Suppression of Allergic Asthma by Ascaris Antigens

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Technology description

Allergic asthma is characterized by antigen-specific IgE production, reversible airway hyper-reactivity and eosinophilic infiltration of the airways. There is a dramatic increase in the prevalence of allergic disorders in emerging and industrialized countries and studies suggest that the hygienic environment in those countries may not provide allergy-protective mechanisms associated with some forms of infection. Recent studies have found that helminth infection may suppress the development of allergic disease. Helminth infections currently affect over 2 billion people worldwide, causing significant morbidity. The most successful geohelminths are members of the Ascaris species, including A. lumbricoides and A. suum , which are known to infect 1.5 billion people. The inventors studied the modulation of allergic disease mediated by a chronic A. suum infection in their murine model of ragweed-induced allergic conjunctivitis and allergic asthma, and demonstrated that the infection prevents allergic inflammation in sites distal from larval migration. This protection was due, in part, to the induction of immunoregulatory cytokines such as IL-10. In further studies, they demonstrated that a cocktail of antigens from the pseudoceolomic fluid (PCF) of A. suum , administered during ragweed sensitization, significantly reduced the eosinophil migration into the conjunctiva, pulmonary eosinophilic inflammation, and total lung pathology induced by the ragweed. PCF exposure also reduced the secretion of the pro-allergic cytokines IL-5 and IL-13 in the broncho-alveolar lavage fluid after ragweed exposure. All findings suggest PCF is capable of suppressing the allergic response to a traditional allergen and at multiple tissue sites.

In further studies, the inventors determined that the protection conferred by PCF to allergic inflammation was through a specific first antigenic protein isolated from PCF, results that were confirmed by using the recombinant form of the first antigen.

Furthermore, it is known that Toll-like receptors (TLRs) on dendritic cells (DCs) and other antigen presenting cells recognize specific molecular patterns on invading pathogens, leading to the development of host immunity. A number of pathogens, including helminths, have used pattern recognition by TLRs to modulate host immunity and inflammation to establish a chronic infection. In further studies, the inventors identified a second specific antigenic protein, also isolated from PCF, which can modulate activation of bone marrow derived DCs in response to stimuli with bacterial lipopolysaccharide (LPS); and to stimulate DCs to produce significant increases in IL-10 but not IL-12

upon co-stimulation with LPS. Studies in various genetically deficient mice suggested that this second antigen augments the IL-10 production dependent on one of the TLRs, TLR4. In further studies with the cloned and expressed form of the second antigen, as well as its two domains, the inventors showed that the activity is dependent on domain 2 but not domain 1. The purified second antigen exhibits different properties than unfractionated PCF. PCF administration prevents an initial response from occurring, as it inhibits the initiation of the inflammatory cascade. By contrast, the second antigen can activate DCs and alter cells such that they ultimately suppress responses through the production of IL-10 and can therefore act on the effector phase of the inflammatory response (i.e. modulate a response that is already occurring).

Application area

The inventions are also applicable to other Th-1 and Th-2 associated immunological diseases.

Advantages

Suppression of allergic responses to traditional allergens by administering the identified Ascaris polypeptide antigens, or active fragments or variants thereof, to the affected subjects. The inventions provide different ways to treat allergic diseases or prevent allergic reactions, rather than merely ameliorating the symptoms.

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