1. Pathogen selection of the immunome of humans today

During the past 40 years, there has been an exponential increase in the incidence of autoimmune and idiopathic inflammatory disorders and atopic disease in ‘developed’ societies, with a similar pattern emerging in modernized areas of developing countries (Farrokhyar et al., 2001; Moroni et al., 2012). While changes in lifestyle have contributed to the epidemic of inflammatory disorders in modern societies there is a major underlying role for genetic predisposition in the development of aberrant inflammatory responses. This raises the spectra that the origins of many inflammatory diseases today are due to genetic traits selected, subject to environmental stimuli, and retained throughout human evolution. Stemming from Darwin’s theory of natural selection is the concept that “infection begets natural selection in Homo sapiens” as attributable to the geneticist Haldane (Haldane, 1949). In the immunological context, as a pathogen will kill a host that has no genes that facilitate survival from infection, it follows that such pathogens have exerted significant evolutionary selective pressures on the host immune genome or “immunome”. Consequently, advantageous genetic mutations that confer a resistant phenotype to survive exposure to pathogens have been positively selected during evolution, whilst those genes causing morbidity from infection have undergone negative selection, and were hence removed from the gene pool. Indeed, the widely investigated Toll-like receptor (TLR) family of innate immune receptors may have had an ancestral function in its development and thus, during evolutionary selection, have been co-opted to play a role in immunity to pathogens in multiple species of the animal kingdom (Leulier and Lemaitre, 2008). Therefore it can be suggested that the human immunome of today is the evolutionary consequence of marked and prolonged genetic selective pressure exerted by infectious pathogens (Barreiro and Quintana-Murci, 2010).

Recent socio-economic changes and advances in medical technology in developed societies may have diminished the selection pressure of pathogens at the population level, whilst accentuating the individual genetic mutations that lead to aberrant immune function (Casanova and Abel, 2005). Collectively, the aberrations in immune function that are causal factors in a range of immune-mediated diseases today, such as arthritis, allergy, inflammatory bowel disease (IBD) or multiple sclerosis (MS), may be the ancestral legacy of gene selection in response to infectious pathogens. For example, diversity generated in human leukocyte antigen (HLA) class I genes was significantly influenced by pathogens (Prugnolle et al., 2005). Indeed the advent of genome-wide association studies has identified single nucleotide polymorphisms (SNPs) within the HLA regions associated with a spectrum of non-infectious diseases found in modern humans, such as psychiatric disorders including schizophrenia. Therefore, understanding the host’s immunological response to infectious pathogens will inform on mechanisms that differentially activate (induce) or suppress...
2. Helminths: the master selectors of the immune system

Infectious pathogens of humans encompass viruses, bacteria, fungi, prions and parasites (protozoa and helminths). All pathogenic groups have exerted substantial selection pressure on the human immune system. In this review we consider the role of helminths in selection of the immune and implications for the use of helminths as therapies. Approximately one-third of the world’s population is currently infected with helminth parasites, prompting helminth infections of humans to be termed “the great neglected tropical diseases” (Hotez et al., 2008). An indication of the sustained level of helminth parasitism of humans is the comparable estimate that ~30% of humans were infected with helminths some 65 years ago (Stoll, 1947); one assumes this high prevalence of helminth infection in humans was also a feature of the primate ancestors of Homo sapiens.

Characteristically, parasitic helminths infect humans early in life and are typified by chronic infections. A consequence of helminths’ propensity to infect humans in the pre-reproductive years is that they have exerted significant selective pressure on mutations in genes implicated in immune function, thus ensuring their survival in the host. Hence, advantageous gene mutations preventing helminth-induced fatality in childhood would be passed to the next generation. The hypothesis that helminths act as the major pathogen group exerting selection pressure on immunity was speculative until recently. A systematic approach was used to determine the relative pressure of helminths, viruses or bacteria exerted on a selection of interleukin (IL) genes. Fumagalli et al. (2009) examined 52 globally dispersed human populations, with diverse levels of pathogen richness, for >650,000 SNPs within 91 IL or IL-receptor genes. Helminths were identified as a major selective pressure on a subset of IL genes that, through genome-wide association studies, are associated with human susceptibility to IBD and coeliac disease (Fumagalli et al., 2009).

These recent studies emphasise the role of helminths in the shaping of the human immune system today and, although not validated, it reinforces a role for helminths in the Hygiene Hypothesis. Thus alterations in the levels of microbial factors, in this context helminths, in the environment in westernised or developing societies may contribute to the epidemic of allergic and autoimmune diseases in such societies. Furthermore, using helminth infections as natural inducers of immune responses in experimental settings has delivered novel insights into multiple facets of immune function. Examples of previous discoveries made using helminth models include: the functions of IgE, mechanisms of T helper (Th) 2-cell induction, type 2 dendritic cells (DCs), generation and function of eosinophils, a role for IL-13 in fibrosis and characterization of alternatively activated macrophages (Pulendran and Artis, 2012).

3. A new immune paradigm

As alluded to earlier, multiple immune-regulatory mechanisms are underutilised by a variety of helminth infections that may ameliorate unrelated inflammatory conditions or, indeed, exacerbate inflammation. These studies have not only yielded essential information on the clinical tractability of helminth therapy but have provided parasite immunologists with insight into the mechanisms involved in helminth immunity. This led to an immune paradigm on helminth immunity. This was based on the simplified but prevailing paradigm of the 1980–90s, that type 1 immune responses caused disease pathology whereas type 2 responses were protective, for example in the context of schistosomiasis (Fallon et al., 2000). More recently the interplay of T regulatory (Treg) cells (Taylor et al., 2012) and the role of alternatively activated macrophages (Anthony et al., 2007; Kreider et al., 2007) have expanded this paradigm. Thus, the introduction of helminths would lead to modified Th2 responses and induction of regulatory cells with a concurrent subsidence in Th1/17 (autoimmune) or allergic (Th2) responses and suppress disease and repair/reverse tissue damage (Fig. 1). More recent advances in immunology have seen the discoveries of new immunological mechanisms that appear to have critical roles in helminth immune modulation. These mechanisms indicate key roles for the resident epithelia (Zeigler and Artis, 2010) and innate cells (Ollphant et al., 2011) that are in proximity to the helminth. These ‘first responders’ are now deemed critical in skewing the adaptive immune response (Fig. 2).

4. The case for helminths as therapies

Whilst the merits of the Hygiene Hypothesis are open to debate (Okada et al., 2010), helminths are widely implicated (Yazdanbakhsh et al., 2002). Thus the absence of helminths in developed societies is argued to contribute to the profound increase in the incidence of allergic and autoimmune diseases observed during the last few decades (Yazdanbakhsh et al., 2002; Dunne and Cooke, 2005; Allen and Maizels, 2011). With respect to allergic diseases, there is considerable overlap between the characteristic, polarised inflammatory type 2 immune response and the regulatory type 2 responses typically evoked by helminth infection (Fallon and Mangan, 2007). However, there is disparity between different helminths and/or epidemiological studies on the relative effects, positive or negative, of helminth infection on allergic phenotypes in humans (Leonardi-Bee et al., 2006). For instance, data from epidemiological studies in helminth endemic populations have shown a negative association between the presence of certain helminths and allergic-like inflammatory responses (see Flohr et al., 2009). Nevertheless, helminth therapies are currently being tested as therapeutic strategem in patients with a range of inflammatory diseases (Table 1), and the use of Trichuris suis ova as an investigational medicinal product (IMP) has been granted by the USA Food and Drug Administration (Elliott and Weinstock, 2009) while Necator americanus has been granted an IMP license by the Medicines and Healthcare Regulatory Authority in the UK (Pritchard, 2011).

Separate from epidemiological association studies in human field studies or, more recently, testing live helminth infections in patients, there is a substantial resource of experimental data on helminth modulation of unrelated inflammatory disorders (Table 2). It is relevant to reiterate that not all helminth infections of humans suppress allergic inflammation and may conversely increase inflammatory responses in infected individuals (Leonardi-Bee et al., 2006). Additionally, in mouse helminth models there is evidence that infection can actually exacerbate inflammation, for example, under certain conditions in experimental IBD (Hunter et al., 2007; Smith et al., 2007) and allergic lung inflammation (Mangan et al., 2006; Smits et al., 2007). As the propensity of live helminth infection to regulate immunity is well established, as indeed is the capacity of antigen extracts from helminths to potently stimulate immune activation, a logical option is to identify and isolate the helminth molecules inducing the modulatory activity (Fallon and Alcami, 2006; Harnett and Harnett, 2010a). Indeed, there are a number of molecules from helminths that have been shown to induce regulatory responses, which may have potential as therapeutic moieties (Adisakwattana et al., 2009; Johnston et al., 2009; Harnett et al., 2010a). A molecule from Acanthocheilonema viteae, ES-62, is the most investigated helminth-derived therapeutic molecule described to date (Harnett et al., 2010b). It remains to be determined whether therapeutic administration of
Fig. 1. The classical helminth immunity paradigm. The imbalance in immunity that can lead to (A) autoimmunity is primarily driven by T helper (Th)1 and Th17 cells with macrophages and dendritic cells (DCs) aiding this through an abundance of pro-inflammatory cytokines. In (B) allergic individuals there is a preponderance of Th2 cells, with fewer Th1 cells and a reduction in regulatory T (Treg) cells and other regulatory T cells such as IL-10-producing T cells. Th2 cell secretion of IL-4, IL-5, IL-9 and IL-13 evoke elevated total and allergen-specific IgE, eosinophilia and increases in mast cell and basophil numbers, as well as goblet cell hyperplasia. The use of (C) helminths as therapeutic stratagem will create a hemostatic balance between autoimmune Th1/Th17 and allergic Th2 responses (A and B) through the induction of a regulated environment with managed tissue damage and repair. TGF-β - transforming growth factor-beta.

Fig. 2. Emerging new helminth immune regulation paradigm. Enhanced understanding of the mechanisms that underpin inflammatory processes has led to a new paradigm in helminth immunity. Helminths have now been shown to act on epithelia, causing the release of IL-25, IL-33 and thymic stromal lymphopoietin (TSLP). These ‘alarmins’ induce innate type 2 cells (ILC2) causing the release of IL-4, IL-5 and IL-13, which can then drive T helper (Th)2 responses. Regulatory B (Breg) cells are upregulated in helminth infection, producing IL-10 and can also induce immune suppression through regulatory T (Treg) cells. Together with regulatory-like dendritic cells (DCs) and macrophages these mechanisms depress Th1 and Th17 cells which are involved in the initial inflammatory response. All of the effects of helminth immune-modulation are in the context of genetic predisposition. Through evolutionary regulation of the ‘immunome’, as well as epigenetic regulation at key developmental stages such as in utero and in early childhood, helminths can alter immune responses.
that more work needs to be conducted in order for a greaterclinical responses. 

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benzene sulfonic acid (DNBS)-induced model of colitis, yet 

disparity in outcome also applies to the inflammatory disease 
geneous group, but important inter-species differences exist. The 
of helminth, the age when infections were acquired and the inten-

Collectively, the studies of interactions between helminths and 

inflammatory disorders reviewed above show variable results, 

with both positive and negative associations reported in human 

and animal models. A possible explanation for this heterogeneity 
in the outcome of these studies can be attributed to the species 
of helminth, the age when infections were acquired and the inten-
sity of infection. Helminths are often implicitly treated as a homo-
genous group, but important inter-species differences exist. The 
disparity in outcome also applies to the inflammatory disease 
model employed in a particular study. An example of this is the ef-
effect of Hymenolepis diminuta reducing disease severity in a dinitro-
benzene sulfonic acid (DNBS)-induced model of colitis, yet 

exacerbating the disease in oxazolone-induced colitis (Hunter 
et al., 2005; Wang et al., 2010). This suggests a degree of caution 
must be taken when using data from animal models. 

Given the substantive body of work described above there is a 
significant aura of positivity which surrounds helminth immunity, 
not only as a useful tool for dissecting immunological mechanisms 
but also as a potential therapy for a range of inflammatory disor-
ders. The advancements in understanding immune responses to 
helminth infection have lent themselves to the discovery of new 
imune populations and a shift in the immune paradigm from a 
primarily adaptive response to a more balanced innate-driven 
adaptive response. On encountering helminths, innate cells can 
be described as sounding the alarm (Fig. 2). However, effective 
immunity demands activation of the adaptive compartment. To 
bridge this transition, a plethora of type 2 innate mechanisms are 
initiated which indicates that helminths utilise several differ-
ent mechanisms by which to first activate and then escape im-

Recently concluded trials and pre-clinical assessments suggest 
that more work needs to be conducted in order for a greater clinical 
consensus to be reached. Murine studies in colitis (Smith 
et al., 2007) and airway hyperresponsiveness (Mangan et al., 
2006; Smits et al., 2007) indicated initial inflammatory events as 
S. mansoni infections underwent acute to chronic phase transition. 
This raises concerns about the levels of tolerance patients would 
have, should they experience such effects. To further this argu-
ment, a trial of T. suis ova in allergic rhinitis demonstrated a lack 
of efficacy whilst reporting a high prevalence of adverse gastro-
intestinal reactions (Bager et al., 2011). 

Clinical trials of helminths as therapies to date have been on pa-

tients from non-endemic countries. It is appropriate to note that 
helminth therapies will probably be used in developed societies, 
where the epidemic of inflammatory disorders is most prevalent, 
and thus in people never previously exposed to helminths. In con-
trast, the desirable protective effects of helminth infection of hu-

mans in field studies have been reported on people in endemic 
areas (Scriven et al., 2001). A unique facet of endemicity is that 
people are infected with helminths early in childhood and may also 
be subjected to in utero sensitization, i.e. women can be in-
fected during pregnancy and the fetus exposed to helminth modula-
tion and antigens. Indeed, prenatal exposure to helminths has 
been shown to alter immunity of neonates and cord blood cellular 
responses in endemic settings (King et al., 1998). There is a grow-
ing recognition that environmental factors during pregnancy and 
early life may lead to epigenetic changes that can profoundly 
change gene function and, by extension, the response in a disease 
setting (Hawrylowicz and Rynnna, 2010). Prominent examples of 
this are the increased risk of cardiovascular disease and type 2 dia-
betes in individuals born during the Dutch Famine of 1944–45 
(Painter et al., 2005), and those who were young children during 
the siege of Leningrad in the 1940s (Sparen et al., 2004). It is not 
known how such early life exposure contributes to any beneficial 
effect helminth infections have on unrelated inflammation. What 
is the outcome of a person infected early in life who is subse-
quently infected with a different helminth as part of a therapy? 
In this context, one consequence of previous infection is that, as 
helminth antigens are highly glycosylated, infected individuals 
can produce antibody responses to glycan structures. This is 
relevant as some new biological therapies have unexpected side-
effects due to the presence of pre-existing anti-glycan antibodies that
cross-react with the drug, for example anaphylactic responses in cancer patients treated with Cetuximab (Chung et al., 2008). This is an issue that requires investigation as helminths may be used therapeutically in naïve (not previously exposed-infected) or sensitised (previously infected) patients.

5. Conclusion

The key to unlocking the potential of helminth therapy is gaining greater understanding of the ‘immunome’. Helminths may not be suitable for all patients, however the ability to ‘genotype’ a cohort for their therapeutic suitability would certainly see efficacy rates improve dramatically. Dissecting and identifying key changes in the immunological genome will occur over time and, armed with this information, a more refined, elegant use for helminths in the clinic could be considered.

At the time of writing at least 16 clinical trials are underway involving helminth therapy in a multitude of diverse conditions including IBD, MS and autism. The juggernaut that is helminth therapy has been gathering pace for some time. It is therefore conceivable that we have reached the ‘chicken and the egg’ scenario where clinical demand outstrips the rate of mechanistic understanding, even with the variability in efficacy seen from study to study. However, there are precedents for this, as many drugs in clinical use today are effective therapies despite an incomplete understanding of their modes of action, such as sulfasalazine (Cotton et al., 2011). Similarly, helminths are currently under clinical...
evaluation despite not knowing their full mechanism of action as therapies. In science, and indeed politics, sometimes we progress despite being unaware of all the outcomes.

“There are known knowns. These are things we know that we know.

There are known unknowns. That is to say, there are things that we know we don’t know.

But there are also unknown unknowns. There are things we don’t know we don’t know.


As argued above, helminths have selected the immunome of to-day, consequentially there are many "unknown unknowns" to emerge as we translate helminths to therapies.

Un cited references


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