Immunology
The Journal of cells, molecules, systems and technologies

British Society for immunology

IMMUNOLOGY REVIEW ARTICLE

Chronic infections with viruses or parasites: breaking bad to make good

Andrew Godkin and Katherine A. Smith[†]

Division of Infection and Immunity, Cardiff University, Cardiff, Glamorgan, UK

doi:10.1111/imm.12703
Received 3 September 2016; revised 2 December 2016; accepted 16 December 2016.

[†]Present addresss: Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa
Correspondence: Katherine A. Smith, Cardiff University, Heath Park, CF14 4XN, Cardiff, Glamorgan, UK.
Email: smithk28@cardiff.ac.uk
Senior author: Katherine A. Smith

Summary

Eukaryotic forms of life have been continually invaded by microbes and larger multicellular parasites, such as helminths. Over a billion years ago bacterial endosymbionts permanently colonized eukaryotic cells leading to recognized organelles with a distinct genetic lineage, such as mitochondria and chloroplasts. Colonization of our skin and mucosal surfaces with bacterial commensals is now known to be important for host health. However, the contribution of chronic virus and parasitic infections to immune homeostasis is being increasingly questioned. Persistent infection does not necessarily equate to exhibiting a chronic illness: healthy hosts (e.g. humans) have chronic viral and parasitic infections with no evidence of disease. Indeed, there are now examples of complex interactions between these microbes and hosts that seem to confer an advantage to the host at a particular time, suggesting that the relationship has progressed along an axis from parasitic to commensal to one of a mutualistic symbiosis. This concept is explored using examples from viruses and parasites, considering how the relationships may be not only detrimental but also beneficial to the human host.

Keywords: chronic inflammation; parasitic helminth; tolerance/suppression/anergy; viral.

Introduction

In humans, infection can result from a variety of organisms including bacteria, viruses, parasites and fungi. Traditionally, pathogenic infections were defined according to Koch's postulates, i.e. they were organisms that could be 'found', isolated, cultured and confirmed as a causative agent of disease by inoculation into a new host. Apart from the obvious limitations of pathogen isolation and culture techniques, Koch's postulates were criticized and adapted in the face of technological advances, such as the identification of pathogen-specific nucleic acids using molecular biology techniques. With the advent of metagenomic sequencing, it has become clear that the presence of a microbe is not necessarily indicative of pathogenesis and instead may represent a degree of co-evolution and symbiosis between the organism and the host.[1] Accumulating evidence demonstrates that commensal organisms colonizing our mucosal surfaces, particularly the gut microbiome, benefit immune functions at all levels.[2] However, opportunistic infections by commensal bacteria and fungi can also occur, usually in the hospital setting of patients who are already ill, resulting in severe nosocomial sepsis or pneumonia.

Chronic infections are either persistent or latent infections within a host. Despite attempts by the immune system to respond to the acute infection, pathogens escape from immune clearance by modulating, or regulating our immune response. For instance, persistence of an unresolved infection can result in immune exhaustion or deviation, for example, by switching of $CD4^+$ T cells to interleukin-10 (IL-10) producers in patients with chronic hepatitis C virus (HCV) infection,[3] or the induction of IL-10 and interferon-γ co-production by $CD4^+$ T cells following parasitic *Toxoplasma gondii* infection.[4] The hijacking of these pathways by pathogens is an effective way for viruses and parasites to avoid immunopathology while establishing a persistent or latent infection.[5,6] In some instances, this immune regulation may also be coupled to significant benefits for the host, dampening underlying inflammatory disorders and resulting in a survival advantage. Below we will consider examples of this mutualistic symbiosis, focusing on examples from chronic viral and parasitic infections.

Viruses

In the case of viruses, metagenomic sequencing of the 'virome' has identified eukaryotic viruses, including acute infections, chronic replicating infections and chronic latent infections. Furthermore, in a complex multicellular eukaryotic host, the virome also includes bacteriophages infecting the microbiota, and virus-derived genetic elements incorporated into eukaryotic chromosomes, e.g. retrovirus-encoded elements, which are thought to make up 8% of the genome.[7] It is difficult to know how stably associated the overall virome is with the host, particularly as viruses relying solely on a lytic life cycle, such as influenza virus, respiratory syncytial virus or dengue virus, cause cell death but tend to produce short-lived acute infections. However, non-cytopathic viruses, which do not cause such profound cell death, can infect and persist for the lifespan of the host.

It is estimated that humans carry between 8 and 12 persistent viral infections, including herpesviruses, retroviruses, *Allenoviridae* and in fewer individuals: papillomaviruses, hepatitis viruses and human immunodeficiency virus (HIV).[8] For most of the life-time of the host, persistent viral infections cause no overt clinical disease. This pathogen-induced immune regulation is also employed by other chronic infections, including parasites (discussed in the next section), to enhance pathogen survival and often confer a survival advantage to the host. This viral mutualistic symbiosis is well recognized in invertebrates and plants, for example infection with cucumber mosaic virus imparts drought resistance to the *Nicotiana benthamiana* plant.[9] Some viruses operate through a bacterial go-between to exert a symbiotic effect, for example aphids are protected from invading wasp larvae by infection with a heritable symbiotic bacteria that harbours a bacteriophage encoding an anti-wasp toxin.[10] In these examples, the virus alters gene expression in the host and confers an advantage, which in the case of a chronically infected host, results in an increased chance of competitiveness and survival.

So can we find examples of mutualistic symbiosis in human (or vertebrate) hosts? The success of the balance between the replication and survival of the invading virus and the immune response and survival of the host can be defined by four key clinical factors: does the presence of viral infection lead to tissue, and hence organ, dysfunction; does the virus compromise the immunity of the host allowing secondary pathogens to invade; conversely does the immune system maintain a state of persistent activation leading to immunopathology; and lastly, is it possible that a persistent viral infection may in some manner benefit the host?

Hepatotropic viruses illustrate the complexity of host–virus relationships.[11] Although these viruses grow and replicate in the liver, some hepatotropic viruses spread by the oral–faecal route (hepatitis A virus and hepatitis E virus). They are adapted to rapid host-to-host horizontal spread by passing from the liver to the gut and the faeces, using the ideal conduit: the biliary tract. These viruses have no need to persist in humans. However, hepatitis B virus (HBV) and HCV are blood-borne infections, whose natural route of infection is perinatal, from the mother to the neonate. For these viruses, the chances of transmission are rarer, and to maximize the likelihood of success, an ideal scenario is persistent infection accompanied by high levels of viraemia. After initial infection with HCV, 80% of people develop chronic infection,[12] exhibit detectable viraemia (ranging from about 10^3 to 10^7 copies/ml) but no evidence of liver disease.[13] Both HBV and HCV have evolved a series of strategies to avoid or evade the innate and adaptive immune responses, including the modulation of antigen presentation and expansion of anti-inflammatory regulatory T cells.[14,15] The maintenance of the host in this state provides a circulating reservoir of infective virus, increasing the statistical chance of viral transmission to a new host.

Once chronically infected with HBV or HCV, there is an astonishingly long period in most hosts, usually of decades, where there is no detriment to health. In some individuals attempted immune control of the virus by the host immune system over time drives liver inflammation and complications, such as liver cirrhosis or cancer. In these patients, there is a direct correlation between the degree of chronic inflammation (in this case the expression of the natural cytotoxicity receptor NKp46) and steadily worsening liver pathology.[16] During chronic infection, HCV and HBV also employ strategies to escape from on-going host immunological attack by key adaptive immune cells such as cytotoxic $CD8^+$ T cells; for instance mutation of key viral epitopes, presented to these $CD8^+$ T cells by MHC class I molecules.[17] Other diverse immune evasion strategies include interference with the signalling pathways required for production of pro-inflammatory cytokines, the up-regulation of inhibitory molecules such as PD-1 on virus-specific $CD8^+$ T cells and the expansion of $CD4^+$ regulatory T cells that can inhibit virus-specific $CD8^+$ T cells (reviewed in Park and Rehermann[18]) (Fig. 1.). These modifications can have a profound impact on the ability of the host to generate an immune response, or on underlying inflammatory conditions.

As the development of hepatitis virus liver-related illness usually takes many years and does not impact on reproductive fitness, the question arises: is there a benefit of viral immune manipulation on the human host population? One possibility is that the infected liver is less accommodating to other hepatotropic pathogens. Indeed studies have shown that patients with higher HBV viraemia have reduced *Plasmodium* spp. parasitaemia and exhibit asymptomatic malaria, characterized by decreased

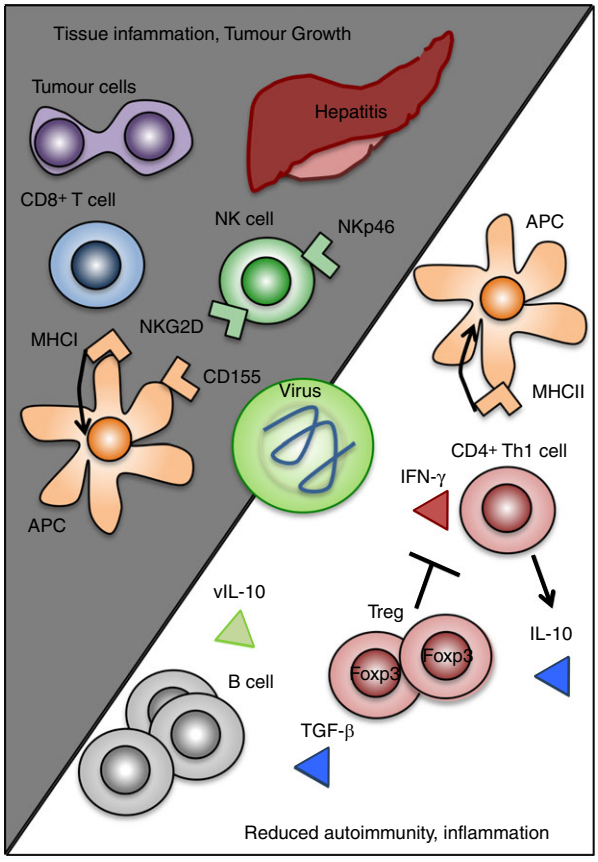

Figure 1. The good (light) and bad (dark) side of chronic virus infection. Infection of tissues by viruses and subsequent chronic inflammation can lead to tissue damage, e.g. hepatitis. In chronic hepatitis C virus (HCV) infection, progression to disease is associated with the expression of the natural killer (NK) cell receptor NKp46. Many other viruses directly infect antigen-presenting cells (APCs) or have a number of molecules that can down-regulate MHC class I expression expressed by these cells; this molecule is important for viral recognition by $CD8^+$ T cells but is also important for elimination of tumour cells. The NK cell killing of cells expressing low MHC class I is prevented by the dismantling of NK activating receptors. viral interleukin-10 (vIL-10) can transform B cells and help the virus to establish a chronic infection. This molecule is also reported to reduce autoimmunity, inflammation and tissue rejection. Chronic virus infection can promote anti-inflammatory responses, including the expansion of regulatory T (Treg) cells and, production of transforming growth factor-β (TGF-β) and is associated with a switch from interferon-γ (IFN-γ) to IL-10-producing $CD4^+$ T cells. Viral infection is also able to reduce antigen presentation and activation of APCs, reducing $CD4^+$ T-cell activation and inflammatory responses.

inflammatory cytokine production.[19] The young children most likely to become infected with HBV are particularly susceptible to malaria infection, illness and death, therefore viral dampening of this anti-malaria response would offer a clear selective advantage for the survival and transmission of HBV.

There are over 100 herpesviruses that infect vertebrate and invertebrate hosts. Eight commonly infect humans: herpes simplex virus types 1 and 2, varicella zoster virus, cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus 6, human herpesvirus 7 and Kaposi's sarcoma-associated herpesvirus. All herpesviruses can establish latent infection within specific niches (e.g. nerve cells for herpes simplex virus, haematological cells for EBV, epithelial cells for CMV) and induce a systemic immune response. Immune control of these viruses, and the dynamics of viruses moving between latency and reactivation, results in fluctuating local and systemic inflammatory responses, which may result in injury and damage of infected tissues or a gradual deterioration of the immune system. A case in point is CMV infection of endothelial cells, where CMV-induced effector T cells cause endothelial cell damage and low-grade long-term vascular injury.[20] CMV can have a profound impact on the T-cell compartment of the host immune system, driving bursts of functional CMV-specific memory $CD8^+$ T-cell expansion during chronic infection.[21] Although the establishment and maintenance of these inflated T-cell populations in adults is thought to be critical for the control of persistent viral infection, it is currently unclear how this process impacts on host immune responses to other pathogens and vaccines in otherwise healthy individuals. Immunosuppressive medical treatment of immunocompromised patients infected with CMV, can lead to virus-related clinical disease, such as CMV colitis, hepatitis or organ rejection. Underlying CMV infection or the opportunistic outgrowth of viral or bacterial commensal species results in loss of immune responsiveness or containment in these patients.[22] The acquisition of CMV during early life has a profound impact on the immune cell subset composition of infants.[23] Although controversial, some suggest that the natural acquisition of CMV infection by young children may prime and boost the adaptive immune system, moulding it for later life.[24]

Herpesviruses have evolved an extraordinary ability to persist and escape immune detection by dedicating much of their large genomic capacity to subverting a diverse array of innate and adaptive immune responses. A major strategy for viral immune evasion is to target the initiation of the host immune response, by inhibiting host MHC class I antigen presentation of virus-specific epitopes to anti-viral cytotoxic $CD8^+$ T cells.[25] To counteract the possible increased natural killer cell killing of infected cells associated with loss of MHC class I, the machinery that alerts these cells is also dismantled by the virus[26] (Fig. 1). However, during chronic Kaposi's sarcoma-associated herpesvirus infection, the inhibition of antigen presentation by the virus can lead to the development of the endothelial tumour Kaposi's sarcoma, particularly in immunocompromised patients.[27.]

For the vast majority of us who live harmoniously with these viruses, again the question arises: is there a fitness benefit for the host? Evidence from animal models

suggests that the presence of persistent latent (but not lytic) γ-herpesvirus infection can confer protection from lethal bacterial infection and lethal lymphoma challenge. Protection was associated with increased macrophage activation and the production of the antiviral cytokine interferon-γ[28] or increased natural killer cell activity.[29] Latent viral infection could also significantly delay type 1 diabetes onset in mice by reducing antigen presentation of autoantigen to $CD4^+$ T cells.[30] Increases in the production of interferon-γ during latent viral infection may underlie protection from other types of inflammatory disease, as supported by epidemiological data demonstrating inverse associations between herpesvirus infection[31,32] and 'type-2' allergic diseases. This skewing of the T helper type 1–type 2 balance will be considered in the following section focusing on the possible protective effects of chronic parasitic infection. Animal models have also shown that viral cytokine homologues, such as EBV IL-10 can provide some benefit to the host. EBV IL-10 can act on multiple cell types and inhibit cytokine synthesis by natural killer and T cells.[33] The molecule is thought to play a critical role in the transformation of B cells, enabling time for the virus to establish latency.[34] However, it has also been shown to inhibit collagen-induced arthritis, autoimmune diabetes and pancreatitis, and to improve survival following sepsis and graft acceptance when expressed or administered *in vivo*[35] (Fig. 1.). These examples demonstrate viral mutualistic symbiosis, as described above for other non-vertebrate eukaryotes.

The study of mutualistic symbiosis allows us to view millions of years of host–pathogen co-evolution. With increased movement of humans around the globe, we are also witnessing emerging new virus infections almost annually, often derived from animal reservoirs. Recognized in the 1980s, HIV has already provided evidence of pathogen-driven selection. Natural elite controllers are found in ~ 3/1000 of untreated HIV-infected individuals and are defined by stable $CD4^+$ T-cell count with very low viral loads; these patients demonstrate superior antiviral $CD4^+$ T-cell[36] and cytotoxic $CD8^+$ T-cell responses.[37] If effective anti-retroviral treatment was not available, it seems inevitable that pathogen-driven natural selection would favour these elite controllers, increasing the population frequencies of beneficial genetic polymorphisms such as HLA-B27, HLA-B51 and HLA-B57.[38] Polymorphisms such as HLA-B27 also promote $CD8^+$ T-cell clearance of HCV but are strongly linked to development of the autoimmune disease ankylosing spondylitis. Interestingly, some suggest that *Plasmodium falciparum* infection may have contributed to negative selection of this gene, due to the greater susceptibility of patients expressing this allele to severe forms of malaria.[39] Genetic selection, the moulding of our immune response and subsequent susceptibility to disease, has occurred as a result of ancient long-standing infections by chronic pathogens, those causing malaria, leprosy, as well as parasitic worms (discussed in the next section).[40.]

Parasites

Helminths affect over one billion people worldwide, mostly within developing regions, such as sub-Saharan Africa, South America and India. Although new epidemiological studies are required, a systematic review in 2011 demonstrated that soil-transmitted helminths are also prevalent in high-income countries.[41] Helminth infections have co-evolved with man and evidence suggests that in a similar manner to chronic viral infections (discussed in the previous section), they have provided selective pressure on the genetic make-up of the host.[42] Helminth infections are acquired in childhood; however, in high-income countries zoonotic helminth infections of adults from cats and dogs are most common. Infection can cause diarrhoea, abdominal pain, weakness and anaemia and contributes to 14 million disability-adjusted life-years (or the cumulative number of years lost to ill-health, disability or early death).[43] For orally transmitted helminths, mortality is rare and infection is often asymptomatic; most patients exhibiting low worm burden and limited clinical pathology.[44.]

Although gastrointestinal and intravascular helminth infections are reported to have some beneficial effects on inflammation-induced pathology in response to co-infection with other parasites,[45] bacterial pathogens[46] or viral infections,[47] it can also impair protective immunity to concurrent parasite infections,[48–51] promoting anaemia and liver pathology following malaria infection,[52–54] exacerbating *Citrobacter rodentium* infection and associated bacterial-induced colitis[55] and aggravating virus-related liver disease.[56] This parasite impairment of host immunity has enormous health burden implications, particularly when immune responses to the biggest killers in the developing world, i.e. HIV, tuberculosis and diarrhoeic infections are affected.[57] A number of mechanisms of immune suppression of co-infections are at play here, including the impairment of mucosal mastocytosis,[58,59] the ablation of protective $CD8^+$ T-cell responses,[60] the induction or alteration of regulatory T-cell subsets[56,61] and the alternative activation of colonic macrophages[62] (Fig. 2).

Apart from an impact on immune responses to primary infection, the presence of chronic parasite infection in endemic areas has important implications for vaccination in the developing world. Epidemiological studies have demonstrated that human helminth infections can impair immune responses to tetanus toxoid and cholera toxin B in endemic areas.[63,64] In murine and large animal models, helminth infection reduces the immune response to malaria and *Salmonella* vaccinations.[65–67] As described previously, and in common with virus-induced immune

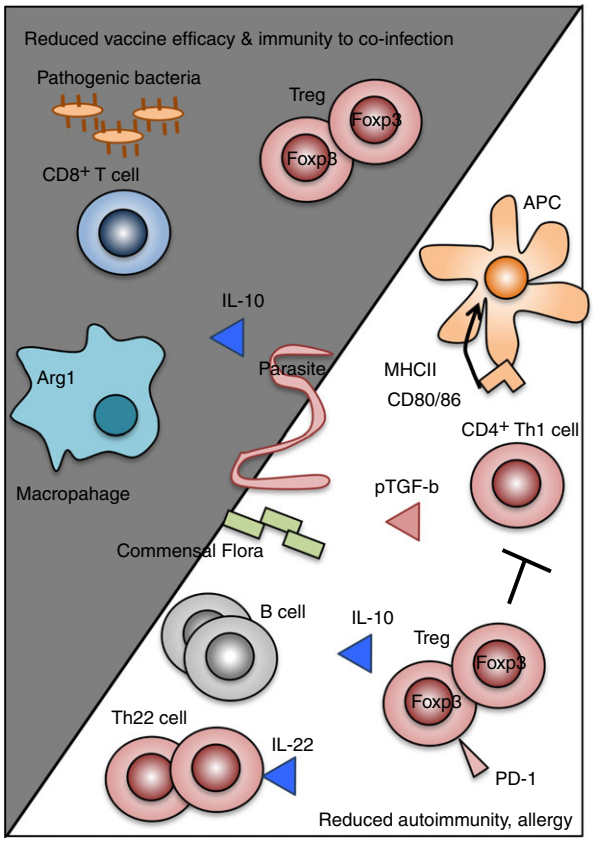

Figure 2. The good (light) and bad (dark) side of chronic parasite infection. Chronic parasite infection can alter the commensal flora of the gut, resulting in reduced airway inflammation/allergy and inflammatory bowel disease. Parasite transforming growth factor-β homologues (pTGF-β) released into the host can promote regulatory T (Treg) cell expansion and up-regulation of programmed cell death protein 1 (PD-1), which inhibit $CD4^+$ T-cell expansion and inflammatory cell production, resulting in reduced autoimmunity and allergy. Infection also promotes interleukin-10 (IL-10) production in the host, which can also promote Treg and reduce inflammation. Some helminth infections can promote the expansion of T cells producing IL-22 (Th22 cells), which are able to promote homeostasis of the gut epithelial lining, reducing inflammatory bowel disease. Finally, infection is also able to promote the formation of B cells, which can regulate inflammatory disorder such as asthma (regulatory B cells). On the bad side, parasite infection promotes Treg cells, which can reduce the efficacy of vaccines and the immune response to other infections. Here, IL-10 produced in the host in response to infection can also promote these Treg cells. Infection with parasites can ablate protective $CD8^+$ T-cell responses against co-infections such as *Toxoplasma gondii*. The alternative activation of macrophages promoted by parasite infection can also impair host protection against concurrent bacterial infection.

suppression, these effects are related to the production of regulatory cytokines such as IL-10 or the induction of regulatory T cells during chronic parasite infection.

A number of chronic parasites, including *Schistosoma haematobium*, *Opisthorchis viverrini* and *Clonorchis sinensis*, are also classified as Group 1 carcinogens, presenting a pertinent health challenge in developing regions. In parasite endemic regions, infection with *Schistosoma mansoni* and *Schistosoma japonicum* resulted in schistosomal colitis and was linked to increased bladder and cervical cancer.[68–70] Studies *in vitro* have shown that the production of signature cytokines associated with murine *Heligmosomoides polygyrus* infection or *S. mansoni* egg administration promoted the replication of a herpesvirus that drives cancer (Kaposi's sarcoma)[71] and recent epidemiological studies associated soil-transmitted helminth infection with an increased prevalence of human papillomavirus (a major cause of cervical cancer).[72] In mouse models, infection with the gastrointestinal helminth *H. polygyrus* substantially reduced the type 1 inflammatory response associated with *Helicobacter pylori* infection and attenuated gastric atrophy, a pre-malignant lesion.[46] Infection with the extraintestinal tapeworm *Taenia crassiceps* reduced the development of colitis-associated tumours in a murine model of colorectal cancer. This effect was associated with increased expression of the type 2 cytokine IL-4 and with alterations in innate immunity, including macrophage alternative activation, neutrophil attraction and the recruitment of inflammatory monocytes.[73]

In a similar manner to chronic viral infections, helminths have evolved potent mechanisms to regulate the host immune response, in order to ensure their long-term survival.[74] As well as notable effects on specific anti-parasite responses, helminth immune regulation is proposed to exert mutualistic symbiosis, similar to the chronic viral infections discussed in the previous section, to further benefit the host – by suppressing responses to a number of allergens and autoantigens.[75] Numerous studies have employed murine models of inflammatory disease to demonstrate that live parasite infection can protect against inflammatory disorders through immunomodulatory mechanisms including the activation of regulatory T cells[46,49] or the production of IL-10.[50] However, the immune-regulatory pathways that live helminths employ to modulate inflammatory disease are multi-faceted, impacting on B cells,[76] macrophages,[77] innate immunity[78] and through alterations to intestinal microbiota and their metabolites.[79,80]

In epidemiological studies, the story is more complex. Some studies have shown clear protection against allergen skin test reactivity in individuals infected with intestinal helminth infections such as *Ascaris lumbricoides*, *Trichuris trichiura*, hookworm and schistosomiasis.[81,82] This protection from pathology is associated with helminth-induced polarization of the inflammatory cytokine response, in a similar manner to chronic viral infections (as discussed in the previous section). A correlation between parasite infection and improvements in multiple sclerosis was associated with increased frequencies of

$CD4^+$ $CD25^+$ $Foxp3^+$ T cells and increased cellular production of the immune-regulatory cytokines IL-10 and transforming growth factor-β.[83] Resolution of colitis in an individual who infected himself with *T. trichiura*[84] was associated with an increase in IL-22-producing $CD4^+$ cells.[85] Interestingly, prior parasite infection can mould subsequent immune responses in the long-term; both increased atopy and eczema were recorded in patients from a parasite endemic region that were treated in a long-term intervention study using the antihelminthic ivermectin.[86] Use of the antihelminthics albendazole and praziquantal during pregnancy was also associated with an increase rick of eczema in infancy,[87,88] suggesting that *in utero* helminth exposure may programme and prime the host immune system of the offspring. These studies clearly demonstrate that helminths can mould the genome of the host, similar to the chronic viral infections discussed in the previous section. Perhaps the best example of this for helminth infections is the selection of sickle cells traits, which confer resistance to malaria in endemic regions.[89]

Live helminths are currently being employed in a number of clinical trials in efforts to alleviate allergic and autoimmune disorders.[90] Successful trials include the treatment of patients with inflammatory bowel disease with eggs from the porcine whipworm *Trichuris suis*.[91,92] However, not all trials using this strategy have had such a profound outcome, as evidenced by repeated treatment of patients exhibiting grass pollen-induced allergic rhinitis with *T. suis* ova.[93] The effectiveness of using parasitic helminth infections to treat inflammatory disorders is called into question in a recent review.[94] This publication discusses the limitations of our current understanding of host–parasite interactions and cites evidence of causal associations between helminth infections and inflammatory disorders. Recent reviews have also revealed the limitations of human studies in poor-resource settings,[95] and indeed the consensus calls for the identification of helminth-derived molecules of therapeutic potential and the use of animal models, alongside appropriately controlled clinical trials, to test these novel treatments of inflammatory disease.

Some progress has already been made on this front; individual helminth-secreted products from the human hookworm *Necator americanus*, the filarial nematode *Acanthocheilonema viteae* and the murine gastrointestinal helminth *H. polygyrus* all suppressed rodent models of inflammatory disease, including arthritis, allergy and asthma.[96,97,98] Each of these parasite-derived products has a unique capacity to modulate the host immune system at many levels, including suppression of mast cell responses,[99] dampening the activation of inflammatory T cells by dendritic cells[96] and by promoting the induction of regulatory T cells.[100] Our increasing understanding of helminth modulation of immune function, has also led to the proposal that helminth-treated populations of cells, such as macrophages, be used in therapeutic applications for inflammatory diseases in humans.[101] These results warrant further studies in animal models and possible clinical trials to determine the efficacy of these findings in humans.

In conclusion, both chronic viral and parasite infections can have both a beneficial and detrimental impact on the host immune system. A consensus on one conserved mechanism of immune suppression has not been reached, although this is mainly due to the complexity of the immune response, the tissue specificity of infection and the underlying health status of the individual. As for chronic viral infections, intestinal parasites have moulded our genome and have an intimate bi-directional relationship with the host. Our increasing understanding of host–pathogen interactions and the complexity of our micro- and macro-biome will enhance our ability to break the bad consequences of chronic infection and make good through tailored treatment of an individual with an inflammatory disorder, or the development of strategies that increase vaccine efficacy and limit infection-associated tumour prevalence, in endemic regions.

Disclosures

There are no competing interests that might have influenced this manuscript.

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