MUSCULAR DISORDERS

Satellite-boosting muscle repair

Satellite cells (SCs) are muscle-associated progenitor cells that can differentiate into myofibres. In old age and disease, however, the ability of muscle to regenerate is limited, in part owing to dwindling numbers of SCs. Two recent papers in *Nature Medicine* show that inhibition of JAK–STAT (Janus kinase–signal transducer and activator of transcription) signalling can help maintain the SC pool and promote muscle repair in mouse models of muscle injury and muscular dystrophy.

In the first paper, Price *et al.* isolated SCs from aged (18-month-old) but healthy mice and transplanted them into cardiotoxin-injured muscle of 6–8-week-old mice that

“increased STAT signalling in older SCs may prevent SC self-renewal”

lacked dystrophin (a model of muscular dystrophy). These SCs gave rise to far fewer donor-derived SCs and dystrophin-positive myofibres than did SCs from younger (3-week-old or 3-month-old) animals; thus, older SCs have reduced ability to regenerate muscle.

Genome-wide expression analyses revealed that SCs from old animals had upregulated expression of STAT activators, as well as higher expression of genes with STAT binding sites. SCs treated in culture with the JAK2 inhibitor tyrophostin AG 490 (Tyr AG 490), the STAT3 inhibitor 5,15 diphenylporphine (5,15 DPP), or siRNAs targeting STAT3 or JAK2 underwent markedly more symmetric cell divisions than did SCs incubated with scrambled RNA or vehicle. The authors concluded that increased STAT signalling in older SCs may prevent SC self-renewal.

Next, the authors injected Tyr AG 490 or 5,15 DPP into the cardiotoxin-injured muscle of young adult and old mice. Compared with vehicle-treated regenerating myofibres, Tyr AG 490- and 5,15 DPP-treated regenerated myofibres (both in the young adult and old mice) were wider and had more SCs, fewer infiltrated macrophages and better architecture. Moreover, leg muscles treated once 3 days after cardiotoxin injury with either of the inhibitors were stronger and slower to fatigue, implying that JAK–STAT inhibition promotes functional recovery of muscle.

In the second paper, Tierney *et al.* found that SCs in notexin-injured mouse muscle had higher levels of phosphorylated STAT3, which were correlated with the expression of

myoblast determination protein 1, indicating SC differentiation. In mice in which STAT3 was conditionally knocked out from SCs, notexin muscle injury triggered an expansion of SCs, and myofibres were repaired more rapidly; however, the diameters of the regenerated myofibres at 25 days after injury were smaller than in non-knockout controls. Therefore, although ablation of STAT3 signalling enhances SC expansion, it also compromises muscle repair.

Tierney *et al.* next investigated whether transient pharmacological inhibition of STAT3 would promote SC expansion, yet allow proper regeneration of muscle fibres. Indeed, intermittent intramuscular administration of a STAT3-inhibiting peptide PpYLKTK-mts accelerated muscle regeneration in notexin-injured muscles of aged (24-month-old) mice, and, in a mouse model of muscular dystrophy, gave rise to larger regenerated myofibres after 4 weeks compared with vehicle-treated animals.

Together, these papers suggest that pharmacological inhibition of JAK–STAT signalling may promote the self-renewal of SCs needed for the repair of muscle. JAK inhibitors and STAT3 inhibitors have been developed as anticancer agents, and the regeneration of diseased or injured muscle may represent another indication for such compounds.

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ORIGINAL RESEARCH PAPERS Price, F. D. *et al.* Inhibition of JAK–STAT signaling stimulates adult satellite cells function. *Nature Med.* <http://dx.doi.org/10.1038/nm.3655> (2014) | Tierney, M. T. *et al.* STAT3 signaling controls satellite cell expansion and skeletal muscle repair. *Nature Med.* <http://dx.doi.org/10.1038/nm.3656> (2014)

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