Review Article

Gut Helminth Infection-Induced Immunotolerance and Consequences for Human Papillomavirus Persistence

Eva H. Clark,^{1,2,3*} Robert H. Gilman,⁴ Elizabeth Y. Chiao,^{5,6} and Patti E. Gravitt⁷

¹Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, Texas; ²Department of Medicine, Section of Health Services Research, Center for Innovations in Quality, Effectiveness, and Safety (IQESt), Michael E. DeBakey VA Medical Center, Houston, Texas; ³National School of Tropical Medicine, Baylor College of Medicine, Houston, Texas; ⁴Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; ⁵Department of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, Texas; ⁶Department of General Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; ⁷Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, Maryland

Abstract. Cervical cancer, a malignancy caused by persistent human papillomavirus (HPV) infection, develops in more than 500,000 women annually. More than 90% of deaths from cervical cancer occur in low- and middle-income countries. A common epidemiological feature of countries with high cervical cancer incidence is a high burden of intestinal helminth infection. The ability of intestinal helminths to trigger immunoregulation, resulting in a “tolerogenic” systemic immune environment, provides fertile soil for the persistence of oncogenic viruses such as HPV. Animal models have shown that intestinal helminth infection permits the persistence of some viruses, however, HPV-specific and human studies are lacking. Large, well-organized trials evaluating the consequences of intestinal helminth infection on the human immune system and HPV persistence may lead to improved strategies for HPV prevention in helminth-endemic regions of the world. Additionally, such studies would offer insight into the specific ways that intestinal helminth infection contributes to immunomodulation, which could identify new therapeutic targets for a range of diseases, from inflammatory disorders to cancer. In this review, we discuss the evidence for helminth-induced systemic and local immune dysregulation, discuss possible mechanisms by which chronic intestinal helminth infection may facilitate HPV persistence, and suggest novel helminth-related interventions that could offer a high leverage (if somewhat unconventional) approach to HPV and cervical cancer control in resource-constrained regions.

INTRODUCTION

Cervical cancer, caused by persistent high-risk human papillomavirus (hrHPV) infection, is the fourth most common female malignancy worldwide.¹ Each year more than 500,000 women develop cervical cancer, resulting in more than 300,000 deaths.¹ The global burden of cervical cancer highlights important disparities; for example, nearly 90% of women who die of cervical cancer live in low- and middle-income countries (LMICs). Reduced access to effective screening programs contributes to the disparity in cervical cancer incidence by failing to detect and treat precancers.^{2,3} However, lack of screening (which intervenes in only a minority [less than 10%] of HPV-infected women with high-grade epithelial abnormalities) does not completely explain the higher population prevalence of human papillomavirus (HPV) across the lifespan in LMICs.⁴ The increased prevalence of HPV in LMICs often directly correlates with invasive cervical cancer incidence⁵; therefore, it is possible that there are additional underlying epidemiological constructs unique to LMICs that contribute to those countries' elevated cervical HPV prevalence and cancer rates.

A common epidemiological feature of countries with high cervical cancer incidence is a high burden of intestinal infection with immune modulating helminths. Chronic helminth infection across the lifespan may compromise immune control of cervical HPV infection, increasing the duration of detectable infection and thus population prevalence of HPV across the lifespan. In a direct test of this hypothesis

in the Peruvian Amazon region, women infected with one or more intestinal helminths (e.g., *Ascaris*, *Trichuris*, hookworm) had a 60% higher HPV prevalence, which was not confounded by differences in sexual behaviors or other sociodemographic characteristics. Careful examination of secretions from the uterine cervix provided evidence of local mucosal immune dysregulation in intestinal helminth-infected women, who showed a type 2 helper T cell (Th2)-polarized immune signature.⁶

In this review, we take a broader look at the evidence for systemic immune dysregulation associated with intestinal helminth infections, discuss possible mechanisms by which chronic intestinal helminth infection may facilitate HPV persistence, and suggest novel approaches to HPV and cervical cancer control in resource-constrained regions, which struggle to implement more complex early detection and treatment interventions for cervical cancer.

NATURAL HISTORY OF HPV INFECTION

Human papillomavirus infection represents a heterogeneous state of infection, where an infected individual may harbor one or more of the 100 subtypes of HPV, at least 13 of which are identified as high-risk, causal agents of cervical cancer (hrHPV).^{7,8} The average age of HPV acquisition is 20 years, and approximately 80% of sexually active women will acquire at least one HPV genotype by age 50 years.⁹ Women with more sexual exposure (i.e., a higher number of sexual partners by themselves or their partners) are likely to acquire multiple HPV infections over their sexual lifespan.^{10,11} In short-term follow-up of newly acquired HPV in observational studies, more than 90% of HPV infections become undetectable within 6–18 months of initial infection.^{12,13} Although often referenced as representing viral

* Address correspondence to Eva H. Clark, Houston HSR&D Center for Innovations in Quality, Effectiveness and Safety (IQESt), Baylor College of Medicine, Michael E. DeBakey VA Medical Center, 2450 Holcombe Blvd., Suite 01Y, Houston, TX 77021. E-mail: eva.clark@bcm.edu

clearance, the natural history of accumulating HPV infections over time is often more complex. Human papillomavirus infections of cervical epithelial cells are asymptomatic, do not produce viremia, and are identified solely through nucleic acid testing of exfoliated epithelial cells.¹¹ At any given time, HPV infections may be detectable, active infections (demonstrated via nucleic acid amplification test), or may remain undetectable in exfoliated cells while retained in the basal cervical epithelium.^{14–17}

It is increasingly recognized that much of the detectable HPV prevalence at a population level, particularly in women well past sexual debut, represents the loss of control of latent HPV infections.^{18–21} While transient-reactivated infections appear to pose little immediate risk for progression to invasive disease,²² persistently detectable hrHPV infection for 2 years or more has a significantly higher risk of progression to advanced neoplasia and cancer.^{23,24} Detectable hrHPV likely is in an active phase of oncogene expression, leading to persistent exposure of cervical epithelial cells to oncogenic proteins and thus loss of several key apoptotic functions that would otherwise be triggered in the event of DNA damage. The longer cervical epithelial cells are exposed to oncogene expression, the higher their risk of accumulating other cancer-causing mutations during unchecked replication, leading to selection of a transformed cellular phenotype. This process, in combination with a permissive immune microenvironment, would tip the scales in favor of malignant transformation and progression.

PERSISTENT HPV INFECTION REQUIRES A TOLEROGENIC IMMUNE ENVIRONMENT

The persistent detectable state of HPV infection reflects a chronic loss of immunologic control. Studies showing increased prevalence of HPV infection and associated anogenital disease among immunosuppressed populations, including solid organ transplant recipients^{25,26} and people living with HIV infection,^{27–29} provide evidence emphasizing the importance of cell-mediated immunity in HPV control. Most studies indicate that worse control of HIV disease and greater immunologic deficit are associated with higher HPV prevalence^{27,30} and longer persistence of HPV infection,^{31–33} though others suggest that positive HIV status independent of CD4 count influences risk of HPV infection and dysplasia.^{34,35}

In immunocompetent subjects, an effective type 1 helper T cell (Th1) response is necessary for HPV control—and lack of an effective Th1 response is associated with persistent HPV infection (Figure 1).¹⁵ Although in vitro and in vivo studies of host immunologic control of HPV infection have yielded disparate results,³⁶ available data suggest that certain cytokines (including tumor growth factor- β [TGF- β], tumor necrosis factor- α [TNF- α], interleukin-1 [IL-1], the type I interferons, and interferon- γ [IFN- γ]) may act to inhibit proliferation of HPV-infected cervical epithelial cells.^{37–40} One study of cytokine mRNA patterns in exfoliated cervical cells demonstrated that women who controlled their HPV infections within 4 months had a Th1 profile (specifically, expression of IFN- γ mRNA and absence of IL-4 mRNA) preceding clearance, compared with highly variable patterns in HPV-negative women,⁴¹ though other studies have found no difference in cytokine profiles or T cell subsets of cervical secretion specimens.⁴² Cervical biopsy studies have demonstrated decreased IFN- γ

mRNA expression in women with cervical dysplasia or cancer compared with those with normal cervical tissue,⁴³ as well as evidence for local transition from Th1 cytokine (e.g., IL-2, IL-12, and TNF- α) predominance to Th2 (e.g., IL-4) to regulatory/immunomodulatory (Treg, e.g., TGF- β and IL-10) as normal cervical epithelium progresses to cancer.^{44,45} Studies of stimulated peripheral blood lymphocytes have suggested that such local changes in cytokine polarization are mirrored by the systemic immune environment during HPV infection as cervical dysplastic disease worsens.^{46,47} Although host defense mechanisms are largely effective at controlling initial HPV infection in immunocompetent individuals,¹² exposure to agents that cause a tolerogenic systemic immune environment could plausibly facilitate hrHPV persistence, leading to an increased risk of developing cervical cancer.

CHRONIC GUT HELMINTH INFECTION PROMOTES A TOLEROGENIC SYSTEMIC IMMUNE ENVIRONMENT

Hundreds of thousands of individuals living in LMICs are infected with one or more multicellular, parasitic worms called helminths.⁴⁸ The largest group of clinically relevant helminths are nematodes (roundworms). In this review, we focus on nematodes that reside in the human gut (intestinal helminths). Examples of intestinal helminths include *Enterobius vermicularis* (pinworm), *Trichuris trichiura* (whipworm), *Strongyloides stercoralis* (threadworm), *Ascaris lumbricoides*, and *Necator americanus* and *Ancylostoma duodenale* (hookworms). As intestinal helminths acutely infect their human hosts and migrate to the human gut, intestinal helminths activate first innate lymphocytes and then effector CD4 T cells, which induce Th2 immune responses^{49–51} (Figure 2), characterized by production of cytokines such as IL-4, IL-5, and IL-13.^{52,53} This cascade has many important downstream effects, including enhanced epithelial mucous production, smooth muscle contraction, eosinophilia, immunoglobulin E production, tuft and goblet cell production, and differentiation of alternatively activated macrophages, which help rid the host of the intestinal helminth infection and prevent reinfection.^{54,55} Additionally, activation of Th2 responses downregulates proinflammatory Th1 and Th17 pathways, which are associated with control of viral diseases such as HPV, among other pathogens.

Following the initial induction of strong Th2 immune responses, adult intestinal helminths eventually establish chronic infection in the human gut and must regulate their host's immune system to ensure their long-term survival.⁵⁶ This process includes induction of regulatory T cells (Tregs), which promote systemic immunotolerance. Specifically, persistence of Th2 immune responses leads to expansion of natural and helminth-induced Tregs.^{52,57} Regulatory T cells represent a lineage of helper T cells characterized by expression of transcription factor Foxp3 and secretion of suppressive cytokines like IL-10 and TGF- β . They modulate the immune response by downregulating T cell activity, suppressing innate immune cells, and expressing suppressor molecules such as cytotoxic T lymphocyte antigen-4 (CTLA-4).⁵⁸ Although a large body of literature supports helminth-induced immunomodulation (Table 1), most relevant studies relied on animal models^{57,59–63} or small human trials. Of the published human studies, most evaluated tissue invasive helminths (e.g., filaria [invasive nematodes] and *Schistosoma*

FIGURE 1. Hypothesized role of the adaptive immune system in control of HPV. The cervical basal endothelium is exposed to human papillomavirus (HPV) via microbreaks in the epithelial layer. **(A)** In individuals with normal nonpolarized immune systems, resting T cells (blue circular cells) and antigen-presenting cells (APCs; yellow cells) exist in the lower layers of the epithelium. APCs take up and present HPV antigens to Th1 cells (green circular cells), leading to expansion of HPV-specific Th1 cells that contribute to destruction of infected epithelial cells. **(B)** If an efficient adaptive immune response does not occur (e.g., due to any agent that facilitates a “tolerogenic” immune environment), active HPV infection may establish in the basal epithelial cells. Epithelial cells containing the HPV genome (red cells) migrate toward the epithelial surface. Persistent and/or prolonged high-risk human papillomavirus (hrHPV) infection can lead to cervical dysplasia. Figure created with BioRender.com. IFN- γ = interferon- γ ; IL = interleukin; Th1 = T helper type 1; TNF = tumor necrosis factor.

FIGURE 2. Outline of key interactions between helminths, the bacterial gut microbiota, and the host immune system. These interactions support the hypothesis that immunomodulatory influences of commensal bacteria and helminths can promote a tolerance phenotype.¹⁴³ IL = interleukin; PSA = polysaccharide A; SCFA = short-chain fatty acids; TGF = tumor growth factor; Th1 = type 1 helper T cell; Th2 = type 2 helper T cell; TNF = tumor necrosis factor; Treg = regulatory T cell.

TABLE 1
Published evidence for helminth-induced systemic immunomodulation

Topic	Study type	Helminth studied	Ref(s)
Helminth production of cytokine mimics and antagonists			
• Identification of two TGF- β homologues in <i>Brugia malayi</i>	In vitro	Filaria	49
• Identification of a TGF- β homologue in <i>B. malayi</i> and <i>Brugia pahangi</i>	In vitro	Filaria	77
• Nematode cystatins have multiple, specific capacities for host immunomodulation	In vitro	Filaria	90
• <i>Ascaris suum</i> -derived products induce human neutrophil activation	In vitro	STH	88
• Helminth-derived molecules share cross reactive epitopes with the host IFN- γ	Mouse	<i>Trichuris muris</i>	62
Depletion of regulatory T cells in mouse models results in helminth clearance			
• Regulatory T cells depletion during early infection leads to reduced helminth burden; absence of Tregs does not interfere with the generation of protective memory	Mouse	<i>Strongyloides ratti</i>	59
• Early Treg depletion post infection results in expedited helminth clearance and is associated with reduced Th1-mediated inflammation of the intestine	Mouse	<i>Trichuris muris</i>	60
Helminth infection can increase host regulatory T cell activity			
• <i>Heligmosomoides polygyrus</i> excretory-secretory antigen induced de novo Foxp3 expression but did not promote Th1 or Th2 development	Mouse	<i>Heligmosomoides polygyrus</i>	57
• Helminth infection is associated with polyclonal expansion of Foxp3(+)Helios(+)CD4(+) thymic (t)Tregs in the gut and periphery	Mouse	<i>Heligmosomoides polygyrus</i>	61
• <i>Strongyloides ratti</i> infection induces expansion of Foxp3 + regulatory T cells that interfere with immune response and parasite clearance in BALB/c mice	Mouse	<i>Strongyloides ratti</i>	59
• <i>Schistosoma</i> antigen induces Foxp3 expression in naïve T cells in a TGF- β -dependent manner	Mouse	<i>Schistosoma</i>	85
• Th2 and regulatory T cell populations expand during STH infections	Human	STH	51
Helminth infection can decrease host immune responsiveness			
• Helminth infections are associated with a generalized suppression of cytokine responses to mitogen	Human	STH	87
• Microfilaremia is associated with specific cellular immune unresponsiveness	Human	Filaria	64
• Low numbers of parasite-specific T and B cells may be partially responsible for severely diminished immunoresponsiveness in patients with filariasis	Human	Filaria	65
• Patients with filariasis have fewer IFN- γ -secreting lymphocytes. Neutralizing anti-IL-10 or anti-TGF- β -enhanced lymphocyte proliferation response to filarial antigens	Human	Filaria	66
• Significant proportions of patients with filariasis show antigen-specific lymphocyte unresponsiveness, and lymphocyte proliferation to filarial antigens correlated negatively with specific IgG4 levels	Human	Filaria	67
• High levels of IL-10 production are associated with antigen-specific hyporesponsiveness in human lymphatic filariasis	Human	Filaria	71
• Antigen-specific cellular hyporesponsiveness in a chronic filarial infection is mediated by IL-10 and TGF- β	Human	Filaria	74
• Interleukin-10 downregulates filarial antigen-driven type 1 responses	Human	Filaria	72
• Cellular responses to filaria infection are vigorous early on but are down-regulated as infection becomes chronic partly via IL-10-dependent mechanism	Human	Filaria	73
• Interleukin-10 contributes to parasite antigen-induced T cell hyporesponsiveness in patients with chronic schistosomiasis	Human	<i>Schistosoma</i>	81
• Interleukin-10 modulates in vitro granuloma formation in schistosomiasis patients	Human	<i>Schistosoma</i>	82
• Interleukin-10 has an important immunomodulatory role in patients with chronic asymptomatic schistosomiasis	Human	<i>Schistosoma</i>	83
Chronic helminth infection leads to skewed cytokine profiles (particularly towards IL-10 and TGF- β)			
• T cells from onchocerciasis patients produce large amounts of IL-10	Human	Filaria	78
• Children in STH hyperendemic regions secrete more IL-10 and TGF- β	Human	STH	86
• A large proportion of children with STH infections produce IL-10	Human	STH	87
Helminth antigen-specific responses recover after anti-helminth treatment	Human	Filaria	68

(continued)

TABLE 1
Continued

Topic	Study type	Helminth studied	Ref(s)
<ul style="list-style-type: none"> • T cell proliferative responses to <i>B. malayi</i> antigen and production of IFN-γ by stimulated mononuclear cells increased significantly after DEC treatment • Cellular responses to <i>Schistosoma</i> antigens vary but poor responsiveness is frequent among those with severe disease. Responses improve after treatment. • Chronic infection with <i>Schistosoma haematobium</i> is associated with the reversible downregulation of T cell proliferative responses and IL-4 release 	Human	<i>Schistosoma</i>	79
<ul style="list-style-type: none"> • Regulatory T cells (CD3⁺/CD4⁺/CD25^{high}) decrease after anti-<i>Schistosoma mansoni</i> treatment 	Human	<i>Schistosoma</i>	80
Regulatory T cell levels decrease after anti-helminth treatment	Human	<i>Schistosoma</i>	84
Use of helminth infection as therapy for inflammatory diseases	Human	STH	91
<ul style="list-style-type: none"> • Interleukin-22 + CD4 + T cells are associated with therapeutic <i>Trichuris trichiura</i> infection in an ulcerative colitis patient • Helminth-infected MS patients have fewer exacerbations; IL-10 and TGF-β production and CD25 + CD4 + FoxP3 + T cell levels increase after helminth infection 	Human	STH + *	92

DEC = diethylcarbamazine; IL-1 = interleukin-1; IFN- γ = interferon- γ ; MS = multiple sclerosis; TGF- β = tumor growth factor- β ; Th1 = type 1 helper T-cell; TNF- α = tumor necrosis factor- α ; Treg = regulatory T cells; STH = soil-transmitted helminths (most of which are intestinal nematodes).

* Patients had infections with intestinal parasites including *Hymenolepis nana*, *Trichuris trichiura*, *Ascaris lumbricoides*, *Strongyloides stercoralis*, and *Enterobius vermicularis*.

[flukes]]^{49,64–85}; few have focused on intestinal helminths.^{51,86–88} Studies of antihelminth treatment have shown that deworming decreases CTLA-4 expression on CD4 T cells, alleviating key T cell suppressor activity.^{51,89}

As intestinal helminths reside within the gastrointestinal tract, they can alter the gut microbiome (Figure 2),⁹³ a major regulator of the systemic immune system.⁹⁴ Disruption of the normal bacterial gut flora by helminth infection may represent a second pathway by which helminths indirectly contribute to systemic immunotolerance. Dysbiosis of the gut microbiota is known to contribute to many chronic diseases including cancer.^{95–97} Although there are studies exploring helminth-induced changes to the distribution of gut flora in animals,^{98–102} few have translated this knowledge to robust investigation in humans,^{103–106} and results of these studies have been disparate. Most existing studies of how the helminth-infected gut microbiome affects host immunity have been conducted in animal models.¹⁰⁷ Several in vivo studies support the idea that intestinal helminth and bacteria species may interact to promote systemic immunomodulation, allowing for symbiotic persistence in the gut. Rodent helminths are known to secrete molecules that mimic cytokines like TGF- β ¹⁰⁸ and exploit the host's own regulatory mechanisms to induce Foxp3 + Treg cells,⁵⁷ as do various intestinal bacteria including *Bifidobacterium infantis*,¹⁰⁹ *Bacteroides fragilis*,¹¹⁰ *Clostridium* spp.,^{111–113} and *Lactobacillus* spp.^{114,115} In one study, mice lacking microbiota-inducible Tregs had greater resistance to infection with murine helminth *Heligmosomoides polygyrus*, implying that Treg induction by the microbiota promotes *H. polygyrus* persistence.¹¹⁶ Other studies provide further evidence for shared immune dysregulation between Treg-promoting helminths and gut microbiota by showing that *H. polygyrus* increased *Lactobacillus taiwanensis* abundance in the murine gut and the administration of *L. taiwanensis* increased *H. polygyrus* burdens.^{117–119} Other coinfection experiments demonstrate that helminth-induced T cell responses can inhibit the growth of certain bacterial pathogens.^{120–122}

CHRONIC INTESTINAL HELMINTH-INDUCED SYSTEMIC IMMUNOMODULATION MAY ALLOW FOR VIRAL PERSISTENCE

Because intestinal helminths affect billions of people living in LMICs, intestinal helminth-induced immunomodulation has a significant potential impact on coinfections (including oncogenic viruses like HPV, hepatitis B virus, and Kaposi sarcoma herpes virus [KSHV]). Most published data evaluating the effect of helminth infection on concomitant and/or persistent viral infection are from animal research. Studies of mice chronically infected with murine gammaherpesvirus-68 (MHV68, which is closely related to KSHV) demonstrate that coinfection with *H. polygyrus* (an intestinal helminth) and *Schistosoma mansoni* (a tissue invasive helminth) triggers reactivation of latent MHV68. In these studies, the Th2 cytokine IL-4 was sufficient to promote viral reactivation and prevent the development of Th1-dependent antiviral immune responses.¹²³ Similarly, studies of mice infected with *Trichinella spiralis* (a tissue invasive helminth) have demonstrated elevated levels of murine norovirus (MNV) replication and decreased MNV-specific T cell responses in coinfecting mice.¹²⁴ Another murine study showed that *Ascaris suum* (an intestinal helminth) and Vaccinia virus coinfection may downmodulate the Vaccinia-specific immune response, allowing for increased virus-associated pathology.¹²⁵ Collectively, these animal model studies suggest that helminth infection impairs the development of protective, anti-viral immune responses, increasing persistence and/or pathogenicity of virus coinfections.^{126,127}

In humans, intestinal helminth-virus coinfection has primarily been studied in people living with HIV infection. These studies suggest that the CD4 T cells of helminth-infected individuals are more susceptible to HIV infection because of helminth-induced chronic immune activation¹²⁸ and because the chemokine coreceptors necessary for HIV infection of CD4 T cells are upregulated in helminth-infected individuals.^{129,130} Additionally, antiviral Th1 responses are suppressed due to helminth-associated Th2 lymphocyte propagation,¹³¹ and

intestinal helminth–HIV coinfecting individuals have higher levels of eosinophilia, increased immunoglobulin (Ig) E levels, and increased levels of additional immunosuppressive cytokines.^{132,133} Several small studies indicate that treating helminth infections in adults with HIV may have small, short-term favorable effects on markers of HIV disease progression, but larger, more robust studies are needed to confirm these findings.^{134,135} Importantly, studying the impact of helminth infection in the setting of HIV coinfection is difficult due to the overwhelming immune suppression that is caused by uncontrolled HIV, which may mask or overpower any effect helminths have on the human immune system.

Even fewer human studies have explored the relationship between helminth infection and oncogenic virus infection. In one such study, *S. mansoni* infection was correlated with increased seroprevalence of KHSV in Ugandan fishing communities.¹³⁶ Given that seroconversion and antibody titer boosting are expected in the presence of viral reactivation, these human data are consistent with the findings from murine studies that suggested helminth-induced MHV68 reactivation.¹²³ A study evaluating hrHPV and parasite coinfection in humans found higher hrHPV prevalence in Peruvian women with intestinal helminth infections than in uninfected or intestinal protozoa-only infected women.⁶ Furthermore, in this study, the Th2 cytokine IL-4 was strongly correlated with multiple cytokines and chemokines involved in the initiation and effector function of Th2 responses (e.g., IL-25, IL-21, IL-5, IL-10, IL-8, and IL-31) in the cervical fluid of intestinal helminth-infected women compared with uninfected women. This cytokine profile pattern suggests induction of a local, Th2-polarized immune response at the cervical mucosa in women with intestinal helminth infections, which provides biologically plausible evidence for intestinal helminth-induced suppression of antiviral (i.e., Th1) responses at the site of hrHPV infection, allowing for persistent replication of hrHPV in cervical epithelial cells.

PUTTING IT ALL TOGETHER: INTESTINAL HELMINTH-INDUCED IMMUNE MECHANISMS COULD FACILITATE HRHPV PERSISTENCE AND EVENTUAL PROGRESSION TO CERVICAL CANCER

Though precisely how chronic intestinal helminth infection may influence hrHPV coinfection persistence and progression to cervical cancer remains unknown, we can speculate as to potential mechanisms based on the studies outlined above. Chronic intestinal helminth infection promotes both a tolerogenic systemic immune environment and a Th2 polarized local cervical immune environment. The resultant non-Th1-polarized local immune environment—whether skewed towards Th2 or Treg activity—provides fertile ground for a virus like hrHPV to proliferate and infect cervical epithelial cells (Figure 1). By downregulating local Th1 pathways, intestinal helminth infection may allow for reactivation of latent hrHPV and promotion of hrHPV replication, as has been shown for MHV68.¹²³ As hrHPV infection takes hold, the viral genome produces oncoproteins that can downregulate proinflammatory host immune mechanisms and prevent apoptosis of infected cervical epithelial cells.^{137–139} Intestinal helminth–hrHPV coinfection may facilitate perpetuation of an increasingly Treg-polarized local immune environment. Thus, this transition of the cervical

immune milieu from Th1 cytokine predominance to Th2 cytokine predominance to tolerogenic cytokine predominance during coinfection allows for continued proliferation of hrHPV-infected epithelial cells, longer duration of expression of viral oncoproteins, and subsequent development of invasive cervical cancer.^{44,45}

APPLICATIONS OF IMPROVED UNDERSTANDING OF THE INTESTINAL HELMINTH–HPV RELATIONSHIP

New studies are needed to expand the understanding of gut parasite–microbiota–immune system interactions. Specific areas of research that should be targeted include:

1. How the presence of helminths in the human gut directly and indirectly influences both the systemic and local (i.e., cervical) immune environment (with particular focus on immunologic mechanisms distinguishing between homeostatic and pathogenic helminth–host interactions).
2. The immunologic relationship between intestinal helminths and gut microbiota and how differential proportions of microbiota genera (and introduction of new microbiota in the form of pre- and/or probiotics) influence helminth-related immunomodulation.
3. The long-term impact of regular treatment with medications commonly used for deworming (e.g., albendazole, mebendazole, ivermectin, and praziquantel) on the systemic immune system and the prevalence of chronic diseases and infections exacerbated by intestinal helminth infection.

A more specific understanding of parasite–microbiota–immune system interactions would facilitate the development of scenario analyses to evaluate the broader impact of helminth treatment across multiple disease outcomes, balancing infection control (e.g., deworming could alter host susceptibility to other bacterial and/or parasitic infections and make vaccines more effective in helminth-endemic regions¹⁴⁰) and autoimmunity. Longitudinal pre- and posthelminth treatment studies could answer many of these questions. At the individual level, such studies would provide more robust immunologic data and require smaller numbers of participants than larger ecological studies. These studies could then be followed by community-based trials to examine the effects of deworming at the population level.

From a public health perspective, if deworming through mass drug administration and water, sanitation, and hygiene (WASH) interventions lowers HPV persistence through elimination of concomitant immune dysfunction, cancer risk in affected women could be significantly reduced using widely available, low-cost interventions. If decreasing helminth burden reduces HPV prevalence by shortening the duration of active, detectable infection, fewer women will test positive in HPV screening, increasing the feasibility of implementation and reducing costs associated with early detection and treatment programs. Bundling HPV and parasite control in community interventions may thus represent a systems-level health intervention with outcomes greater than the sum of its parts. Further, such large-scale deworming strategies—and, potentially, correction of intestinal dysbiosis (e.g., providing pre- or probiotics)—could revolutionize the treatment of gut helminth infections. Currently, most mass deworming programs target

school-age children, not reproductive-age adult women. Although school-based programs are less expensive, modeling studies suggest that community-based deworming would be more cost-effective, even when modeling health benefits only among children.¹⁴¹ By demonstrating substantial health benefits to a wider population of adults, such programs could further promote broader policies supporting community-based, mass deworming of reproductive-age women.¹⁴²

CONCLUSION

The ability of intestinal helminths to trigger immunoregulation, resulting in a “tolerogenic” systemic immune environment, provides fertile soil for the persistence of oncogenic viruses such as HPV. Animal models have shown that intestinal helminth infection permits the persistence of some viruses; however, HPV-specific and human studies are lacking. Large, well-organized trials evaluating the consequences of intestinal helminth infection on the human immune system and HPV persistence may lead to improved strategies for HPV prevention in helminth-endemic regions of the world. Additionally, such studies would offer insight into the specific ways that intestinal helminth infection contributes to immunomodulation, which could identify new therapeutic targets for a range of diseases, from inflammatory disorders to cancer.

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Authors' addresses: Eva H. Clark, Department of Medicine, Section of Infectious Diseases, Baylor College of Medicine, Houston, TX, Department of Medicine, Section of Health Services Research, Center for Innovations in Quality, Effectiveness, and Safety (IQUES), Michael E. DeBakey VA Medical Center, Houston, TX, and National School of Tropical Medicine, Baylor College of Medicine, Houston, TX, E-mail: eva.clark@bcm.edu. Robert H. Gilman, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, E-mail: gilmanbob@gmail.com. Elizabeth Y. Chiao, Department of Epidemiology, University of Texas MD Anderson Cancer Center, Houston, TX, and Department of General Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, E-mail: eychiao@mdanderson.org. Patti E. Gravitt, Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, E-mail: pgravitt@som.umaryland.edu.

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