Specialized Lipogenic Macrophages in Diabetic Peripheral Neuropathy

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PUBLIC ABSTRACT

Peripheral neuropathy is a common complication of prediabetes and type 2 diabetes (T2D) and is becoming an increasingly widespread problem. It is characterized by nerve damage that can lead to pain, reduced sensation, and an increased risk of limb amputation. Unfortunately, current treatment options are limited and often rely simply on controlling glucose levels, which has shown to be less effective in preventing neuropathy in T2D. A better understanding of the mechanisms leading to nerve injury is imperative for developing new therapies.

This grant application is focused on mechanistic studies to inform treatment development for neuropathy in those with T2D. Neural inflammation due to altered glucose and fat levels in diabetes contributes to nerve fiber damage. Previous studies showed local inflammation activated brown fat-like cells in the nerve. Recent data unexpectedly suggests these cells are actually a new macrophage population not previously described. These cells have a unique metabolism and may be activated in diabetic neuropathy. They were identified within nerves from individuals with T2D. This project aims to further characterize these novel cells and determine the role they may play in diabetic peripheral neuropathy (DPN). The presence and typical features of these cells will be determined as neuropathy progresses. These studies will also determine if depletion of these cells prevents or slows neuropathy. These cells will be isolated from human nerves and analyzed using the latest biomedical technologies capable of determining the unique genetic profile expressed by single cells.

DPN is a major concern for the military and civilians given the increasing number of people with prediabetes and diabetes. This research should identify a novel macrophage population in nerves induced in T2D, their contribution to DPN, and the inflammatory and metabolic signals regulating their activation. These studies could also define new pathways or biomolecules to target for development of DPN therapies. Results may be applicable to other conditions associated with nerve damage and inflammation, such as inflammatory neuropathies and traumatic nerve injuries.