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*The Role of Neuronal-Derived MD-1 on Cutaneous Inflammation*

**Abstract**

Impaired healing of surgical incisions is the second leading cause of chronic wound care in the post-acute setting, with Medicare estimates of $7 billion annually. Optimal healing requires coordination and signaling between sensory neurons and the immune system. These neural immune interactions are poorly defined and are the focus of this proposal. Completion of these studies will better define the function of nonpeptidergic sensory neurons (those with limited proinflammatory neuropeptides, i.e., calcitonin gene related peptide (CGRP)) in the inflammatory response evoked by surgical incision and during wound repair. My initial studies and other recent reports suggest nonpeptidergic afferents have a suppressive action on immune signaling. My preliminary studies and published transcriptomic studies have identified myeloid differentiation 1 (MD-1, encoded by gene Ly86), a molecule of the innate immune system, to be expressed predominantly in nonpeptidergic neurons. Our preliminary data using MD-1 knockout mice suggest that **MD-1, produced by nonpeptidergic sensory neurons, functions as a regulator of neural-immune communication and has anti-inflammatory effects**. Nonpeptidergic afferents, via MD-1, may also promote normal healing. We propose to determine the role of MD-1 in these neurons in regard to the cutaneous inflammatory response and wound healing. We will determine if loss of neuronal MD-1 alters immune cell recruitment and activation during inflammatory and proliferative phases of healing. We will also examine tissue architecture as a metric of healing and changes in pain behaviors in relation to the inflammatory state. **The finding that MD-1 expressed by neurons regulates the immune response to injury is novel and offers a potential new target for optimizing wound repair.**

Regional anesthesia is used to manage perioperative pain associated with surgery and has also been demonstrated to be protective of immune cells by decreasing sympathetic tone and its adverse immune effects. However, the role of peripheral nerve blocks (PNBs) in neural immune communication at the surgical site have not been delineated. **Another goal of my research is to characterize the role of PNBs in the immune response to surgical incision**. These studies will use the plantar incision model and sciatic nerve blocks in mice to define the effects of PNBs on the immune response to injury and on wound healing. We will define how type and concentration of local anesthetic and duration of nerve block affects the immune response. Finally, using the MD-1 knockout mice, we will determine the effect of PNBs on the role of neuronal MD-1 signaling in surgical incision inflammation and healing.