THE HARTWELL FOUNDATION

2017 Individual Biomedical Research Award

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Targeting Virally Induced Inflammation to Prevent the Development of Asthma

Acute respiratory infections are extremely common in young children and are often caused by viruses. These infections typically lead to inflammation and constriction of the airways, which is termed bronchiolitis. There is no treatment for childhood bronchiolitis and well over 100,000 US children under the age of one each year are hospitalized for related complications. Moreover, numerous studies now link the presence and severity of a viral respiratory infection in infants with the eventual development of asthma as a child. As the most common chronic childhood illness, asthma affects an estimated 7 million children in the US, with 5-17% experiencing limited physical activity and a diminished quality of life as a direct result. Unfortunately, the mechanism responsible for how a viral infection in early life contributes to latent development of asthma is poorly understood, which has limited the development of targeted therapeutics to stop the progression. Most respiratory viruses that infect children are categorized as “acute” and are completely cleared from the host after the infection is resolved by the immune system. In this context, it has long been assumed that all infected epithelial cells that line the respiratory passages are also eliminated by the immune system as the viral infection is cleared. However, based upon a recent discovery by Nick, it appears that some virally infected epithelial cells are not removed by the immune system and persist in the lung. Despite these cells clearing all traces of the virus, they are genetically modified by infection to maintain the release of pro-inflammatory cytokines, which cause inflammation and negatively alter the normal function of the lung respiratory epithelium to moisten and act as a barrier to foreign particles and potential pathogens. Since high levels of pro-inflammatory cytokines are a hallmark of asthma development in children, his working hypothesis is that this population of “survivor cells” in the developing lung initiates the development of asthma and chronic lung disease. To determine the nature of the prolonged cytokine response after viral infection that leads to chronic respiratory disease, Nick proposes to collect samples from sick children and then compare this information to data he collects from a mouse model of neonatal infection. After determining which cytokines are differentially expressed in humans and conserved in mice, he will use the mouse model to perform targeted interventions with cytokine neutralizing antibodies in an attempt to to break the linkage between respiratory viral infection in early life and latent development of asthma. If Nick is successful, translation of his research outcomes will yield novel therapeutics that can reverse the latent effects of viraly-induced acute respiratory infections and prevent asthma in children.