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IMMUNE MECHANISMS IN ALLERGIC DISEASE

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Asthma is a chronic disease of the airway that evolves in certain individuals as a consequence of continued or intermittent aeroallergen exposure. The disease encompasses three cardinal processes: a Th2 polarized immune-inflammatory response, a functional abnormality of the airway manifested by bronchial hyperreactivity (BHR) and airway structural changes, commonly referred to as remodeling. The airway remodeling phenotype includes goblet hyperplasia, peribronchial deposition of collagen and other extracellular matrix proteins, and an accumulation of contractile tissue. Although knowledge about these three individual processes: inflammation, bronchial hyperreactivity and airway remodeling has dramatically increased over the last decade, important aspects concerning the connection between the immune-inflammatory phenotype and the structural-functional phenotype still remain to be fully understood. Specifically, whether these structural-functional changes are the consequence of chronic airway inflammation, or of a specific type of inflammation, has not been formally examined.

A great deal of our current understanding of the basic tenets of the asthmatic process has been acquired through research in murine experimental models. Traditionally, conventional models of allergic airways inflammation employ ovalbumin (OVA), an intrinsically innocuous antigen with immunological and biochemical characteristics fundamentally distinct than those of common aeroallergens. Indeed, introduction of ovalbumin into the respiratory mucosa leads to inhalation tolerance, not immunity. Consequently, models using this antigen rely on the intraperitoneal introduction of OVA in conjunction with a chemical adjuvant, generally aluminum hydroxide, to elicit sensitization. This implies that these models, albeit very useful to address certain questions, are inherently unable to inform about the requirements for allergic sensitization. A further limitation of models using OVA is that chronic administration of OVA into an already sensitized animal leads to a diminution, in fact complete abrogation, of the airway inflammatory response.

In this context, our laboratory embarked a few years ago on an effort to develop experimental models that would better mimic the way humans are sensitized and exposed to aeroallergens. To this end, we have recently established experimental models that involve exposure of mice to a house dust mite (HDM) extract, the most pervasive indoor aeroallergen in Western countries, though the respiratory route and without additional adjuvants. In some instances, and to account for the chronic nature of the disease, exposure was continued for up to 7 weeks. Under these experimental conditions, a process with all the cardinal immuno-biological, structural and functional features of asthmatic inflammation was generated. Importantly, discontinuation of allergen exposure resulted in a full resolution of the inflammatory response, a partial resolution of the functional abnormality (BHR) and no resolution at all of the remodeling changes. Thus, this experimental model affords the opportunity to dissect different aspects of a chronic asthmatic phenotype induced by exposure to a common aeroallergen, as well as to investigate the impact of different treatment strategies in the context of chronic aeroallergen exposure.

As indicated earlier, a relevant question is whether the structural-functional phenotype typical of asthmatic inflammation is related to a specific type of inflammation or, alternatively, to the chronic presence of an inflammatory process in the airway. To address this issue, we elected to create divergent immune-inflammatory responses.
The strategy that we chose was to investigate the response of IL-4 competent and IL-4 deficient mice to continued HDM exposure expecting that the genetic deficiency of IL-4 would hamper the full development of a Th2 immune response. Our data show that, interestingly, both strains of mice were clearly able to mount an inflammatory response. However, this response was remarkably different in that the genetic absence of IL-4 was associated with Th2 depolarization and the acquisition of features of Th1 immunity. Indeed, the type of airway inflammation, the profile of cytokines produced by both lung mononuclear cells and splenocytes and the pattern of serum immunoglobulins were overtly distinct between both strains. Importantly, despite evident inflammation of the airways, IL-4 deficient mice chronically exposed to HDM did not exhibit either the structural or functional airway changes typically observed in genetically intact mice. Furthermore, we used an adenoviral–mediated airway gene transfer approach to transiently overexpress murine IL-4 in the airways of IL-4 deficient mice concurrently exposed to HDM. This intervention led to a partial re-emergence of the Th2 immune-inflammatory response in the airway compartment, a partial reconstitution of bronchial hyperreactivity and a complete reconstitution of the remodeling abnormalities of the airway. At present, the mechanisms underlying the phenotypic changes elicited by the transient, local overexpression of IL-4 remain to be elucidated and are the subject of ongoing investigation.

In our view, this experimental paradigm exemplifies the decisive importance of the genetic background, in this case the genetic absence of IL-4, in the elaboration of the full asthmatic phenotype. Indeed, the absence of this archetypic Th2 cytokine, does not preclude the host from mounting an inflammatory response to chronic exposure to a relevant aeroallergen but determines the nature of the response that is generated. Moreover, the data illustrate that a specific structural–functional phenotype is directly related to the specific nature of the immune–inflammatory response, and not merely the consequence of chronic airway inflammation.