THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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Achieving Allergen Tolerance in Children with Asthma through Dendritic Cell Paralysis

Asthma is a chronic inflammatory disease of the airways that causes difficulty breathing. It most often results from abnormally heightened sensitivity of the immune system to environmental allergens that trigger lung inflammation and damage to the airways. Children with asthma experience attacks of wheezing, coughing, chest tightness and trouble breathing, especially early in the morning or at night. According to the Centers for Disease Control, an estimated 7.1 million children live with asthma in the U.S. and this number continues to increase. In children, the severity of the condition can lead to secondary complications that alter sleep patterns, limit physical activity, and in severe cases, can lead to permanent alterations of the airway. If asthma is not adequately treated, ER visits are required to control the symptoms. The side-effects from long term use of available medications to control asthma are equally undesirable. For example, treatment with steroids is a common option to control severe asthma, but can stunt normal growth and increase the risk for pneumonia, bronchitis and other types of respiratory infections. Without treatment, asthma attacks become more frequent and more severe, which unattended may even cause death. It is unknown why some children become hyper-sensitive to certain otherwise "innocuous" environmental allergens. It is also unknown why some children will overcome their sensitization to allergens and "outgrow" asthma. Stephanie proposes that this phenomenon suggests allergic disease is not fixed and can even be reversed under the right conditions. Recently, she discovered a unique dendritic cell receptor, NLRP10 that regulates when and how the immune system responds to allergens. She demonstrated how loss of NLRP10 in a mouse model of asthma completely prevents a response to allergens (impaired adaptive immunity) while apparently leaving immunity against pathogens unaffected (innate immunity intact). Using this animal model, Stephanie intends to delineate how NLRP10 works to control allergen sensitization and to find therapeutic interventions to achieve allergen tolerance. Because the migration of dendritic cells from the lung to the lymph node is a critical step in priming inflammation in asthma, she seeks to stop the immune system from responding to triggers of asthma by effectively blocking the migration of dendritic cells. If she is successful, her strategy to redirect the immune response will pave the way for all children to overcome their asthma, thereby avoiding the need for long-term medications and reducing the debilitating effects of the condition on early childhood development. As autoimmunity is governed by these same fundamental immune processes, it is possible that her approach will hold promise for reversing pediatric type 1 diabetes and similar autoimmune diseases.