RESEARCH HIGHLIGHT

Intestinal tête-à-tête: helminths blunt immunity against flaviviruses

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Intestinal helminth infections are known to alter host immune responses, but their impact on neurotropic flaviviruses is poorly understood. A recent study in *Cell* by Desai et al. finds that helminth infection promotes a tuft cell immune response, via IL-4, that increases susceptibility to subsequent challenge by the mosquito-transmitted flavivirus, West Nile virus.

Helminth infection continues to affect ~1.5 billion people globally with significant consequences on human health. These infections cause intestinal disease, malnutrition, impaired growth and development, and altered susceptibility to other infections. Interest in the impact of helminth infection on host immunity has steadily grown, as some helminths can skew host immune responses in ways that prevent immune disorders including asthma, allergy, and autoimmune disease.¹ The tropical and subtropical regions where helminth infections are common also experience a large number of mosquito-borne flavivirus infections, and understanding the complex interplay between immune responses to parasitic helminth and viral infections in cases where co-infection occurs may have important implications for treating these diseases.

Helminth infections are characterized by robust T helper 2 (Th2) cell responses and production of the cytokine IL-4, which is important for parasite clearance. While enteric helminths can protect against some infections, including influenza A virus and respiratory syncytial virus,² co-infection with the intestinal murine norovirus results in increased susceptibility due to IL-4-mediated impairment of virus-specific CD8⁺ T cell responses.³ Therefore, the mechanisms through which the immune response to helminths modulates other infections should be evaluated more closely.

Recent work has examined the impact of infection with the helminth *Heligmosomoides polygyrus bakeri* (Hpb) on neurotropic flaviviruses, primarily West Nile virus (WNV).⁴ During acute infection with Hpb, mice were more susceptible to lethal infection with three neurotropic flaviviruses (WNV, Zika virus, and Powassan virus (POWV)) compared with helminth-free mice. With WNV, co-infection also significantly impaired gut function, which was not observed during either single infection, and resulted in increased WNV levels in the intestinal neurons and central nervous system (CNS).⁴ Infection with a more virulent WNV strain (New York, 1999), in the absence of helminth infection, is able to induce similar intestinal dysfunction.⁵ Hpb/WNV co-infected mice exhibited intestinal changes including altered epithelial morphology, proliferation, and cell death, with minimal inflammation. These changes increased gut permeability and bacterial dissemination.⁴ Previously, killing of infected enteric neurons by CD8⁺ T cells was associated with the disruption of gut function,⁵ but during Hpb/

WNV co-infection, the increased systemic spread of bacteria was correlated with attenuated WNV-specific CD8⁺ T cell responses and reduced survival.⁴ Systemic spread of gut bacteria has previously been reported to impair CD8⁺ T cell responses to viral infection through various mechanisms.⁶

The immune mechanisms driving the altered host immune response to Hpb/WNV co-infection provide important direction for strategies to combat these potentially fatal infections. For instance, type 2 immunity induced by Hpb had a detrimental impact on WNV infection. STAT6, a key regulator of type 2 immunity, was essential for the Hpb-mediated enhancement of lethal WNV infection and changes in intestinal pathology, which were correlated with increased dissemination of gut bacteria. Treating co-infected mice with antibiotics reduced bacterial dissemination and restored protective WNV-specific CD8⁺ T cells, further suggesting that bacterial spread from the dysfunctional intestine impairs protective T cell immunity to WNV.

Furthermore, addition of exogenous IL-4 increased susceptibility to WNV and POWV in the absence of Hpb, further establishing that IL-4–STAT6 signaling impairs host immunity to neurotropic flavivirus infection. Similar to co-infection, IL-4 alone disrupted normal gut function, resulting in impaired WNV-specific CD8⁺ T cell responses. Additionally, conditional knockout mice lacking the IL-4 receptor (IL-4Rα) on epithelial cells were protected from intestinal dysfunction and displayed attenuated WNV infection, further highlighting the importance of this signaling axis. IL-4 can also promote severe colitis,⁷ suggesting that IL-4 may induce pathology across infectious and inflammatory diseases.

Critical regulators of intestinal type 2 immunity include tuft cells, which mediate host protection against helminths.⁸ Conversely, tuft cells are detrimental during co-infection with WNV. Tuft cells can be activated by the metabolite succinate, which may be derived from helminths or changes in the microbiota.⁹ Indeed, exogenous succinate rendered mice susceptible to WNV infection without helminth co-infection. Tuft cells produce IL-25, which acts on type 2 innate lymphoid cells (ILC2s) to promote production of type 2 cytokines including IL-4, IL-5, and IL-13. Addition of exogenous IL-25 or IL-4 promoted intestinal pathology and enhanced susceptibility to lethal WNV infection. Together, these findings describe a signaling cascade involving succinate activation of tuft cells to produce IL-25, which signals to ILC2s to produce type 2 cytokines that act via IL-4Rα on intestinal epithelial cells, enhancing WNV infection (Fig. 1). The induced intestinal pathology allows for gut bacterial dissemination, which is correlated with a blunted CD8⁺ T cell response against WNV, which may directly, or through changes in other inflammatory

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Fig. 1 Model of intestinal co-infection by Hpb and WNV. Infection with the helminth Hpb alters the gut immune homeostasis via activation of tuft cells, ILC2s, and epithelial cell IL-4Rα signaling. The type 2 immune response to helminth infection results in impaired immunity to a subsequent infection by enteric flaviviruses, including WNV. This signaling cascade also permits increased WNV replication in enteric neurons and the CNS. Created with BioRender.com.

responses, permit increased viral replication in the intestine and CNS.

Type 2 immunity is important for protection against helminths and promoting tissue repair and humoral immunity. While often beneficial, the activation of type 2 immunity during enteric helminth infection also negatively impacts the host during enteric viral infection. This shared tissue tropism may be an important factor driving this outcome, as enteric helminth infection protects against respiratory viral infections, where the tissue-specific and pathogen-specific immune responses are less likely to impact one another.^{2,3,10} Type 2 immunity likely impairs the type 1 immune responses necessary for control of viral infections, especially when the infected tissues are shared. Whether helminth-induced enhancement of WNV infection continues during chronic helminth infection or whether immune regulatory signaling eventually resolves the impairment of viral immunity remains to be seen. Additionally, whether T cells or ILC2s are the main source of IL-4 that causes damage to the gut will be important to understand, as it may further inform our perception of tissue-specific immune responses. Understanding broadly how the immune circuitry is

interconnected and influenced by infection or therapeutic intervention, while complex, has important implications for treating a wide range of infectious and inflammatory diseases.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests

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