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REVIEW
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The Influence of Genetic and Environmental Factors and Their Interactions on Immune Response to Helminth Infections

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Helminth infection currently affect over 2 billion people worldwide, with those with the most pathologies and morbidities, living in regions with unequal and disproportionate access to effective healthcare solutions. Host genetics and environmental factors play critical roles in modulating and regulating immune responses following exposure to various pathogens and insults. However, the interplay of environment and genetic factors in influencing who gets infected and the establishment, persistence, and clearance of helminth parasites remains unclear. Inbred strains of mice have long been used to investigate the role of host genetic factors on pathogenesis and resistance to helminth infection in a laboratory setting. This review will discuss the use of ecological and environmental mouse models to study helminth infections and how this could be used in combination with host genetic variation to explore the relative contribution of these factors in influencing immune response to helminth infections. Improved understanding of interactions between genetics and the environment to helminth immune responses would be important for efforts to identify and develop new prophylactic and therapeutic options for the management of helminth infections and their pathogenesis.

Keywords: genetics, environment, interaction, Helminth infection, heterogeneity

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INTRODUCTION

Research into factors that influence host response during helminth infection are usually focused on use of inbred mice raised in a specific pathogen free environment as found in most research institutes and academic institutions across the world. However, in the real-world setting, helminth infections are characterized by infections of individuals living in various communities with different lifestyles as well as with wide genetic variations. Also, the intensity of helminth infection among individuals varies markedly and can be influenced by various genetic and environmental factors (1, 2). Therefore, in this review, we discuss the influence of genetic and environmental diversities in the regulation of helminth induced immune response and their contribution to inter-individual variation seen in responses during helminth infection (3, 4). Furthermore, we highlight ongoing studies and future opportunities to examine the interaction between environment, genetics and other variables that influences the interindividual variation seen during helminth infection.

IMMUNE RESPONSE TO HELMINTH INFECTION

Studies with genetically modified mice on the C57BL/6 background has transformed our understanding of Type 2 responses to helminths in the last few decades. Immune responses during helminth infection are characterized by recruitment and accumulation of innate immune cells such as eosinophils, basophils, innate lymphoid cells (ILC2), neutrophils, alternatively activated macrophages as well as cell of the adaptive immune system such as B cells, Th2 and T regulatory CD4 T cells (5–11). These cells produce Type 2 and regulatory cytokines and other mediators which play important protective and regulatory functions during helminth induced inflammation (12–14). Recent advances demonstrate the critical role other previously overlooked cells such as epithelial, neuronal, and stromal cells play in contributing to and regulating Type 2 immune responses during helminth infection (5, 15, 16). These non-immune cells can produce cytokines, alarmins and other bioactive mediators that crosstalk with innate and adaptive immune cells to regulate the response during helminth infection. Despite these advances, inter-individual variation in these responses and the influence of the environmental interaction with host genetics in free-living mammals is not well understood.

GENETIC VARIATION IN RESISTANCE TO HELMINTH INFECTION

Our ability to genetically manipulate mice has been fundamental for increased understanding of mammalian physiology. As this technology evolved over time, the C57BL/6 strain of mice has emerged as the inbred strain of choice for most immunological studies. As a result, our understanding of the basic mechanisms that surround immune response during helminth infection has also improved significantly with the use of genetically modified mouse models for dissecting various mediators and immune cell populations in the regulation of helminth induced immune responses. Increasing complexity of mouse models include cell specific knockouts, genetic inducible fate mapping models, in addition to the global knock-out and/or transgenic mice models have been critical in identifying new pathways that regulate Type 2 and immunoregulatory responses to helminths. To reduce variation in these reductionist experiments to characterize detailed mechanisms, genetically identical mice strains of similar age groups and sometime sex are used to isolate and study the role of specific cell types and immune mediators.

However, various other studies have used in-bred strains of mice to study the role of genetic variations in resistance to helminth infection (17). For example, previous studies have shown that the BALB/c strain of mice are more susceptible to *Litomosoides sigmodontis*, a filarial nematode, compared to the C57BL/6 mice or the C57BL/10 mice (18–20). This contrasts with other intestinal helminth parasites such as *Trichuris muris* (21–23) and *Heligosomoides polygrus* (24–26) where the BALB/c strain has been shown to be more resistant. Other studies have also examined inbred strains with various other helminth parasites (**Table 1**). While genetic variation clearly influences susceptibility and resistance to helminth infection in mouse models, our understanding of the basic mechanisms elicited during helminth immune response critical for mediating these differences remain unclear. While mechanisms driving these differences include the role of various effector immune cells, cytokines, and immunoglobulins (**Table 1**), the role of genetic variation in regulating primary and/or secondary sentinels of Type 2 inflammation (55–57), such as epithelial, stromal, and neuronal cells is currently less appreciated and has not been well studied. For example, in the area of epithelial cell biology, C57BL/6 and BALB/c mice show differences in tuft cell response at steady state and in response to a protozoa parasite, *Trichomonas muris*, but no significant difference was seen in tuft cell response following chronic infection with *H. polygyrus* at peak of parasite establishment (58). The dynamics of tuft cell hyperplasia in the different inbred strain of mice could vary wherein the BALB/c mice might have higher response than the C57BL/6 mice (59). Hence, the role of these sentinels in the pathogenesis and outcome to helminth infection should be examined in different inbred strains of mice.

Studies in other free-living mammals such as the livestock population and wild animals has also highlighted the importance of genetic factors in susceptibility to helminth infection (60–64). For example, farmers and livestock breeders will often use their knowledge of breed specific resistance and susceptibility to helminth infection to minimize cost and losses associated with infection with helminths, by selecting helminth parasite resistant strains for breeding. Some studies have linked these genetic resistant and susceptibility patterns to the protective Type 2 mechanism (60, 64, 65).

There are fewer studies in the human population that provides a mechanistic understanding to the influence of genetic variations on susceptibility to helminth infection, despite substantial evidence for the role of genetics in determining susceptibility to infections (1). Logistical and ethical constraints often limit human population studies to correlational observations rather than a study of cause-and-effect relationships. Currently, host genetics is said to account for about 20 to 40% of variation in intensity of worm burdens seen during helminth infections (1). For example, a few studies have demonstrated the role of genetic factors in susceptibility to human Ascaris infection (66–68). Notably, they were able to associate this genetic factor to a peak in chromosome 13 which is close to the known locus of a major candidate gene, *TNFSF13B*, involved in the regulation of B cell activation and immunoglobulin secretion (68–71). A few other genetic factors such as during *Trichuris trichiura* infections have also been identified (72) and associated with localization of two significant quantitative trait loci on chromosomes 9 and 18, which contains genes that can influence immunoregulatory cytokines like IL-10 (73). Susceptibility to other helminth parasites such as blood flukes like *Schistosoma mansoni* and hookworms like *Necator americanus* and *Ancylostoma duodenale* has also been linked to genetic factors (74–78). What is unclear is when linkage of susceptibility to helminth infection involves more than one genetic locus, whether this is dependent

TABLE 1 | Understanding the role of naturally occurring genetic variation in resistance and outcomes to helminth infections – mice models.

Genetic Susceptible strains	Helminth infection	Type of Helminth Parasite	Protective/Susceptible mechanistic explanation	References
BALB/c	*Litomosoides sigmodontis*	Filarial Parasites	CD4 T lymphocytes; production of IL-4	(18–20, 27)
AKR; B10.BR	*Trichuris muris*	Whipworm	Higher Th1 effector response characterized by increased IFN gamma production	(21–23, 28–31)
CBA; C3H; SLA/J; C57BL/6; C57BL/10	*Heligmosomoides polygyrus*	Hookworm	Decreased Th2 driven effector response characterized by lower IgE responses, lower intestinal mast cell densities, alternatively activated macrophages and a concomitant increase in TNFα and IFN γ response; Increased proportion of CD103+FoxP3+ activated T Regulatory cells in susceptible strains;	(24–26, 32–37)
C57BL/6	*Ascaris suum*	Round worms	Hepatic factor, less intense inflammatory and repair response in the liver? Role of secretory IgA	(38–40)
CBA; BALB/c; C57BL/6;	*Nippostrongylus brasiliensis*	Round worms	Developmental arrest in the lungs or migration deficiency of larva into the intestinal tissue in resistant mice, FVB/N; Immunological mechanism is not clear, possibly a Type 2 dependent immune response that limits tissue associated immune response	(41–43)
BALB/c, DBA/2	*Taenia crassiceps*	Tape worms	T cell dependent mechanism. Role of Regulatory T cells	(44–48)
C57BL/6	*Trichinella spiralis*	Round worms	Mucosal mast cells	(49)
CBA; C57BL/10	*Schistosoma mansoni*	Blood flukes (trematodes)	Increased IL-1β and IL-23 cytokines by DCs and T helper 17 polarization; Proinflammatory T helper 1/ T helper 17 responses persist along with T helper 2; Reduction of the alternative activation marker	(50–54)

on one gene or if genetic variation in other genes could affects resistance to helminth parasite. Perhaps mechanistic insights could be gleaned from mouse models, if these regions are conserved, to understand the relationship and function of those genes. Therefore, such clinical and genetic epidemiology studies may guide the conduct of fundamental and basic immunology experiments.

Host genetics could also indirectly influence other host associated factors which then indirectly influence the immune system. For example, difference in expression of major histocompatibility complex molecules can influence the composition of the gut microbiome (79–82) through differences in antibody responses against commensal bacteria (80). Incidentally, these MHC associated differences in gut microbiome may then influence subsequent susceptibility to helminth infection (79). Hence, genetic factors may alter the host microenvironment to affect subsequent outcomes to helminth infections. However, because these are observational studies in primates, it is challenging to mechanistically isolate the effect of immune mechanisms resulting from different MHC haplotype and effects due to microbiome differences.

GENETIC VARIATION IN PATHOGENESIS OF HELMINTH INFECTION

It is important to distinguish between the role of genetic variation in resistance and pathogenesis to helminth infections. Although resistance and pathogenesis are linked because disease morbidity is often observed in heavily infected individuals, mechanisms that drive disease pathogenesis may be unrelated to mechanisms responsible for parasite resistance. Our understanding of pathogenesis during helminth infections is based primarily on studies with genetically modified mouse models, which provide insights into the pathways, cytokines and other mediators that regulate the disease processes. Also, differences in disease outcomes from infection of inbred strains of mice have provided additional clues in the heterogeneity of immune response and severe pathology.

The cytokine balance during infection is an important determinant of pathogenesis, mediating both resistance and tolerance to infection. Rapidly after infection, pathogen associated molecular patterns are detected by pattern recognition receptors (PRRs) together with release of alarmins like IL-33, IL-25 and TSLP at epithelial barriers (83, 84). This leads to activation of transcription factors, such as STAT6 and GATA3, which subsequently induce the upregulation of sets of genes including receptors, cytokines, chemokines, and genes regulating the production of eicosanoids (85–87). Cytokines, chemokines, and eicosanoids can induce recruitment, accumulation, and differentiation of immune cells with release of additional sets of effectors cytokines that then induce repair, differentiation, and release of effector molecules from the epithelial barrier to help in the clearance of the worms (87–90). Thus, cytokines, chemokines, eicosanoids, and other mediators are key in the initiation as well as in the pathogenesis of anti-helminth immune responses.

Alterations to the balance of the cytokine response because of host genetic variation can affect the inflammatory mediator profile which can determine the pathogenesis of helminth infection. For example, C57BL/6 and CBA mice show different levels of immunopathology during *S. mansoni* infection, when challenged with a similar number of cercariae. This may be due to differences in the switch from a pro-inflammatory T helper 1 (Th1)/T helper 17 (Th17) response to a tissue protective Type 2 response. The CBA mice show higher levels of proinflammatory Th1/Th17 cytokines which does not diminish but instead persists alongside the rising T helper 2 (Th2) responses, while C57BL/6 mice can regulate the Th17 response during the expansion of Th2 cells resulting in milder

pathology (50–52). However, it is notable that a prolonged Th2 response may lead to other forms of pathology such as increased fibrosis in the BALB/c mice (91). Similarly, *S. mansoni* infection in humans can have different outcomes and pathophysiology, ranging from the mild symptoms to severe symptoms such as the development of severe hepatic fibrosis, hepatosplenic disease, ascites, and encephalopathy, irrespective of the intensity of infection (77, 78). In some cases, a genetic explanation has being proposed in individuals with severe pathological outcomes with some evidence of polymorphisms in cytokine and cytokine receptor genes like *IFN-γR1* gene, which encodes the receptor for the Type 1 cytokine, IFN-γ (78, 92), those involving *TGFBR2* which encodes for receptor of regulatory cytokine, TGF-β (78) and *IL-22RA2*, which encode the receptor for IL-22 (93). Other genes such as polymorphisms in *CNN2* gene, which encodes for the connective tissue growth factor (CTGF), a stromal factor, has also been implicated in the pathophysiology of these disease (94, 95).

Resistance to helminth infection in host of different genetic backgrounds may also be associated with roles of different cytokines in regulating the outcome to infection. For example, differences in susceptibility to *T. muris* infection in C57BL/6 mice compared to BALB/c mice might be due to the role of different cytokines with IL-4 playing a predominant role in C57BL/6 mice and IL-13 playing a more predominant role in BALB/c mice (96). In addition, the protective immunity in C57BL/6 mice vaccinated with radiation-attenuated (RA) larvae of *S. mansoni* is associated with Th1 immune response, while on BALB/c background the protection depends on Th2 responses. Here, injection of RA-attenuated larvae produced lower levels of IgG1 antibodies in serum IL-4Rα deficient mice (IL-4Rα$^{-/-}$) on BALB/c background, but the serum from vaccinated wild-type BALB/c mice confers protection to IL-4Rα$^{-/-}$ mice, suggesting the Th2 antibodies is crucial for parasite elimination and resistance in BALB/c mice (97).Genetic differences due to a distinct pattern of cytokines secreted and markers expressed by myeloid cells can also correlate with different helminth infection outcomes. For example, dendritic cells (DCs) from *S. mansoni*-infected high morbidity CBA mice display increased expression of CD209a (C-type lectin receptor – CLRs) which is necessary for the production of IL-1β and IL-23 that drives pathogenic Th17 cells, as opposed to the low morbidity C57BL/6 mice (51, 52, 98). Similarly, C57BL/10 mice develop more severe schistosomiasis, as defined by significant larger granulomas, increased proinflammatory cytokines production by DCs and higher levels of IL-17 compared to C57BL/6 mice. This phenotype is tightly connected to DCs function, because DCs from C57BL/6 mice expressed high levels of Ym1 and RELMα, marker of alternative activation that regulates the tissue repair in responses to *S. mansoni* eggs (53).

Population genetics studies in humans have shown that the number of pathogens in a specific geographic region can have selective pressure on genes related to cytokine production and responsiveness (99–101), regulation of cellular responses (102) as well as transcription factors important for the induction of protective Type 2 immune response during helminth infection (103, 104). This suggest that evolutionary pressure in different geographic location with different parasite profiles can influence polymorphism of genes and regulatory elements that can then affects response to parasites endemic in those regions.

Parasite Factors as Source of Variation to Host Responses During Helminth Infection

In addition to host genetic factors, variation in parasite species and genetics can also be a major contributor to heterogeneity in susceptibility and resistance patterns during helminth infection (105–108). For instance, variation in reproductive output and consequently egg production following helminth infection has been attributed to parasite genetic factors (108). Parasite genetics could also influence the properties of excretory and secretory proteins released from the worms, which could in turn influence host-parasite interactions as well as parasite chronicity patterns (109, 110), the ability of the parasite to evade the host immune system (110) or the pathogenesis of immune response in the host (107, 108, 111–114). For example, differences in lifecycles and egg properties between *S. haematobium* and *S. japonicum* results in varied cellular and humoral immune responses despite belonging to the same helminth parasite genus (108, 111, 112).

Moreover, different stages of the lifecycle are also an important source of heterogeneity in host responses. As seen in *S. mansoni*, there is a clear shift from a Th1 mediated immune response to a Th2 immune response at the onset of egg production (115), while the cercariae and larva induce Th1 dominated immune response (116). The different lifecycle stages also produce different suites of excretory/secretory products that modulate the host response in diverse ways to promote invasion, infection, adhesion and the immunoregulatory process (108, 117, 118). Hence, parasite factors are a critical source of heterogeneity in immune responses during helminth infection.

Furthermore, in mouse models of infection, strain specific differences have also been described. Strains of *T. muris* isolated and maintained in different parts of the world, including the S strain (isolated in Sobreda, Portugal), the E strain (isolated in Edinburgh) and the E-J strain (originally E strain, which has been maintained in Japan since 1969) can induce different immune response following infection of mice. The E and E-J strains of *T. muris* generally induce a Th2 skewed response whereas the S-strain induces a Th1 skewed response characterized by production of IFN-gamma and IL-12 (107, 113, 114). Therefore, heterogeneity in parasite genetics can be a source of variation in immune response and perhaps helminth parasites can adapt their metabolism and alter the immune response to fit into their environment (109, 119). Since most laboratory strains have been maintained and passaged in different laboratories for several years, it is possible that parasites used in most laboratories diverge significantly from wild helminth parasites that are present in their natural environment.

ROLE OF ENVIRONMENT DURING HELMINTH INDUCED TYPE 2 IMMUNE RESPONSE

There are many environmental variables that can affect parasite burden in an endemic population and dissecting the relative

contribution of each variable can be difficult. Most helminth infections are soil transmitted parasites; thus, the host environment is important in determining exposure to and transmission of helminth parasites (2). In addition, the environment also plays a crucial role in determining variation in immune responses, pathogenesis of diseases as well as susceptibility versus resistance patterns during helminth infection. This can be the biotic environment of the individual which can constitutes the commensal microbial communities within the host or the other free living organismal life the host interacts within the environment including vectors and intermediate host for parasites. Other biotic factors including previous microbial experience and infection history of the host are important in influencing susceptibility and resistance to helminth infection (120–122). For example, primary infection activates memory $CD4^+$ T cells and alternatively activated macrophages that mediate resistance against secondary helminth infection (43, 123–125). There are also examples whereby previous helminth infection can make the host more susceptible to secondary helminth infection (126). Indeed, helminth co-infection may influence outcome of other infections and many studies have investigated the influence of previous helminth infections on the pathogenesis of other infectious diseases – including bacterial, protozoan, and viral diseases (120–122, 127–134). This experimental study design stems from the idea that mammals have co-evolved with helminth parasites and they could be part of the natural macrobiota of the host (135, 136). However, pre-existing disease and co-infections may also influence outcomes during helminth infection. For example, prior infection and co-infection of the protozoan parasite *Toxoplasma gondii* with the enteric nematode *H. polygyrus* can limit the host protective Type 2 immune response directed against the helminths making the host more susceptible to the worms (137). This results from the immune landscape in the host being skewed towards a Type 1 response by the protozoan parasite (137). A similar phenomenon has been reported wherein prior infection with protozoan parasites like *T. gondii* and *Plasmodium* parasites and viral pathogens like Human T-lymphotropic virus 1 (HTLV-1), which all induce a Type 1 immune response, can limit the host response during subsequent infection with helminth parasites like *Fasciola hepatica*, *Nippostrongylus brasiliensis* and *Strongyloides stercoralis* (122, 138–141). Hence, prior and co-infections by other pathogens can influence pathogenesis and susceptibility to helminths, thereby potentially contributing to inter-individual variations in immune response during helminth infection. In addition to biotic factors, these could also involve abiotic factors which constitute climatic factors such as the temperature, humidity, rainfall; physical factors such as the soil and mineral composition of the environment; and chemical factors such as the oxygen, nitrogen, and CO_2 levels in the environment. Factors such as this can influence the lifecycle of the parasite outside the host and therefore transmissibility of the helminth parasite. These biotic and abiotic factors can also have major implications on the tone of immune response as well as host susceptibility to helminth parasite infection thereby contributing to inter-individual variation during helminth infection (142).

Several studies have shown that the environmental differences can significantly influence the host immune phenotype and profile (143–146) and consequently susceptibility to subsequent helminth infections (147) (**Figure 1**). The importance of the role of environmental influences on the immune system can be appreciated from twin studies which show that variability in immune responses can be dictated in large part by acquired and not only genetic factors especially with increasing age emphasizing the influence of environmental factors on immune responses (148). Although, similar twin studies experiment in the context of helminth infection have not really been done in humans to understand the role of environment versus genetics during helminth infection. The use of mice models such as the rewilding mice model has helped us appreciate the critical role the host environment can play in outcomes during *T. muris* infection (147, 149). However, there is still a need to understand how the tissue microenvironment (3) and/or host macroenvironment (142, 150) can influence susceptibility patterns and helminth infection outcomes during exposure to various other helminth parasite types (hookworms, roundworms, tapeworms). New environmental mouse models such as "rewildings", "wildlings", "co-housing", "sequential infection models", "co-infection models", "chimeric wild mouse" etc (142, 146, 151–153) provide new opportunities to understand the role of environmental factors in influencing susceptibility to infection and re-infection by helminth parasite.

Rewilding mice involves introducing laboratory mice into an outdoor enclosure. This outdoor enclosure exposes mice to a natural environment including soil, weather, vegetation, microbial population, but protects against predation, and serves as a bridge between laboratory controlled experiments and what happens in a more natural environment (147). The rewilding mice model has already provided critical insights into the role of host macroenviroment on helminth infection outcomes (147, 149). Rewilded mice were more susceptible to the intestinal helminth parasite *T. muris* with higher worm burdens as well as more worm biomass than the laboratory controls (147). Rewilding experiments have also revealed how the environment contributes to the microbial diversity in the gut (149), provided insights into the role of fungal colonization to neutrophil circulation (143) as well as uncovered the role of environment and genetic factors in immune composition and responsiveness (144).

Besides rewilding, other approaches focus on increasing the microbial diversity in the gut environment, including fecal transplants, co-housing, exposure to dirty bedding (formites) and embryo transfer from wild and pet store mice (145, 146, 151, 153, 154). Thereby leading to various model including "wildlings", "chimeric lab-wild models", which have a natural and diverse metaorganisms at all body sites similar to wild and petstore mice (145, 146). These mice may have better translational value than specific pathogen free laboratory mice found in most biomedical centers with immune systems that are a better reflection of the human situation (142, 146, 152, 153).

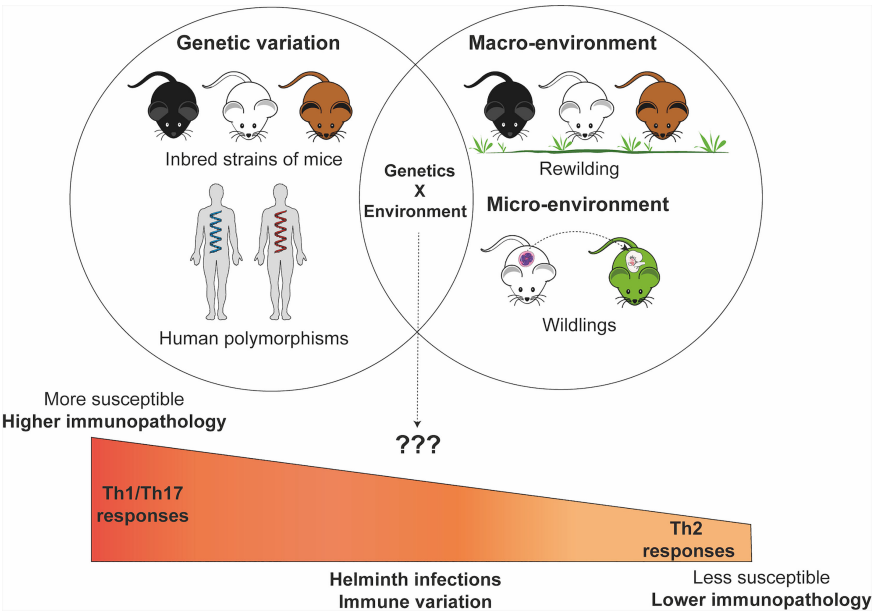

FIGURE 1 | Genetic and environmental factors contribute and interact to influence susceptibility patterns and pathogenesis of immune response during helminth infections. The Figure in this manuscript was created using images from the Servier Medical Art's image collection (smart.servier.com) and licensed under a Creative Commons Attribution 3.0.

These mice mount an immune response that limits exuberant responses which promotes survival following intense inflammatory conditions and are better able to control pathogen exposure compared to their SPF counterparts (145, 151). However in some cases, these mice generate stronger immune responses than their controls, for example, during exposure to house dust mite antigen (155). Other models have focused on sequentially infecting, co-infecting, persistently infecting SPF mice with various known microbial pathogens to expand their microbial experience, immunological landscape and microenvironment so that they better reflect the human experience (129, 156). This delivers a controlled set of pathogens to the mice and eliminates the requirement for special housing facility in order to use these mice to test various hypotheses in biomedical research.

In conclusion, there is considerable interest in developing these new tools (142, 152) to better model the human immune response in mice and to assess the role of environment and its interaction with genetic factors on susceptibility and resistance patterns during helminth infection.

The Microbiome as a Major Environmental Variable

The microbiome contributes immensely to an individual's biotic environment and could be an important environmental variable influencing outcomes to helminth infection. Since these microbial communities are found at epithelial barrier and mucosal surfaces where they can directly interact with helminth parasites, they can shape the tissue micro-environment niches and influence helminth infection outcomes (157–160). For example, the microbiome composition in mice prior to *H. polygyrus* infection or *S. mansoni* infection can influence the worm burden following helminth infection (157, 158). Similarly, oral colonization of mice with commensals such as *Lactobacillus casei*, *Bifidobacterium animalis* prior to helminth infection can alter the outcome of *T. muris* and *Strongyloides venezuelensis* infection in mice (161, 162). Furthermore, treatment of mice with *L. casei*, significantly increase the cecal worm burdens during *T. muris* infection while feeding mice with *B. animalis* significantly reduced *S. venezuelensis* worm burden and egg output (161, 162). There could be direct or indirect effects of these interactions. The effects of the microbiome composition on immune cell populations and epithelial cell function could influence infection outcomes (157, 163, 164). For example, the expression of *Pla2g1b*, an epithelial derived phospholipase A_2, that is also a host-derived anthelminthic factor is dependent on the intestinal microbiota (163). Similarly, the intestinal microbiome composition and abundance is associated with IL-10 signaling in the host (164). Sometimes, it is mechanistically unclear how microbiome changes can influence susceptibility and pathogenesis of disease during helminth infection, although studies have shown that helminth infection can influence the microbiome composition and diversity in the host recently reviewed here (159). A recent study by Moyat et al., 2022 using germ-free, antibiotic-treated, and specific pathogen-free mice clearly demonstrated that the intestinal bacteria composition can have an impact on host resistance to intestinal helminth *H. polygyrus* (165). Depletion of a complex microbiota through long term-treatment with antibiotics or in germ free mice resulted in more susceptibility to worm infection *via* a mechanism that is dependent on intestinal acetylcholine, a neurotransmitter,

necessary for intestinal motility (165). This suggests that the microbiome as a biotic factor, can influence the production of critical signaling molecules necessary for parasite clearance through the "weep and sweep" response. In contrast, *S. mansoni* infection requires a complex microbiome for greater parasite fecundity and pathology during infection (166, 167). Germ-free mice and antibiotic treated mice infected with *S. mansoni* infection resulted in decreased fecal egg counts as well as reduced intestinal pathology and inflammation (166, 167). In summary, the microbiome is a major biotic environmental factor that contributes to inter-individual variation during helminth infection through its effects on the immune and epithelial cell function of the host.

Other studies have suggested that the intestinal bacteria can directly influence parasite establishment, hatchability, and development (168–172). Various *in vitro* and *in vivo* methods demonstrated that the presence of *Escherichia coli*, a common intestinal commensal (173), is important for hatchability of *T. muris* eggs. The role of *E. coli* in parasite establishment is driven by the presence of Type 1 Fimbriae as well as release of microbial byproducts (168, 169). Differences in egg hatching following infection could affect the establishment of the parasite and subsequently the parasite burden, hence the presence or absence of specific commensal bacteria may directly influence parasite burden independently of the host immune response. Experiments with germ free mice or gnotobiotic animals in helminth infection models also demonstrate that the success of parasite infection and fitness is dependent on presence of commensal bacteria (174–178). Therefore, differences in abundance and composition of intestinal bacteria, which could be influenced by use of antibiotics, could contribute to inter-individual variation in parasite burden observed in population studies during helminth infection.

Additionally, the contribution and role of many other components of the microbiome such as fungi, viruses, and archaea (179) in host immune response and parasite development remains poorly understood and whether these components also influence susceptibility and disease pathogenesis during helminth infection needs to be further explored.

INTERPLAY BETWEEN ENVIRONMENT AND HOST GENETICS

While host genetics are important contributors towards response to helminth infections (102). Twin studies suggest that there are both heritable and non-heritable explanations for variation in immune responses (148). However, these two critical factors rarely exist in isolation (142, 180). There are limited studies that assess the additive and interactive effect of environmental and genetic effect on immune responses. As individuals with similar genetic profiles would usually live within the same communities and environment, it is challenging to dissociate one from the other in human studies.

Therefore, mouse models could be helpful in dissociating the complex interactions that exist between genetic and environmental contributors to variation in helminth infection (**Figure 1**). For example, there are indicators that genetic differences in parasite resistance in the laboratory setting may be lost in a natural environment. While *H. polygyrus* infection of BALB/c and C57BL/6 mice in a laboratory setting shows clear differences in resistance to infection, natural infection results in no observable significant differences between these two inbred resistant and susceptible mice (181). Although mechanistically unexplained, a subsequent study suggests that the chronicity of the infection model could explain why the difference was lost between these two different inbred strains of mice (182). In our own studies, differences in susceptibility between wild-type mice and susceptible STAT6$^{-/-}$ knockout mice to *T. muris* infection in the lab setting are no longer observed when these mice are were placed in the re-wilded environment and infected with *T. muris* (147).

Such interactions between genetics and the environment could be complex and mechanistically distinct. As described above, genetic factors such as MHC haplotype may indirectly influence microbial communities within the host (biotic environmental factors) to alter susceptibility to helminth infection (79). How the environmental pressures influences the heritability of helminth resistance genes in the population is also of interest, as shown in a study in sheep whereby significant genotype by environment interactions persists following infection with another helminth parasites (183).

Other host variables such as age, sex, nutritional status could interact with genetics and environmental factors to influence immunity and affect the outcome of helminth infection. A combination of controlled re-wilding experiments (142–144, 147) and perhaps twin studies in helminth endemic populations with detailed questionnaires may provide further insights into the dynamics of interactions of such complex factors.

DISCUSSIONS AND CONCLUSIONS

Environmental exposure and host genetic background are important drivers of inter-individual variation in susceptibility and outcome of helminth parasite infections. Both play a role in driving heterogeneity of responses either as independent variables or through specific interactions that remain poorly understood. Since disease morbidity and parasite burden is observed primarily in small subsets of infected individuals, it is important that necessary resources and research efforts are allocated into studies deciphering how genetic and environmental interactions influences susceptibility to the world's most neglected disease in human and veterinary medicine. This will require bringing together skillsets and technologies from diverse fields including ecology, quantitative genetics, genomics, immunology, biostatistics, and parasitology. Together, such studies can improve our understanding of key translational factors that regulate immune responses during parasitic helminth infection. Findings from a diverse range of inbred and outbred strains of mice in different environments might provide a more accurate reflection of factors important in diverse human and animal population under free living conditions. There are also opportunities for the identification of new pathways and alleles or regulatory elements that regulate responses in other Type 2 immune mediated diseases such as allergic, metabolic and

fibrotic diseases (3, 88). Additionally, there is a need to address the rising incidence of drug resistance seen in the use of anti-helminthics in human and veterinary medicine (184, 185). To further complete this picture, exciting new studies are beginning to show the importance of heterogeneity in helminth parasite genetic factors in the susceptibility and resistance patterns during helminth infection (105–107). The role of parasite genetic diversity in the pathogenesis and outcome of helminth infection, remains a relatively understudied and interesting area to investigate. Parasite genetic heterogeneity could influence the excretory/secretory products produced from these parasites and influence the immunomodulatory properties of these factors. How this might contribute to inter-individual variation to helminth infection is an interesting area to explore.

AUTHORS CONTRIBUTIONS

OO wrote the first draft of the manuscript. CS and P'NL made significant direct and intellectual contribution to the manuscript. CS made the figure. P'NL edited the manuscript. All authors contributed to the article, read, and approved the submitted version.

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