THE HARTWELL FOUNDATION

2023 Nominee Individual Biomedical Research Award

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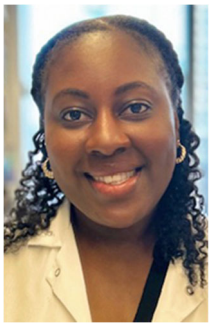

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IgE-Mediated Processes as Potential Therapeutic Targets for Respiratory Virus Disease Progression in Asthma

Asthma is chronic respiratory condition characterized by airway inflammation, hyperreactivity and airway remodeling (permanent structural changes) that leads to a decrease in lung function due to the narrowing of the airways. Asthmatic children endure trouble breathing, coughing, wheezing, and fatigue due to poor sleep; symptoms that interfere with school and normal play activity. In the U.S., nearly 6 million children aged 0-17 years have asthma, many that develop the disease before the age of 5 years. There is no cure for asthma, but it can be managed by medications and avoiding irritating triggers. Fortunately, many children outgrow it. Viral respiratory infections have been identified as a major cause of asthma and may contribute to asthma inception, especially in high-risk young children with a susceptible genetic background. Conversely, impaired immunity in children with asthma has been proposed as a mechanism for increased susceptibility to infectious disease, which is supported by several clinical studies that have revealed pediatric patients with asthma have a higher risk of adverse responses to respiratory viral infections such as those caused by rhinovirus. A variety of potential mechanisms have been proposed to explain the increased susceptibility to certain viral pathogens and not surprisingly, elevated immunoglobulin E (IgE) antibody levels in the blood, a hallmark of allergic disease, have been shown to play a major role in the susceptibility and progression of respiratory viral infections. In this regard, IgE is the most heavily glycosylated (presence of bound sugar) monomeric antibody in the immune system, where its glycan structure is thought to play an important role in IgE biological function. In young adults it has been observed that an asthmatic background with high levels of IgE predispose individuals to heightened responses during the acute phase of respiratory virus infection, including rhinovirus, respiratory syncytial virus, and SARS-CoV-2. By contrast, anti-IgE medications have been shown to reduce the severity and duration of COVID-19 disease following SARS-CoV-2 infection. Notably, low levels of IgE have been associated clinically with a higher prevalence of autoimmune disease, chronic fatigue, some cancers, chronic sinusitis, and otitis media. Therefore, considering the essential role of IgE in asthma and anti-viral immunity, I hypothesize that progression of viral infections in asthmatic children is mediated partly through an IgE-dependent pathway associated with distinct patterns of IgE glycosylation and pro-inflammatory markers. In order to understand the development of symptomatic illness among children with asthma, I will use SARS CoV-2 infection as a model for respiratory viral infections, which will enable the evaluation if IgE glycan variation, the strength of IgE antibody binding to antigens (avidity) and guide the downstream identification of mediators of IgE activity as a function of antiviral immunity. If I am successful, understanding how asthma can modulate the immune response to respiratory virus infection will lead to new and more effective therapeutics for the management of respiratory virus disease, providing relief for children affected with asthma and improving their quality of life.