Human Adaptation to Parasitism

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ABSTRACT
Parasites are accomplished evaders of host immunity. Their evasion strategies have shaped every facet of the immune system, driving diversity within gene families and immune gene polymorphisms within populations. The presence of allelic forms for many adaptive immune system genes, in particular Treg-associated loci, suggests that there is no certain genetic optimum and that, in an environment with diverse pathogens demanding conflicting response patterns, the fine-tuning effect of multiple allelic variants allows the immune system to be variably calibrated across the population. The first line of defense against parasites, as with other pathogens, is the innate immune system, which is harnessed and pruned even in the absence of infection. Immune immunity alone, however, seldom eliminates successful parasites, but inhibits growth while recruiting the antigen-specific T and B cells of the adaptive immune system to proliferate and differentiate into effector cells competent enough to attack infections. In addition, the ability of hormones to contribute to immunological responses directed against pathogenic agents has also been recently demonstrated. This is evident during various parasitic diseases such as malaria, schistosomiasis, toxoplasmosis, cysticercosis, trypanosomiasis and leishmaniasis, in which strong hormonal regulation of the immune response has been described.

Key words: Immune system, Polymorphism, immunopathology, Hormone, Immune Response

INTRODUCTION
Parasites are eukaryotic pathogens, and broadly comprise protozoa, fungi, helminths and arthropods that complete part or all of their life cycle within a host organism. Like other pathogens, parasites must survive in the face of a highly potent immune system. They succeed in this through a great diversity of strategies for avoiding immune detection, suppressing cellular immunity and deflecting immune attack mechanisms. It has been suggested that the need to overcome suppressive mechanisms of parasites may have led to compensatory adjustments in immune genes that, in an environment where parasitic infection is not endemic, may increase the likelihood of inappropriate responsiveness to self-antigens (autoimmunity) and environmental allergens (allergy), a phenomenon termed the hygiene hypothesis [1; 2; 3].

Parasites are accomplished evaders of host immunity. Their evasion strategies have shaped every facet of the immune system, driving diversity within gene families and immune gene polymorphisms within populations [4]. As with Toll-like receptor (TLR) polymorphisms, the presence of allelic forms for many adaptive immune system genes, in particular Treg-associated loci, suggests that there is no certain genetic optimum and that, in an environment with diverse pathogens demanding conflicting response patterns, the fine-tuning effect of multiple allelic variants allows the immune system to be
variably calibrated across the population. In the absence of infection, and where genotypes tend to the higher end of reactivity (for example, where they result in low Treg frequencies), the immune response is more likely to overshoot, and responses may develop to innocuous targets such as self-antigens and allergens [1; 2]. Parasite-driven selection leaves a footprint on human DNA in the form of mutations known as single nucleotide polymorphisms (SNPs). Making sure that genetic variation, in the form of multiple SNPs, is maintained within certain immune genes over time helps ensure that the host can fend off different infections in different environments. In a new study, Fumagalli et al. [2], sift through 1,052 SNPs in genes that code for immune proteins called interleukins from roughly 1000 people worldwide. Of 91 genes assessed, 44 bore signatures of evolutionary selection, meaning that the genetic variation, which correlated with the diversity of parasites that live alongside humans, was neither due to chance nor to the migration of populations over time. The workers concluded that having lots of different parasites around has shaped the evolution of human interleukin genes.

In general, parasitic worms appear to have had a more powerful influence on certain interleukin genes than smaller microbes such as viruses, bacteria, and fungi. This isn’t surprising because worms typically evolve slower than bacteria or viruses, giving their human hosts time to adapt in response. Some of the genes that were shaped by worm diversity made perfect sense, as the proteins they encode help generate the precise type of immune response required to rid the body of worms [2].

The goal of this review was to define further the role played by human immune responses to various parasitic infections. Specifically, we sought to: 1) confirm that diversity exists within immune response genes; 2) determine how hormones regulate a variety of cellular and physiological functions of organisms; and 3) assess the contribution of specific gene-environment (and more specifically, gene-parasite) interactions to the development of damaging immune reactions in autoimmunity and allergy.

**POLYMORPHISM IN THE IMMUNE SYSTEM**

Immune system genes are exceptionally polymorphic, reflecting in part, selection by diverse and rapidly varying pathogens, but also the need to balance effective pathogen elimination against the risk of self-destructive reactions. This is well recognized for polymorphisms affecting the structural domains of proteins that function in pathogen recognition which is less well recognized for the regulation of immune responses. The effect of parasites, for example, has been to dampen, rather than fully ablate, immune responsiveness, and the degree of immunosuppression varies markedly between pathogen species. These gradated effects may, in turn, have driven quantitative polymorphisms in the contemporary immune system that control the strength of the immune response, exemplified by nucleotide variation in regions controlling expression levels rather than variations in amino acid sequence in structural domains [4].

This may be the explanation for the link between pathogen richness (number of diverse species) and host genetic diversity that has recently been documented in a report on cytokine gene polymorphism by Fumagalli et al. [2]. In an analysis of nearly 100 human interleukin genes, the workers found the highest single nucleotide polymorphism (SNP) frequencies in geographical areas with the highest number of endemic helminth species; those loci showing greatest variability included some encoding cytokines controlling both innate immune responses (such as the IL-1 family) and adaptive Th2 responses (such as IL-4 and IL-13). Strikingly, in terms of the hygiene hypothesis, 6 out of 9 alleles known to predispose to inflammatory bowel disease, an immunopathology due to reactivity with commensal bacteria, were more frequent in pathogen-rich locations.

Earlier studies have linked non-coding polymorphisms in immune gene variants previously identified as asthma predisposition loci with resistance to parasitic helminths [5]. For example, the IL-13 promoter allele -1057T increases risk of asthma, but decreases schistosome egg load [6]; similarly, non-coding variants of the transcriptional regulator STAT-6, which is on the IL-4 pathway, are associated with higher asthma incidence and decreased susceptibility to the roundworm *Ascaris* [5]. Most SNPs associated with both helminth resistance and predisposition to allergy appear to be in non-coding regulatory regions (promoters, intronic regions or 3' untranslated regions (UTRs)), although some structural alleles are known, for example, in IL-4R [5]. This suggests that, in the main, parasite-maintained polymorphisms control the intensity of an immune response (or indeed, the strength of a suppressive Treg effect). Such ‘allelic rheostats’ are also known in autoimmune-associated loci: for example, in one cohort of systemic lupus erythematosus (SLE) patients, the

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frequency of circulating Tregs was depressed in those carrying a disease-associated 3' UTR SNP allele of CTLA-4, a surface molecule of T cells that acts as a brake on T cell activation [7].

IMMUNE RESPONSE TO PARASITIC INFECTIONS

The first line of defense against parasites, as with other pathogens, is the innate immune system, which is hardwired and primed even in the absence of infection. It is characterized by families of molecules - serum proteins and intracellular and cell-surface receptors - known as pattern recognition receptors (PRRs) that recognize generic molecular structures associated with different groups of pathogens. Among other actions, these receptors mobilize macrophages and granulocytes, unleashing antimicrobial proteins and reactive metabolites. They also mobilize dendritic cells, which activate the lymphocytes of the adaptive immune system, inducing proliferation of T cells and antibody-producing B cells with variable receptors that specifically recognize the parasite [4].

The canonical pattern-recognition receptor of the innate immune system is the cell surface Toll-Like Receptor-4 (TLR-4), which binds to the cell wall lipopolysaccharide (LPS) of Gram-negative bacteria [8]. Detailed phylogenetic analysis of the TLR family indicates strong conservation of sequence and function [9], but there is significant fine-detail polymorphism across the TLR-related pathway within the human population, linked to differences in immune responsiveness to bacterial infection [8]. It is most likely that such polymorphisms are maintained by variations in TLR ligands among pathogens. But while the function of the innate receptors is to activate immediate reactions to microbial infection, some eukaryotic parasites can negatively signal through the same receptors [10], suggesting a complex trade-off for the host. Resulting in selection of both ligand-binding and signaling variants which would resist pathogen repression [2]. Innate immunity alone however seldom eliminates successful parasites, but it inhibits growth while recruiting the antigen-specific T and B cells of the adaptive immune system to proliferate and differentiate into effector cells competent enough to attack the infection. It is therefore the evasion of adaptive immunity that is indispensable to parasite survival [11], and for rapidly proliferating protozoan an effective evasion strategy is antigenic variation, in which the expression of distinct surface molecules allows new variants to escape immune recognition, quickly replacing those killed by the adaptive immune system [4].

HORMONAL TRANSCREGULATION OF PARASITE GROWTH AND REPRODUCTION

Hormones regulate a variety of cellular and physiological functions of organisms, such as growth, reproduction and differentiation [12; 13]. Recently, the ability of hormones to affect the immunological response directed against pathogenic agents has gained attention [14; 15]. This is evident during various parasitic diseases such as malaria, schistosomiasis, toxoplasmosis, cysticercosis, trypanosomiasis and leishmaniasis [16; 17] in which strong hormonal regulation of the immune response has been described [18]. In Taenia crassiceps infection for example, the interaction of the immune and endocrine systems is dynamic and bidirectional [19].

Adrenal hormones

It has been demonstrated that adrenal hormones exert a profound effect on several parasites. For instance in vitro cortisol treatment of Plasmodium falciparum merozoites was found to increase the number and size of gametocytes produced [20]; on the other hand, when these parasites were treated with dehydroepiandrosterone (DHEA) analogue, 16a-bromodehydroepiandrosterone, growth rates diminished by 25% [21]. In addition, cortisol was found to stimulate Entamoeba histolytica proliferation in a dose-dependent manner, while exposure of trophozoites to DHEA inhibited proliferation, reduced adherence and motility, and caused lysis in a dose-dependent manner. Consistent with this, cortisol increased, whereas DHEA decreased, levels of synthesis of parasite DNA (as determined by 3H-thymidine incorporation). Lysis of trophozoites by DHEA seems to be caused by a necrotic rather than apoptotic process, as determined through patterns of DNA fragmentation and enzymatic in situ labeling of apoptosis-induced DNA-strand breaks (detected by Tdt-mediated dUTP-biotin nick-end labeling (TUNEL) assays) [22].

A possible mechanism of action of trophozoite lysis by DHEA was suggested from relationship existing among the bloodstream form of DHEA – DHEA sulfate (DHEA-S), the intensity of Schistosoma mansoni infection and humoral immune responses in humans. Similarly a substantial increase in serum levels of DHEA-S in teenagers (15–19 years old), concomitant to a progressive decline in the intensity of infection, has been reported [23]. Furthermore, peak levels of DHEA-S at

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Although the hygiene hypothesis is couched in very general terms, there is strong evidence that specific gene-environment (and more specifically, gene-parasite) interactions can contribute to the development of damaging immune reactions in autoimmunity and allergy [4]. Some examples include:

a) Cerebral malaria: this is caused by the presence of TNF, INF and other proinflammatory cytokines to the brain.

b) Hepatosplenic schistosomiasis: caused by anti-egg immune responses initiate granuloma formation in the liver.

c) Onchocerciasis: anti-microfilaria responses in the eye lead to blindness. This is caused by autoimmune response via cross reactive antigens in the eye and microfilaria. The immune response is not protective as it is against stage specific surface antigens; thus there is no cross reaction with infective L3 larvae.

d) Lymphatic filariasis: this disease is associated with the response to adult worms in the lymphatic system leading to acute lymphangitis, followed by lymphoedema and elephantiasis or hydrocele. Some individuals are unresponsive to the parasite and have high levels of circulating microfilaria, but no disease. As in onchocerciasis, this response against microfilaria is not cross-reactive with infective L3 and therefore not host protective.

e) Anaphylactic shock: following rupture of hydatid cyst immediate hypersensitivity reaction initiated by systemic release of parasite antigens reacting with IgE and mast cells results in degranulation of the mast cell leading to release of mediators, e.g. histamine.

f) Nephropathy: this is caused by immune complexes resulting from cross-link binding between parasite antigens, antibodies and complement in the kidney. It is mostly common in malaria and schistosomiasis infections [25].

CONCLUSION

Parasites may harm their hosts by causing physical damage (such as the destruction of host cells or the blockage of blood vessels) or by triggering unpleasant physiological changes (such as the induction of fever). Some harmful effects result directly from parasites' activities, while others are side-effects of the mechanisms by which the host's immune system attempts to kill the parasites. In the case of malaria (and many other parasitic diseases), it is increasingly recognized that effects of the cytokines released by the host's immune system in response to the parasite are responsible for many of the symptoms of disease. Furthermore, by means of genomic and non-genomic mechanisms, host hormones have been found to regulate important parasite processes such as growth, differentiation and reproduction through a mechanism described as transregulation. This process benefits the host directly by reducing the success of parasite infection.

Finally in order to limit the damage done by an invading parasite, a host's immune system must respond in a balanced and well-regulated manner, as too weak responses will fail to rid the host of parasite infections while excessive or inappropriate immune response may exacerbate the harm parasites cause to their hosts.

REFERENCES


