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GEOHELMINTH INFECTIONS MAY HAVE DELETERIOUS EFFECTS ON IMMUNITY TO ORAL VACCINES

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SUMMARY

There is compelling evidence that immune responses to mucosal vaccines are impaired in non-affluent populations living in the Tropics and enteric co-infections such as geohelminths may contribute to this effect. Geohelminths have been associated with impaired immune responses to the live attenuated oral cholera vaccine CVD 103-HgR and treatment for geohelminths prior to vaccination partially reversed the impaired immune responses. Other factors such as host nutrition and the presence of environmental enteropathy with which geohelminth infections are associated are likely to contribute also to this tropical barrier to mucosal immunization. There is a need for research on the mechanisms by which geohelminths may suppress immunity to mucosal vaccines and such research could contribute to the development of more effective mucosal vaccines.

INTRODUCTION

The geohelminth (also known as intestinal or soil-transmitted helminth infections) parasites, *Ascaris lumbricoides*, *Trichuris trichiura*, hookworm, and *Stronglyoides stercoralis*, are common infectious diseases of childhood in tropical regions, particularly among populations living in poverty with poor access to sanitation and clean water. In endemic areas, geohelminth infections are chronic infections and individuals generally become infected during the second year of life and remain infected into adulthood through repeated infectious exposures. An estimated 2 billion humans are infected with geohelminths worldwide (*Savioli* et al., 2005). Infections are considered to cause significant morbidity particularly among pre-school and school-age children in whom infections are associated with adverse effects on nutrition, growth, and cognition (*Bethony* et al., 2006). The level of morbidity caused by geohelminth infections is strongly associated with parasite burden (*Anderson* and *May,* 1985) that is greatest among children.

Geohelminth infections induce an immune responses in humans characterized by elevated IgE and eosinophilia and the production of Th2 cytokines by peripheral blood leukocytes (PBLs) when stimulated with parasite antigen *in vitro* (*Cooper* et al., 2000a; *Cooper* et al., 2008). Chronic infections are associated with a tightly regulated inflammatory response in which anti-

parasite allergic reactions appear to be suppressed (*Maizels* and *Yazdanbakhsh*, 2003; *Cooper*, 2009a). Such a response reflects a stated of balanced parasitism allowing the parasite to survive but protecting the host from potentially damaging immunopathology.

There is evidence that the regulation of host immunity by chronic geohelminth infections may affect responses not just to parasite antigens but also other exogenous antigens such as the antigenic constituents of vaccines (*Malhotra* et al., 1999; *Cooper* et al., 2001; *Elias* et al., 2001). Because many mucosal vaccines are poorly immunogenic among poor populations living in the Tropics, an observation that has been referred to as a mucosal barrier to vaccination in such populations (*Czerkinsky* and *Holmgren*, 2009), there is growing awareness of how enteric parasites such as geohelminths may contribute to such an effect through their effects on the intestinal mucosa and mucosal immunity (*Czerkinsky* and *Holmgren*, 2009; *Cooper*, 2009b).

STUDIES OF EFFECTS OF GEOHELMINTH INFECTIONS ON MUCOSAL IMMUNITY IN CHILDREN

Geohelminth parasites have intimate contact with the mucosal immune system being separated from the intestinal tissues by a single layer of epithelium. Although there are extensive data available from experimental animals of the mucosal immune response to intestinal helminth infections, such data from human populations are limited. This is because of difficulties in accessing mucosal tissues in humans although useful data can be obtained by collection of mucosal secretions (e.g. faeces and saliva) and peripheral blood for sampling of B and T cells that traffic between mucosal sites after mucosal vaccination (*Lewis* et al., 1991; *Castello-Branco* et al., 1994; *Wasserman* et al., 1994). Developments such as wireless endoscopy will allow the easier sampling of intestinal mucosa in future studies although such technology is rarely available to researchers working in populations where geohelminth infections are present.

CHANGES IN THE INTESTINAL MUCOSA ASSOCIATED WITH GEOHELMINTH INFECTIONS

The expulsion of intestinal helminth parasites in animal models has been associated with marked changes in the intestinal mucosa characterized by villous atrophy, crypt hypertrophy, and increases in mucous-secreting goblet cells (*Finkelman* et al., 1997; *Anthony* et al., 2007). The intestinal epithelium proliferates so that parasites that live partly or completely in the epithelium (e.g. *Trichinella spiralis* and *Trichuris* spp.) are shed into the gut - the so-called epithelial escalator (*Artis* and *Grencis*, 2008). Such alterations make the intestinal lumen a hostile environment and reduce the surface area for parasite attachment. Both parasite expulsion and intestinal enteropathy are considered to be Th2-dependent processes (*Garside* et al., 2000; *Anthony* et al., 2007).

There are limited data from humans on the histological changes in the intestine associated with geohelminth

infections. Geohelminth parasites that dwell in the small intestine, *A. lumbricoides*, hookworm, and *S. stercoralis*, have been associated with enteropathy although generally the mucosa appears histologically normal (*Arean* and *Crandall*, 1971; *Burman* et al., 1970; *O'Brien*, 1975; *Garcia* et al., 1977) in individuals living in endemic areas. A minority with chronic infections show changes of partial villous atrophy, crypt hyperplasia and increased inflammatory infiltrate in the lamina propria (*Burman* et al., 1970). Humans infected experimentally with hookworm larvae develop eosinophilic enteritis (*Croese* et al., 2006), although this inflammation tends to largely resolve after repeated infections (*Croese* and *Speare*, 2006). *T. trichiura* that inhabits the large intestine has been more extensively studied because of the ease of sampling particularly of the rectal mucosa. Such infections may occasionally cause a dysentery-like syndrome (*Trichuris* dysentery syndrome [TDS]) (*Cooper* et al., 1991) associated with an increase in inflammatory cells in the lamina propria (*MacDonald* et al., 1991), and an increase in numbers and state of activation of mucosal mast cells (*Cooper* et al., 1991; *MacDonald* et al., 1994). The histological picture observed is likely to be determined by chronicity of infection, intensity of infections, and host genetic factors. Chronic infections may be associated with minimal inflammatory response in the mucosa and mild histologic alterations (e.g. partial villus atrophy) reflecting active immune regulation by host and or parasite. Chronic infections in a few individuals may be associated with severe inflammation (e.g. TDS) but most children are likely to be asymptomatic. Chronic infections down-regulate inflammatory responses in the intestinal mucosa to avoid the long-term consequences of an inflamed intestinal mucosa on host nutrition. During initial infections, benefit to the host may be obtained by mounting strong inflammatory responses to expel parasites. The findings of partial villus atrophy and crypt hypertrophy in the small intestine (*Keusch* et al., 1972; *Gracey*, 1979; *Fagundes-Neto* et al., 1984; *Haghighi* and *Wolf*, 1997; *Veitch* et al., 2001) and a non-specific inflammatory infiltrate in the small and large intestine (*Mathan* and *Mathan,* 1985) has been referred to as tropical or environmental enteropathy/colonopathy. Tropical enteropathy is a common histologic finding in apparently healthy individuals living in the Tropics (*Humphrey*, 2009) and may reflect a T-cell mediated inflammatory process (*Veitch* et al., 2001) to intestinal microbiota and pathogens such as geohelminths.

EFFECTS OF GEOHELMINTHS ON MUCOSAL VACCINATION

Current mucosal vaccines are designed to stimulate immune cells in the intestinal tract to induce both mucosal and systemic immunity. The most widely used are trivalent oral poliovirus (OPV) and oral rotavirus vaccines, both of which are live attenuated vaccines. There are several new oral vaccines under development, some of which may become available for widespread use during the next decade.

Several oral vaccines have been shown to be less immunogenic in populations in non-affluent compared to affluent regions including trivalent oral poliovirus vaccine, rotavirus vaccines (Rotashield, Rotarix, and RIT 4237 bovine vaccines), oral cholera

Table 1: Barriers to effective vaccination with oral vaccines in non-affluent populations living in the Tropics. Other factors include high cost and logistic considerations such as cold-chain and vaccine distribution and delivery systems.

- Nutritional deficiencies
  - Vitamin A
  - Zinc
- Tropical/environmental enteropathy
- Chronic diarrhoea
- Co-infections
  - Enteric bacterial infections
  - Intestinal protozoa (e.g. *Giardia intestinalis*)
  - Intestinal helminths
    - *Ascaris lumbricoides*
    - Hookworm
    - *Strongyloides stercoralis*
    - *Trichuris trichiura*
- Microbiota
- Previous exposures to natural infections (e.g. intestinal sIgA)
- Maternal antibodies in breast milk

vaccine (CVD-103HgR), and *Shigella flexneri* 2a SC602 vaccine (*Czerkinsky* and *Holmgren*, 2009). Effective vaccine immunity with such vaccines in non-affluent populations has required an increase in the dose or number of doses administered to achieve adequate vaccine immunity (*Patriarca* et al., 1991, *Perez-Schael* et al., 1997).

Geohelminth infections may have deleterious effects on immunity to oral vaccines. Children infected with geohelminths had reduced vibriocidal antibody levels (*Cooper* et al., 2000b) and IL-2 responses to cholera toxin B–subunit (*Cooper* et al., 2001) following vaccination with a single dose of live attenuated oral cholera vaccine (CVD 103-HgR), and these deficits were reversed partially by anthelmintic treatment before vaccination. Similarly, *Heligmosoisdes polygyrus* a natural and chronic infection of the mouse small intestine, was associated with impaired IFN-γ production to OVA following vaccination with a novel OVA-expressing Salmonella vaccine (*Urban* et al., 2007).

However, geohelminth infections alone are unlikely to explain impaired immunity to oral vaccines. A study investigating the impact of *A. lumbricoides* infection on responses to oral BCG Moreau, failed to demonstrate post-vaccination increases in the frequencies of tuberculin-stimulated PBMCs expressing IFN-γ among children with either active infections or those who had received either short or long courses of anthelmintics before vaccination (*Cooper* et al., unpublished data). The same vaccine showed strong boosting of post-vaccination IFN-γ responses in healthy UK adults (*Cosgrove* et al., 2006). These data indicate the presence of a mucosal barrier to

oral vaccination among children living in the rural Tropics that is present in the absence of geohelminth infections. Factors that may contribute to poor vaccine immune responses in populations living in non-affluent regions are listed in Table 1.

An important issue for evaluating the potential effects of enteric infections such as geohelminths on immune responses to oral vaccines is the age of acquisition of infection. Geohelminth infections, in most endemic settings, are acquired towards the end of the first year of life, and are unlikely to affect immune responses to vaccines given during the first 6 months of life (e.g. oral poliovirus and rotavirus vaccines). Geohelminth infections may have significant effects on oral vaccines given to children of pre-school or school age. However, there is evidence that maternal infections with geohelminths may modify the infant immune response (*Malhotra* et al., 1999; *Pit* et al., 2000; *Elliott* et al., 2005; *Guadalupe* et al., 2009) and such effects have been associated with impaired immunity to parenteral vaccines given during the first 6 months of life such as BCG (*Malhotra* et al., 1999), *Haemophilus influenzae* type B (*Labeaud* et al., 2009), and tetanus toxoid (*Cooper* et al., unpublished data). The extent to which effects of maternal geohelminth infections could contribute to impaired mucosal immune responses in infants is not known but is being investigated in birth cohorts being conducted in populations endemic for these parasites.

MECHANISMS OF MODULATION OF MUCOSAL IMMUNE RESPONSES BY GEOHELMINTHS

The limited inflammatory response observed in the intestinal mucosal in the presence of chronic geohelminth infections is likely to reflect potent immune regulation. The mechanisms by which such infections modulate mucosal immunity are not well understood. Findings from experimental murine models show that intestinal helminth infections suppress dendritic cell-responses to TLR ligands (*Balic* et al., 2004; *Segura* et al., 2007) and the production of IL-12 (*Balic* et al., 2004; *Cervi* et al., 2004), and induce the development of alternatively activated macrophages (*Kreider* et al., 2007) and IL-10-producing immune cells. Several studies have pointed to a central role for IL-10 in suppressing systemic inflammation associated with human helminth infections (*Fallon* and *Mangan*, 2007). Peripheral blood leukocytes from infected individuals produce elevated levels spontaneously of IL-10 (*Turner* et al., 2008; *Figueiredo* et al., 2010) and TGF-β (*Turner* et al., 2008). CTLA-4 is more highly expressed during chronic helminth infections (*Steel* and *Nutman*, 2003). Co-culture of peripheral blood leukocytes (PBLs) with hookworm antigen impaired PBL proliferation and cytokine production (*Geiger* et al., 2007) while dendritic cells show lower expression of CD86, CD1a, HLA-ABC, and HLA-DR and have a reduced capacity to promote cell proliferation (*Fujiwara* et al., 2009). Similarly, the co-culture of PBLs with parasite antigen has been shown to increased the expression of regulatory (e.g. CTLA-4, TGF-β, PD-1, and ICOS) and anergy-associated markers (e.g. cbl, Itch, and Nedd4), an effect that can be reversed at least partially by neutralization of CTLA-4 and TGF-β (*Babu* et al., 2006).

The modulation of intestinal mucosal immune responses by geo-

helminths may not only have adverse effects on immune responses to oral vaccines, but may increase susceptibility to infection with pathogenic bacteria (*Mansfield* et al., 2003; *Chen* et al., 2005). A study of severe cholera infection provided evidence that patients with concurrent intestinal helminth infections including *A. lumbricoides* had attenuated IgA responses to CTB in faeces and serum (*Harris* et al., 2009), although it is unclear if such effects were associated with an increased risk of severe illness. The potent regulatory effects of geohelminths on mucosal inflammation have been used therapeutically to treat inflammatory bowel diseases (*Summers* et al., 2005a,b; *Croese* et al., 2006) - although the efficacy of such treatment remains controversial it may be useful in specific sub-groups of patients (*Reddy* and *Fried*, 2009; *Cooper*, 2009b).

CONCLUSION

Chronic geohelminth infections have potent regulatory effects on intestinal immune responses and may contribute to the impaired immunogenicity of oral vaccines observed in non-affluent populations. The mechanisms by which geohelminth infections may suppress mucosal immune responses to vaccines are poorly understood. Under some circumstances, treatment with anthelmintic drugs before vaccination may improve such responses. The efficacy of new mucosal vaccines in infants from non-affluent populations will require detailed evaluation in geohelminth-endemic settings before widespread distribution. An understanding of the mechanisms by which geohelminths and other enteric infections may suppress mucosal vaccine responses could lead to the development of new interventions designed to enhance the effectiveness of mucosal immunization in non-affluent populations.

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