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Medicine in focus

Geohelminth infections: Impact on allergic diseases

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Abstract

Geohelminth infections are highly prevalent infections with a worldwide distribution. Epidemiological studies have shown an inverse relationship between geohelminth infection and allergy leading to the suggestion that geohelminths protect against allergy. A causal association is supported by the findings of intervention studies in humans and experimental animal models. Geohelminths cause chronic infections during which an intimate host–parasite interaction develops permitting the parasite to survive but protecting the host from damaging inflammation. Geohelminth parasites modulate allergic inflammation directed against parasite antigens and the same mechanisms may affect responses to inhalant aeroallergens. The mechanisms proposed to explain the allergy-modulatory effect of geohelminths include the induction of regulatory T cells and the creation of an immunosuppressive environment in relevant tissues. New treatments being considered for the treatment of asthma include live infections with hookworms. Insights provided by how geohelminths modulate inflammatory responses may allow the development of new treatments that mimic these effects.

1. Introduction

1.1. Geohelminth infections and allergy

Geohelminth (or intestinal helminth) infections are important enteric pathogens that affect poor populations with limited access to clean water and sanitation. The most prevalent geohelminth parasites are *Ascaris lumbricoides*, *Trichuris trichiura*, hookworm, and *Strongyloides stercoralis* that between them are estimated to infect over two billion humans (Savioli & Albonico, 2004). Geohelminths tend to cause chronic infections in populations that live in endemic regions and these infections cause significant morbidity through effects on nutrition, growth, and physical fitness.

In contrast to geohelminth infections, allergic diseases (including asthma, rhinoconjunctivitis, eczema, and food allergy) are relatively rare in less-developed areas of the world but are recognized as the most common chronic diseases in industrialized countries where they may affect up to 40% of the population. There is strong evidence that the prevalence of allergic disease has increased dramatically over the past 30 years in industrialized countries and allergic disease also appears to be becoming an important cause of morbidity in urban populations living in non-industrialized countries. The inverse relationship between the prevalence of allergic disease and geohelminths has led to suggestions of a causal association in which geohelminth infections have been hypothesized to provide protection against the development of allergic disease.

Epidemiological studies that have examined the relationship between geohelminths and allergy are inconclusive and have provided stronger evidence for an inverse

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association between geohelminths and asthma or atopy than for other types of allergy (Cooper, 2004). The strongest evidence for a causal association between geohelminth infections and allergy has been provided by small intervention studies that have shown increases in the prevalence or risk of atopy after treatment of infected children (Lynch et al., 1993; van den Bigelaar et al., 2004).

Allergic diseases have multifactorial aetiologies and develop from complex interactions between genes and environment. The role of individual environmental factors in determining the development of allergy is likely to be limited and geohelminth infections may be one of several chronic infectious exposures that can interact with host genotype and other environmental factors to influence allergy development.

The human immune system has evolved in the presence of intense exposure to geohelminth and other helminth infections, and the allergic response may have evolved as a host protective mechanism against these parasites. For example, there is evidence that an important asthma-associated gene, a variant of STAT6, is associated with resistance to ascariasis (Peisong et al., 2004).

Successful parasitism has required an adjustment between host and parasite, permitting the parasite to survive but protecting the host from immune pathology. The relative absence of helminths and other chronic infectious exposures capable of inducing strong immunoregulatory signals in modern industrialized societies may have contributed to the development of dysregulated immunity to exogenous antigens such as aeroallergens that can cause inflammatory disease.

2. Pathogenesis

2.1. Modulation of immune response by geohelminth infections

A key feature of geohelminth infections is the ability to cause chronic infections. This is essential for geohelminth survival because the parasites, with few exceptions, are unable to replicate within the human host, and must contaminate extensively and continuously the host's environment to ensure survival to the next generation of fertile adult worms in the human intestine.

The requirement for causing long-lasting infections may have led to the ability of the parasite to induce immunoregulatory mechanisms in the host that prevent or limit parasite killing and expulsion. These mechanisms cause a 'tolerization' of the host to parasite antigens such that continuing infections do not elicit a strong host effector response against the parasite.

Geohelminth infections are potent inducers of type-2 immune responses and the drive to Th2 polarization is so potent in many helminth infections that bystander proteins become targets for Th2 cell responses including the induction of a Th2-cell phenotype in naïve T cells that express receptors for unrelated antigens (Liu et al., 2002).

Because helminths are such potent adjuvants for type-2 immunity, then why don't these infections exacerbate rather than ameliorate allergic responsiveness? In fact they can, and a classic example is Loeffler's syndrome, which is an asthma-like illness associated with acute exposures to ascariasis. However, with repeated infections, the host may down-regulate allergic inflammatory responses and a chronic infection phenotype develops (Fig. 1). There are tight controls on immune pathology during chronic infections, even in an environment that is strongly Th2-polarized, and the immune regulatory mechanisms induced may suppress allergic inflammation to non-parasite allergens such as aeroallergens.

2.2. Mechanisms of helminth-induced suppression of allergy

There are two distinct phases in the allergic response that could be modulated by concurrent geohelminth infection: sensitization and effector stages. The sensitization phase is characterized by the induction of Th2 responses (i.e., production of specific IgE) while the effector stage includes reactions that follow the early expansion of type-2 responses such as degranulation of IgE-primed mast cells (M), the release of pro-inflammatory mediators, and the local recruitment of effector cells of the innate and adaptive immune response. The effector phase is responsible for the expression of allergic inflammation and allergic disease.

Studies of experimental animal models of asthma using ovalbumin (OVA) or house dust mite as the allergen stimulus, have provided evidence for a suppressive effect of geohelminth infections against allergic inflammation in the lungs (Wohlleben et al., 2004). For example, infecting mice with *S. stercoralis* before OVA sensitisation results in a suppression of chemokine mediator levels in bronchoalveolar lavage fluid, and chronic *Heligmosoides polygyrus* infections reduce airway allergic responses to OVA and house dust mite (Maizels et al., 2004). In these models, both the sensitization (IgE production) and effector phases appear to be affected by concurrent helminth infection.

In the case of humans, there is little evidence to suggest that sensitization is suppressed by geohelminth