THE HARTWELL FOUNDATION

2023 Nominee Individual Biomedical Research Award

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Mitochondrial Function and Homeostasis as Targets to Promote Neutrophil Production for Transfusion

Neutrophils are key immune system cells that in response to inflammation play a role in our immediate response to pathogens. As the most abundant innate immune cells, they are also important in the initiation of wound healing and for the integrity of our gastrointestinal lining. Low numbers of circulating neutrophils, termed neutropenia, can cause repeated infections, painful ulcers, and place patients at risk of life-threatening, invasive infections. Pediatric patients experience severe neutropenia in three key contexts. First, in the setting of chemotherapy which makes it more difficult for the bone marrow to fight infections. In the United States, there are an estimated 16,000 new cases of pediatric cancer diagnosed every year. For those children whose cancer diagnoses require aggressive chemotherapy, it is estimated that roughly 50% of patients experience episodes of fever and neutropenia. The second is in the period following bone marrow transplant, estimated to impact nearly 2,500 pediatric patients per year. Prior to the establishment of new donor-derived mature neutrophils, patients are at extremely high risk for serious infectious complications, including death. Finally, patients with severe congenital neutropenia (low levels of neutrophils) suffer from life-long complications with painful mouth sores and frequent infections. Unlike other blood products which can effectively raise the red blood cell or platelet numbers, there is regrettably, no effective form of neutrophil transfusion. This is in part due to the transition of immature neutrophils to mature cells and their counterparts, which has limited the ability to develop effective neutrophil transfusions and related novel therapeutics. To address this problem, I hypothesize that the regulation of neutrophil metabolic activity (mitochondrial function) and its contribution to neutrophil stability (immune homeostasis) are essential characteristics of neutrophil precursor proliferation, survival, and differentiation. Determining how maturing neutrophils generate and utilize energy will thus enable identification of new druggable targets for neutrophil recovery and improve the state of the art of neutrophil transfusions. Using genome editing, I will identify those genes involved in mitochondria homeostasis that are required for neutrophil differentiation using a reverse-genetic screen by means of arrayed CRISPR/Cas9, which can define the nuclear-encoded mitochondrial genes that are positive or negative regulators of neutrophil maturation. To determine whether enhanced mitochondrial function leads to improved neutrophil precursor proliferation and survival, I will utilize a series of clinically relevant small molecules to enhance mitochondrial function (energy production). If successful, readily available neutrophil transfusions will open the possibility for timely life-saving interventions for pediatric patients that will improve their quality of life.