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Title of Presentation:
INTERLEUKIN-4/ SIGNAL TRANSDUCER AND ACTIVATORS OF TRANSCRIPTION 6 (IL-4/STAT6) SIGNALLING PATHWAY IN MUSCLE REGENERATION

Abstract

Type 2 innate immunity is involved in regeneration of skeletal muscle after injury. A few days after damage eosinophils rapidly recruit to the muscle and secrete IL-4 to activate the regenerative actions of muscle resident fibro/adipocyte progenitors (FAPs). FAPs are a population of Lin- α7 integrin- Sca1+ PDGFRα+ multipotent mesenchymal progenitor cells that proliferate efficiently in response to damage to provide a transient source of pro-differentiation signals for proliferating myogenic progenitors. In conditions favoring degeneration however, FAPs persist in the tissue and differentiate into collagen-producing fibroblasts and adipocytes causing intramuscular fibrofatty infiltration. IL-4/IL-13 signaling serve as a key switch to control the fate and functions of FAPs. Activation of IL-4/IL-13 signaling promotes proliferation of FAPs to support myogenesis while inhibiting their differentiation into adipocytes.

Macrophages (MQs) have been historically classified into two main groups, M1 and M2. M1, or classically activated MQs, are pro-inflammatory MQs whereas alternatively activated MQs (M2) have anti-inflammatory function. It has been shown that monocytes displaying an M1 pro-inflammatory profile heavily infiltrate muscle early after damage and then likely switch to a distinct M2 MQs at later stages. IL-4/IL-13 signaling showed to be involved in M2 MQ polarization. However, it was mostly studied in vitro and on MQs derived from barrier organs in which both bacterial products and T-cell derived cytokines were part of the environment. Whether IL-4/IL-13 signaling plays a role in MQ polarization in sterile injuries has not been well studied yet.

In this study we are going to explore the role of IL-4/IL-13 signaling pathway in MQ polarization during acute sterile muscle injury. First of all, we tried to confirm the role of IL-4 signaling in FAP proliferation using STAT6 K/O mice. STAT6 is the main signaling pathway activated by in vitro IL-4 stimulation of FAPs. Four days after Notexin injection proliferation of FAPs, assessed by in vivo EDU incorporation assay, was significantly impaired in STAT6 K/O mice compared to the wild type control (16.75 ± 4.66 vs. 31.26 ± 3.46, p-value <0.05). This phenotype could exclusively result from intrinsic loss of IL-4 signaling in FAPs or it could also be an indirect consequence of impaired macrophage polarization to M2 phenotype, which we are going to address in this study by quantification of the expression profile of a large number genes encode cytokines and transcription factors that have been shown to have a functional role in MΦ polarization.