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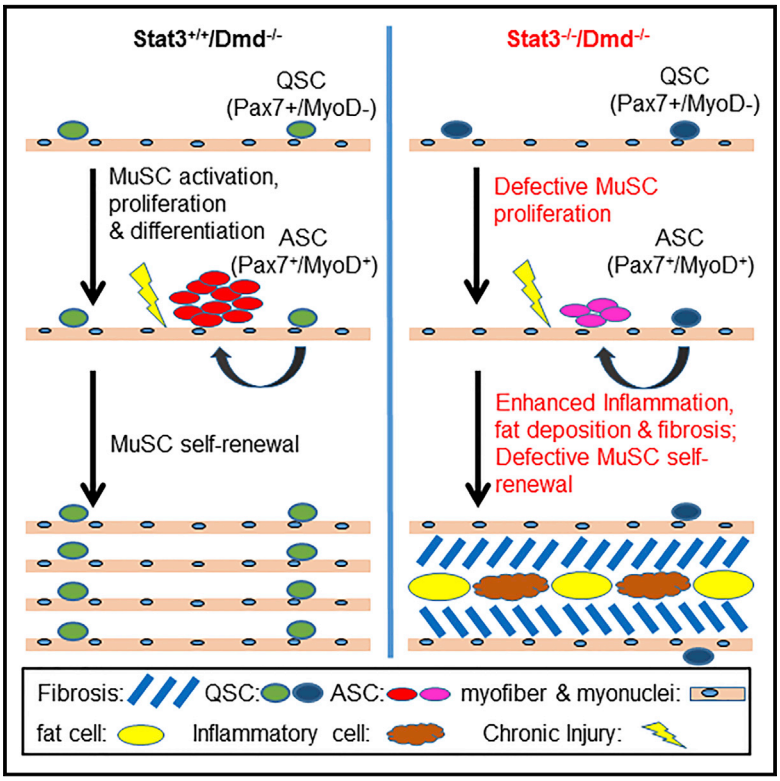
STAT3 Regulates Self-Renewal of Adult Muscle Satellite Cells during Injury-Induced Muscle Regeneration

Graphical Abstract



Highlights

- STAT3 is not required for the initial establishment of the adult muscle stem cells (MuSCs) pool
- Loss of *Stat3* in MuSCs impairs their proliferation and self-renewal upon injury
- Loss of *Stat3* in MuSCs of dystrophic mice dysregulates many genes, including *Pax7*
- Loss of *Stat3* in MuSCs of dystrophic mice leads to severe fibrosis and inflammation

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In Brief

Zhu et al. find that STAT3 in muscle stem cells (MuSCs) critically regulates their proliferation and self-renewal during injury-induced muscle regeneration. Loss of *Stat3* in dystrophic MuSCs leads to progressively severe regeneration deficits, including a sharply decreased MuSC pool, muscle inflammation, fat deposition, and severe fibrosis.

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STAT3 Regulates Self-Renewal of Adult Muscle Satellite Cells during Injury-Induced Muscle Regeneration

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SUMMARY

Recent studies have shown that STAT3 negatively regulates the proliferation of muscle satellite cells (MuSCs) and injury-induced muscle regeneration. These studies have been largely based on STAT3 inhibitors, which may produce off-target effects and are not cell type-specific in vivo. Here, we examine the role of STAT3 in MuSCs using two different mouse models: a MuSC-specific *Stat3* knockout line and a *Stat3* (MuSC-specific)/*dystrophin* (*Dmd*) double knockout (dKO) line. *Stat3*$^{-/-}$ MuSCs from both mutant lines were defective in proliferation. Moreover, in both mutant strains, the MuSC pool shrank, and regeneration was compromised after injury, with defects more pronounced in dKO mice along with severe muscle inflammation and fibrosis. We analyzed the transcriptomes of MuSCs from dKO and *Dmd*$^{-/-}$ control mice and identified multiple STAT3 target genes, including *Pax7*. Collectively, our work reveals a critical role of STAT3 in adult MuSCs that regulates their self-renewal during injury-induced muscle regeneration.

INTRODUCTION

In vertebrate muscles, muscle satellite cells (MuSCs) are responsible for both embryonic and postnatal muscle growth and muscle regeneration upon injury (Brack and Rando, 2012; Buckingham and Relaix, 2007; Murphy and Kardon, 2011; Scharner and Zammit, 2011; Yin et al., 2013). Adult MuSCs are quiescent and characteristically express Pax7, a paired domain- and homeodomain-containing transcription factor (Buckingham and Relaix, 2007; Seale et al., 2000). In addition, the majority of adult quiescent MuSCs also express *Myf5*, one of the four genes encoding myogenic regulatory factors (MRFs) that also include *MyoD*, *myogenin*, and *MRF4* (Beauchamp et al., 2000; Berkes and Tapscott, 2005; Comai and Tajbakhsh, 2014; Kuang et al., 2007). Although quiescent MuSCs do not express MyoD, upon injury, activated MuSCs start to express both Pax7 and MyoD, re-enter the cell cycle to proliferate, and undergo differentiation to repair the damaged muscles (Buckingham and Relaix, 2007; Yin et al., 2013). Some activated MuSCs can self-renew during regeneration to maintain the MuSC pool (Brack and Rando, 2012; Buckingham and Relaix, 2007; Murphy and Kardon, 2011; Scharner and Zammit, 2011; Yin et al., 2013). Defects in self-renewal could gradually deplete the stem cell pool and result in defective tissue regeneration.

The JAK/STAT pathways are activated by a variety of extracellular stimuli, including cytokines and growth factors (Kisseleva et al., 2002; O'Shea et al., 2002). They are known to regulate diverse biological processes ranging from immune system development and inflammation, to embryonic development (Kisseleva et al., 2002; O'Shea et al., 2002; Schindler et al., 2007). Among seven STATs in the mouse genome, only STAT3 is indispensable during embryo development because the germline *Stat3* knockout (KO) leads to embryonic lethality (Takeda et al., 1997). In myoblasts, we showed previously that a pathway consisting of JAK1, STAT1, and STAT3 potently inhibits myogenic differentiation in cell culture models in response to leukemia inhibitory factor (LIF) or Oncostatin M (OSM) (Diao et al., 2009; Sun et al., 2007; Xiao et al., 2011). In addition, we found that STAT3 could also promote myoblast differentiation by acting with JAK2/STAT2 in cell culture (Wang et al., 2008). As for the in vivo role of STAT3 in adult MuSCs, two recent papers reported that inhibition of STAT3 in MuSCs by either small interfering RNAs (siRNAs) or chemical inhibitors enhanced proliferation, whereas intramuscular injection of STAT3 inhibitors promoted