STAT3 signaling controls satellite cell expansion and skeletal muscle repair.

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Authors: Matthew Timothy Tierney, Tufan Aydogdu, David Sala, Barbora Malecova, Sole Gatto, Pier Lorenzo Puri, Lucia Latella, Alessandra Sacco

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Public Summary:
A goal of our research is to define how the microenvironment instructs muscle stem cell (MuSC) behavior upon stress and tissue damage. This work demonstrates that STAT3 signaling promotes the transition of MuSC to the committed progenitor stage and that its pharmacological manipulation promotes MuSC expansion and enhances skeletal muscle tissue repair in contexts of aging and muscular dystrophy. Understanding the molecular players involved in the decline in MuSC function in chronic conditions is a major goal in regenerative medicine to restore muscle function. Through molecular, genetic and pharmacological approaches we show that IL6-activated Stat3 signaling promotes MuSC myogenic lineage progression through Myod regulation. Conditional ablation of Stat3 in MuSC resulted in increased expansion during regeneration, but compromised myogenic differentiation prevented their contribution to regenerating myofibers. In contrast, transient Stat3 inhibition promoted MuSC expansion and enhanced tissue repair in both aged and dystrophic muscle. Finally, the effects of STAT3 inhibition were conserved in human myoblasts, identifying this inflammatory mediator as a promising therapeutic target for muscle diseases. The results of this study indicate that pharmacological manipulation of STAT3 activity can be used to counteract the functional exhaustion of MuSC, thereby maintaining the endogenous regenerative response and ameliorating muscle-wasting diseases. Given the major role of this signaling pathway in cancer, major efforts in recent years have led to the development of several JAK/STAT inhibitors currently in clinical trials, thus this provides an unprecedented opportunity for repurposing these drugs for the treatment of muscle wasting conditions and accelerate the translation of our findings to the clinic.

Scientific Abstract:
The progressive loss of muscle regenerative capacity with age or disease results in part from a decline in the number and function of satellite cells, the direct cellular contributors to muscle repair. However, little is known about the molecular effectors underlying satellite cell impairment and depletion. Elevated levels of inflammatory cytokines, including interleukin-6 (IL-6), are associated with both age-related and muscle-wasting conditions. The levels of STAT3, a downstream effector of IL-6, are also elevated with muscle wasting, and STAT3 has been implicated in the regulation of self-renewal and stem cell fate in several tissues. Here we show that IL-6-activated Stat3 signaling regulates satellite cell behavior, promoting myogenic lineage progression through myogenic differentiation 1 (Myod1) regulation. Conditional ablation of Stat3 in Pax7-expressing satellite cells resulted in their increased expansion during regeneration, but compromised myogenic differentiation prevented the contribution of these cells to regenerating myofibers. In contrast, transient Stat3 inhibition promoted satellite cell expansion and enhanced tissue repair in both aged and dystrophic muscle. The effects of STAT3 inhibition on cell fate and proliferation were conserved in human myoblasts. The results of this study indicate that pharmacological manipulation of STAT3 activity can be used to counteract the functional exhaustion of satellite cells in pathological conditions, thereby maintaining the endogenous regenerative response and ameliorating muscle-wasting diseases.