Immunol*. 31(C): 31–37.
6. Chaiyadet, S. (2015). Carcinogenic liver fluke secretes extracellular vesicles that promote cholangiocytes to adopt a tumorigenic phenotype. *J. Infect. Dis*. 212(10): 1636–1645
7. Chalmers, I.W. and Hoffmann, K.F. (2012). Platyhelminth Venom Allergen-Like (VAL) proteins: revealing structural diversity, class-specific features and biological associations across the phylum. *Parasitol*. 139(10): 1231–1245.
8. Chaurasia, G. (2002). Investigations to identify Biodiversity determinants in Ichthyoparasitology. Unpubl. D. Phil. Thesis Univ. Allahabad. p129.
9. Chubb, J.C. (1982). Seasonal occurance of helminthes in freshwater fishes. Part IV. Adult Cestoda, Nematoda and Acanthocephala. *Adv. Parasitol*. 20: 1–292.
10. Clark, W.C. (1994). Origins of the parasitic habit in the Nematoda. *Int J Parasitol*. 24: 1117–1129.
11. Coakley, G., Buck, A.H. and Maizels, R.M. (2016). Host parasite communications: Messages from helminths for the immune system. *Mol. Biochem. Parasitol*. 208: 33–40.
12. Cooper, P., Walker, A.W., Reyes, J., Chico, M., Salter, S.J., Vaca, M., Parkhil, J. (2013). Patent human infections with the whipworm, *Trichuris trichiura*, are not associated with alterations in the faecal microbiota. *PLoS One,* doi:10.1371/journal.pone.0076573.
13. Correale, J. and Farez, M. (2007). Association between parasite infection and immune responses in multiple sclerosis. *Ann. Neurol*. 61: 97–108.
14. Correale, J. and Farez, M.F. (2011). The impact of parasite infections on the course of multiple sclerosis. *J. Neuroimmunol*. 233(1-2):6–11.
15. Cunningham, A.A. (2005). A walk on the wild side: Emerging wildlife diseases. *Br. Med. J.* 331: 1214–1215.
16. Dogiel, V.A. (1964). General Parasitology. Oliver and Boyd. London. p516.
17. Dogiel, V.A., Pertrushevski, G.K. and Polyanski, Y.I. (1961). Parasitology of fishes. Edinburgh, Oliver and Boyd. p384.
18. Donnelly, S. (2010). Helminth cysteine proteases inhibit TRIF-dependent activation of macrophages via degradation of TLR3. *J. Biol. Chem*. 285: 3383–3392.
19. Eberhart, C.E. and Dubois, R.N. (1995). Eicosanoids and the gastrointestinal tract. *Gastroenterol.* 109: 285–301.
20. Everts, B. (2012). Schistosome-derived omega-1 drives Th-2 polarization by suppressing protein synthesis following internalization by the mannose receptor. *J. Exp. Med*. 209(10): 1753–1767.
21. Fleming, J., Isaak, A., Lee, J. et al. (2011). Probiotic helminth administration in relapsing-remitting multiple sclerosis: A phase-1 study. *Multiple Sclerosis,* 17: 743–754.
22. Fricke, W.F., Song, Y., Wang, A.J., Smith, A., Grinchuk, V., Mongodin, E., Pie, C., Ma, B., Lu, N. Urban, J.F.Jr., Shea-Donohue, T., and Zhao, A. (2015). Type-2 immunity-dependent reduction of segmented filamentous bacteria in mice infected with the helminthic parasite *Nippostrongylus brasiliensis*. *Microbiome*, 3: 40–51.
23. Gairola, D.D.N. (1989). Population biology and taxometry of helminth parasites of certain economically important food fishes. Unpubl. D. Phil. Thesis Univ. Allahabad, p599.
24. Gracia, H.H., Moro, P.L. and Schantz, P.M. (2007). Zoonotic helminth infections of humans: Echinococcosis, cysticercosis and fascioliasis. *Curr. Opin. Infect. Dis*. 20: 489–494.
25. Giugliano, S. (2015). Hepatitis-C virus infection induces autocrine interferon signaling by human liver endothelial cells and release of exosomes, which inhibits viral replication. *Gastroenterol.* 124(2): 392–402.

26. Gomez-Escobar, N. (2005). Heterologous expression of the filarial nematode alt gene products reveals their potential to inhibit immune function. *BMC Biol*. 3(8): 1–16.
27. Grencis, R.K. (2015). Immunity to helminths: resistance, regulation, and susceptibility to gastrointestinal nematodes. *Annu. Rev. Immunol*. 33: 201–25.
28. Grogan, J.L., Kremsner, P.G., Deelder, A.M. and Yazdanbakhsh M. (1996). Elevated proliferation and interleukin-4 release from CD4+ after chemotherapy in human *Schistosoma haematobium* infection. *Eur. J. Immunol*. 26: 1365–1370.
29. Hayes, K.S. (2010). Exploitation of the intestinal microflora by the parasitic nematode *Trichuris muris*. *Science* 328(5984): 1391–1394.
30. Hayes, K.S., Bancroft, A.J, Goldrick, M., Portsmouth, C., Roberts, I.S. and Grencis, R.K. (2010). Exploitation of the intestinal microflora by the parasitic nematode *Trichuris muris*. *Science* 328: 1391–1394.
31. He, Y., Li, J., Zhuang, W., Yin, L., Chen, C., Li, J., Chi, F., Bai, Y. and Chen, X.P. (2010). The inhibitory effect against collagen-induced arthritis by *Schistosoma japonicum* infection is infection stage-dependent. *BMC Immunol*. 11: 28–37.
32. Hewitson, J.P., Grainger, J.R. and Maizels, R.M. (2009). Helminth immunoregulation: the role of parasite secreted proteins in modulating host immunity. *Mol. Biochem. Parasitol*. 167: 1–11.
33. Jaiswal, N. (2006). Spectral signatures in ichthyophthiraisis and co-occuring parasitic infracomminity variations in freshwater and marine habitats. Unpubl. D.Phil. Thesis, Univ. Allahabad. p387.
34. Jaiswal, N., Upadhyay, S.K., Malhotra, A. and Malhotra, S.K. (2013). Multifactorial Etiology of Infections by Larvae of *Eustrongylides tubifex* (Nematoda: Dioctophymidae) in Silver Whiting of the Central West Coast of India at Goa. *Asian J. Biol. Sci.* 6(1): 21–39.
35. Jaiswal, N., Upadhyay, S.K., Malhotra, A. and Malhotra, S.K. (2014). Ecological morphotaxometry of trematodes of garfish (Teleostomi: Belonidae) from Gangetic riverine ecosystem in India. III. Principal Component Analysis for hydrobiological correlates to dynamics of infections by *Cephalogonimus yamunii* (Upadhyay, Jaiswal, Malhotra and Malhotra, 2012). *J Parasit Dis.* 38(2): 153–162.
36. Jenkins, T.P., Rathnayaka, Y., Perera, P.K., Peachey, L.E., Nolan, M.J., Krause, L., Rajakaruna, R.S., Cantacess, C. (2017). Infections by human gastrointestinal helminths are associated with changes in faecal microbiota diversity and composition. *PLoS One,* doi: 10.1371/journal.pone.0184719.
37. Johnston, C.J., McSorley, H.J., Anderton, S.M., Wigmore, S.J. and Maizels R.M. (2014). Helminths and immunological tolerance. *Transplantation* 97(2): 127–132.
38. Jones, V.E. and Ogilvie, B.M. (1972). Protective immunity to *Nippostrongylus brasiliensis* in the rat III. Modulation of worm acetylcholinesterase by antibodies. *Immunol*. 22: 119–129.
39. Keiser, J. and Utzinger, J. (2005). Emerging foodborne trematodiasis. *Emerg. Infect. Dis.* 11: 1507–1514.
40. Kennedy, C.R. (2009). The ecology of parasites of freshwater fishes: The search for patterns. *Parasitol.* 136: 1653–1662.
41. Kennedy, C.R. and Bush, A.O. (1992). Species richness in helminth communities: the importance of multiple congeners. *Parasitol.* 104: 189–197.
42. Klotz, C., Ziegler, T., Figueiredo, A.S., Rausch, S., Hepworth, M.R., Obsivac, N., Sers, C., Lang, R., Hammerstein, P., Lucius, R. and Hartmann, S. (2011). Helminth immunomodulator exploits host signaling events to regulate cytokine production in macrophages. *PLoS Pathog*. 7(1): e1001248. doi:10.1371/journal.ppat.1001248.
43. Kumar, S. (2012). Ecological attributes and biochemical variants in the dynamics of infections of vertebrates. Unpubl. D.Phil. Thesis, Univ. Allahabad. p310.
44. La-Flamme, A.C., Ruddenklau, K. and Backstrom, B.T. (2003). Schistosomiasis decreases central nervous system inflammation and alters the progression of experimental autoimmune encephalomyelitis. *Infect Immun*. 71: 4996–5004.
45. Loke, P. and Lim, Y.A. (2015). Helminths and the microbiota: parts of the hygiene hypothesis. *Parasite Immunol.* 37: 314–23.
46. Maizels, R.M. (2004). Helminth parasites: masters of regulation. *Immunol. Rev*. 201: 89–116.
47. Maizels, R.M., Hewitson, J.P. and Smith, K.A. (2012). Susceptibility and immunity to helminth parasites. *Curr. Opin. Immunol*. 25: 459–466.

48. Malhotra, A., Jaiswal, N., Upadhyay, S.K., Kumar, S. and Malhotra, S.K. (2009). Parasite stress response in zoonoses of *Cephalogonimus* sp. *Indian J. Helminthol.* (N.S.), 27: 73–80.
49. Malhotra, S.K. (1982). Bionomics of hill-stream cyprinids. III. Food parasites and length weight relationship of Garhwal mahaseer, *Tor tor* (Ham.). *Ind. Acad. Sci.* 91: 493–499.
50. Manoury, B., Gregory, W.F., Maizels, R.M. and Watts, C. (2001). *Bm*-CPI-2, a cystatin homolog secreted by the filarial parasite *Brugia malayi*, inhibits class II MHC-restricted antigen processing. *Curr. Biol*. 11: 447–451.
51. Mas-Coma, S., Bargues, M.D. and Valero, M.A. (2005). Fascioliasis and other plant-borne trematode zoonoses. *Int. J. Parasitol*. 35: 1255–1278.
52. Massacand, J.C. (2009). Helminth products bypass the need for TSLP in Th-2 immune responses by directly modulating dendritic cell function. *Proc. Natl. Acad. Sci. U.S.A*. 106: 13968–13973.
53. McCarthy, J. and Morre, T.A. (2000). Emerging helminth zoonoses. *Int. J. Parasitol*. 30: 1351–1360.
54. McCarville, J.L. and Ayres, J.S. (2018). Disease tolerance: concept and mechanisms. *Curr. Opin. Immunol*. 50: 88–93.
55. McSorley, H.J., Blair, N.F., Smith, K.A., McKenzie, A.N.J and, Maizels R.M. (2014). Blockade of IL-33 release and suppression of type 2 innate lymphoid cell responses by helminth secreted products in airway allergy. *Mucosal Immunol*. 7: 1068–1078.
56. Medzhitov, R., Schneider, D.S. and Soares, M.P. (2012). Disease tolerance as a defense strategy. *Science* 335: 936–941.
57. Oppenheim, J.J. and Yang, D. (2005). Alarmins: Chemotactic activators of immune responses. *Curr. Opin. Immunol*. 17(4): 359–365.
58. Osada, Y., Shimizu, S., Kumagai, T., Yamada, S. and Kanazawa (2009). *Schistosoma mansoni* infection reduces severity of collagen-induced arthritis via down-regulation of pro-inflammatory mediators. *Int. J. Parasitol*. 39: 457–464.
59. Ramanan, D., Bowcutt, R., Lee, S.C., Tang, M.S., Kurtz, Z.D., Ding, Y., Honda K., Gause, W.C., Blasér, M.J., Bonneau, R.A., Lim, Y.A.L., Loke, P. and Cadwell, K. (2016). Helminth infection promotes colonization resistance via type-2 immunity. *Science* 352(6285): 608–612.
60. Reynolds, L.A., Finlay, B.B. and Maizels R.M. (2015). Cohabitation in the intestine: interactions among helminth parasites, bacterial microbiota, and host immunity. *J. Immunol*. 195(9): 4059–4066.
61. Salinas-Carmona, M.C., Del C.G. and Perez-Rivera, I., Solis-Soto, J.M., Segoviano-Ramirez, J.C., Vazquez, A.V. and Garza, M.A (2009). Spontaneous arthritis in MRL/lpr mice is aggravated by *Staphylococcus aureus* and ameliorated by *Nippostrongylus brasiliensis* infections. *Autoimmun*. 42: 25–32.
62. Sartono, E. (1995). Elevated cellular responses and interferon-γ release after long-term diethylcarbamazine treatment of patients with human lymphatic filariasis. *J. Infect. Dis*. 171: 1683–1687.
63. Semnani, R.T. (2006). Filaria-induced monocyte dysfunction and its reversal following treatment. *Infect. Immun*. 74(8): 4409–4417.
64. Sewell, D., Qing, Z., Reinke, E. et al. (2003). Immunomodulation of experimental autoimmune encephalomyelitis by helminth ova immunization. *Int. Immunol.* 15: 59–69.
65. Steinfelder, S., Andersen, J.F., Cannons, J.L., Feng, C.G., Joshi, M., Dwyer, D., Caspar, P., Schwartzberg, P.L., Sher, A. and Jankovic, D. (2009). The major component in schistosome eggs responsible for conditioning dendritic cells for Th-2 polarization is a T-2 ribonuclease (omega-1). *J. Exp. Med*. 206(8): 1681–1690.
66. Upadhyay, S.K and Singh, R. (2018). Polyfactorial etiology on demography of parasitic allocreodoidean trematodes in the Gangetic ecosystem. *AASCIT Am. J. Biomed. Sci. Engin.* 04(02): 17–23.
67. Upadhyay, S.K. (2012). Transmission dynamics and environmental influence on food borne parasitic helminthes of the Gangetic plains and central west coast of India. Unpubl. D.Phil. Thesis. Univ. Allahabad, p400.
68. Upadhyay, S.K. (2017). Environmental impact on helminth parasites of fresh water garfish from river Yamuna at Allahabad, Uttar Pradesh, India. *Proc. Zool. Soc. India,* 16(02): 63–75.
69. Upadhyay, S.K., Jaiswal, N., Malhotra, A. and Malhotra, S.K. (2013). Ecological morphotaxometry of trematodes of garfish (Teleostomi: Belonidae) from Gangetic riverine ecosystem in India. II.

Correlation of seasonality and host biology with distribution pattern of *Cephalogonimus yamunii* n.sp. *J. Parasit. Dis*. 37(2): 211–217.

70. Upadhyay, S.K., Yadav, D. and Pathak, R.K. (2015). The impact of water quality on the population distribution pattern of cephalogonimid trematodes *Cephalogonimus yamunii* in fresh water fish *Heteropneustes fossilis* at Allahabad, Uttar Pradesh. *J. Kalash Sci.* 3(2): 11–17.
71. Valadi, H. (2007). Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat. Cell Biol*. 9(6): 654–659.
72. Vorou, R.M., Papavassiliou, V.G. and Tsidras, S. (2007). Emerging zoonoses and vectore-borne infections affecting humans in Europe. *Epidemiol. Infect*. 135: 1231–1247.
73. Walk, S.T., Blum, A.M., Ewing, S.A. et al. (2010). Alteration of the murine gut microbiota during infection with the parasitic helminth *Heligmosomoides polygyrus*. *Inflamm. Bowel Dis*. 16: 1841–1849.
74. Zaiss, M.M. and Harris, N.L. (2016). Interactions between the intestinal microbiome and helminth parasites. *Parasite Immunol*. 38(1): 5–11.
75. Ziegler, S.F. and Artis D. (2010). Sensing the outside world: TSLP regulates barrier immunity. *Nat. Immunol*. 11(4): 289–293.