THE HARTWELL FOUNDATION

2021 Individual Biomedical Research Award

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Preserving Lung Function in Premature Infants by Targeting the Immune System

While modern interventions can save premature babies from the near-term threat of death, prematurity and lifesaving measures such as mechanical ventilation often result in a chronic lung disease called bronchopulmonary dysplasia (BPD). Children with BPD suffer a spectrum of life-long and life-threatening disease risks including airway obstruction (difficulty breathing), increased risk for respiratory viral infection, and pulmonary hypertension, and even complete lung failure. Unfortunately, a diagnosis of BPD comes with a lifelong expectation of illness, hospital visits, long-term medication, and dramatically reduced life -expectancy, which clearly represents an incredible strain on infants and their families. A key factor in the development of BPD is the inflammation generated by the physical stress imparted during mechanical ventilation of preterm infant lungs with high levels of oxygen. The immune system is essential to the generation of this inflammatory state, but the precise nature of the process is poorly understood. Dendritic cells (DC), a critical immune cell population that acts as messengers between the innate and the adaptive immune systems, are known to play a critical role in provoking and resolving inflammation, but how they influence development of BPD remains a mystery. Based upon my recent discoveries in mice that several uncharacterized and unique populations of DC appear in the lungs much earlier in fetal development than was previously thought raises important new questions about their role in this disease. Contrary to existing dogma, when classified according to distinct sub-populations based on their origination, function and expression of specific markers, the phenotypic variation of newborn mouse lung DC differs from their adult counterparts. To explain these observations, I hypothesize that a subset of previously undiscovered fetal immune DC influence BPD development by initiating inflammation. If true, it would make them a viable BPD-specific target for therapeutic intervention. My plan is to characterize the types of DC and their roles in the developing lung. Doing so will enable identification and interrogation of candidate interventions for the development of treatments to prevent BPD. On this basis, a comprehensive atlas of the DC populations in the developing mouse lung will be assembled that defines cell identities based on proteins expressed at the cell surface, transcriptomic definition of cell identity, alteration in molecular phenotype across development, and identification of early-stage DC lineage. The atlas will enable translational research in non-human primates and future detailed examination in humans. If I am successful, unraveling the immunological mechanisms leading to BPD will suggest actionable targets and new therapeutic interventions for the early onset of chronic lung inflammation in preterm infants, which, if clinically translated, will reduce the lifelong complications experienced by those children born prematurely.