Project Description

Skeletal muscle injuries related to aging, disease and sports are the most common musculo-skeletal conditions reported in the US, costing up to 80 billion annually. Skeletal muscle regeneration is a complex process orchestrated by multiple steps. Recent findings indicate that the innate immune system plays a central, coordinating role in the initial inflammatory response to muscle injury and in timely regeneration of new muscle tissue. Various types of immune cells and cytokines play key roles in this process. Neutrophils are one of the most important immune cell types in the first wave of the proinflammatory response to muscle injury. Neutrophils within the injured muscle are activated immediately after injury and release proinflammatory cytokines including TNF-\(\alpha\) (tumor necrosis factor alpha), IFN-\(\gamma\) (Interferon-\(\gamma\)), and IL-1\(\beta\) (interleukin-1\(\beta\)).

Despite a growing recognition that the immune response is essential for the proper completion of regeneration, it remains poorly understood. Less is known about the role of neutrophils in skeletal muscle injury and repair.

This research is based on our recent discovery that removing KLF2 expression in all myeloid lineage cells in mice (myeKlf2-/-) positively enhances and accelerates regeneration. Our long term goal is to uncover the genetic program(s) that regulate myeloid immune cells during muscle regeneration and, ultimately, to manipulate this program to improve outcomes after injury. Our central hypothesis is that KLF2 regulates myeloid cell activation during muscle regeneration and that KLF2 expression can be manipulated to improve outcomes. The objective of this study is to define the role of the zinc-finger transcription factor, KLF2, in myeloid cell functions during skeletal muscle regeneration after acute injury.

Our Specific Aim is to: 1) Determine the role of KLF2 in neutrophil activation during skeletal muscle injury. Our hypothesis is that KLF2 regulates the expression of cytokines, growth factors and signaling molecules
that determine neutrophil functions in muscle repair and regeneration. 2) Determine the migratory properties of KLF2 ablated neutrophils and evaluate their ability to infiltrate the injured muscle. Our hypothesis is that KLF2 regulates receptors that mediate the migration of circulating neutrophils to the site of injury. Furthermore, we propose that the C-C cytokine receptor CCR5 and CXCR4 are regulated by KLF2 and play important roles in determining these functions. Upon conclusion, we will have gained a more complete understanding of the role of KLF2 in neutrophil cell functions during muscle repair and regeneration. This research is significant because it will provide mechanistic insights into the immunobiology of muscle regeneration, it will validate myeloid KLF2 as a potential therapeutic target.

The student will be trained and perform the following components of the research:
- Perform RTq-PCR to identify KLF2-regulated genes and neutrophil markers that are altered during skeletal muscle injury and regeneration. Timeline: 4 weeks
- Perform western blot to identify the KLF2-regulated signaling protein in neutrophils isolated from injured skeletal muscle. Timeline: 3 weeks
- Perform flow cytometry to assay the neutrophil activation during skeletal muscle injury. Timeline: 3 weeks