THE HARTWELL FOUNDATION

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Targeted Blockade of Toll-like Receptors in Respiratory Viral Infection

Influenza is a viral infection of the upper respiratory system that in children often turns into pneumonia. While the mortality rate for early-life respiratory infections is relatively low, the morbidity rate is high, with latent and debilitating long-term chronic lung disease (e.g., asthma). Infants younger than six months, however, cannot mount an adequate response to existing vaccines; and antiviral drugs have limited value given safety considerations and the need for timely identification of the infection. There remains a critical need for antiviral therapeutics that will modulate beneficially the immune response rather than target a specific viral pathogen. Ironically, poor outcomes have traditionally been attributed to failure of the immature immune system to overcome the virus, but infants are known to often mount comparable or higher immune responses than adults. In this regard, an essential component of the host response is pathogen recognition and initiation of the innate immune response, which is required to activate an adaptive immune cell response mediated by antigen-specific interactions with cell membrane proteins called Toll-like receptors (TLR). Thirteen functional receptors have been identified in humans and mice and each TLR has a distinct function in terms of pathogen recognition and immune response but the role of specific TLR proteins during early development in infants has not been established. Therefore, I propose to determine if specific TLR blockade could be used as a therapeutic intervention for protecting infants during respiratory viral infection. In preliminary experiments using a clinically relevant mouse model of neonatal influenza virus infection I demonstrated that neonatal mice have a delayed and reduced viral-specific cell response compared to adult mice. Specifically, 3-day old neonatal mice devoid of the TLR2 receptor (TLR2-/-) when infected with influenza virus improved dramatically compared to wild type, and the protection was not evident in adult animals. By contrast, I found no significant difference in survival between neonatal wild type and TLR4-/- mice, or by blockade of TLR4 by Eritoran, a potent synthetic TLR4 antagonist previously shown to protect wild type *adult* mice against lethal influenza virus infection. Remarkably however, I found that Eritoran failed to protect TLR2-/- neonatal mice. These data suggest a novel role for TLR2 in protecting against respiratory viral infections and a reason to pursue whether a specific TLR blockade can be used therapeutically to protect newborns. My plan is to test specific drugs in both my newborn mouse infection model and with human blood cells isolated from term and preterm cord blood. If I am successful in identifying a way to diminish the initial immune response to viral influenza in neonates an effective therapy will reduce suffering and complications in this pediatric population at most risk for respiratory viral infections.