

Inflamm-aging: STAT3 Signaling Pushes Muscle Stem Cells off Balance

Bénédicte Chazaud^{1,*} and Guy Mouchiroud¹

¹Center of Genetics and Molecular and Cellular Physiology – CNRS UMR5534, Université Lyon 1 Claude Bernard, 69100 Villeurbanne, France

*Correspondence: benedicte.chazaud@inserm.fr

<http://dx.doi.org/10.1016/j.stem.2014.09.010>

Two recent studies shed light on mechanisms underlying muscle dysfunction in age and disease. They reveal that JAK-STAT signaling regulates myogenic differentiation, leading to a reduced reservoir of muscle stem cells. Both genetic and pharmacologic inhibition of STAT3 signaling improve stem cell homeostasis and physiology of aged and dystrophic muscles.

STAT3 belongs to a downstream signaling pathway of a series of receptors, which include receptors for IL6, HGF, IL15, and EGF (reviewed in [Yin et al., 2013](#), [Brack and Rando, 2012](#)), expressed by myogenic cells during myogenesis. Regenerative capacities of muscle stem cells, or satellite cells, decline with age. Extrinsic/environmental cues have been implicated in this process (reviewed in [Brack and Rando, 2012](#)), which is not surprising given the tight interactions muscle stem cells develop with the microenvironment, including immune cells ([Mounier et al., 2011](#); [Paylor et al., 2011](#)). However, recent studies have shown that alterations in intrinsic cell signaling also contribute to the declined functionality of aged satellite cells. Two papers recently published in *Nature Medicine* ([Tierney et al., 2014](#); [Price et al., 2014](#)) now identify a specific role for JAK-STAT3 signaling in muscle stem cells in inducing myogenic differentiation to the detriment of their expansion. They also show that this pathway predominates in aged and dystrophic muscle stem cells, providing a new molecular mechanism regulating muscle stem cell homeostasis and an opportunity for therapeutic targeting.

The study from the Sacco team shows that silencing STAT3 in myogenic stem cells increases their expansion both in vitro and in vivo and results in an increase of Pax7^{pos} stem cells in the muscle. The increased number of muscle stem cells correlates with a decreased size of the newly formed myofibers as a result of an altered choice between expansion and differentiation during muscle regeneration. [Tierney et al. \(2014\)](#) further investigated the in vivo effects of pharmacological inhibition of STAT3

signaling. A single—and thus transient— inhibition of STAT3 just after injury triggers the acceleration of the regeneration process in both adult and aged animals. Moreover, they show that weekly injections of the STAT3 inhibitor improve the phenotype of dystrophic muscle. At the molecular level, STAT3 activity stimulates *Myod1* expression through binding to a specific locus upstream its transcriptional start site, marked by histone H3Lys27 acetylation, indicative of its activation.

The study from the Rudnicki lab ([Price et al., 2014](#)) focuses on the JAK2-STAT3 pathway in muscle stem cells during aging. Interestingly, activation of the pathway, including phosphorylation of STAT3 itself and the expression of downstream genes, increases with age in myogenic (Pax7^{pos}) cells. Meanwhile, the capacity of these cells to engraft into dystrophic muscle decreases with age. Upon transplantation, purified Pax7^{pos} cells that have been ex vivo silenced for STAT3 (by either siRNA or treatment with STAT3 inhibitors) engraft much better than untreated cells with the strongest effect on cells isolated from the oldest mice. Similar to results obtained in the study of [Tierney et al. \(2014\)](#), intramuscular injection of STAT3 inhibitors soon after injury leads to accelerated muscle regeneration associated with an increased number of Pax7^{pos} cells in the muscle. Interestingly, [Price et al. \(2014\)](#) have investigated the effects of STAT3 inhibition at the cellular level in the floating myofiber model using the *Myf5-cre;R26R-YFP* strain in which 10% of the Pax7^{pos} cells are Myf5^{neg}, thereby placing them upstream in the myogenic hierarchy. STAT3 inhibition (through siRNA or

pharmacological inhibitors) triggers an increase of the planar divisions of muscle stem cells, leading to a final increase of the number of stem cells, to the detriment of apico-basal divisions that give rise to cells committed into myogenesis. Here again, the effects of STAT3 inhibition are more pronounced on stem cells derived from older animals.

Taken together, these two studies define a role for the JAK-STAT3 signaling pathway in the control of muscle stem cell expansion at the time of muscle regeneration, adding a function to this pathway known to control the fate of various stem cells. STAT3 is required for self-renewal and pluripotency of embryonic stem cells ([Raz et al., 1999](#).) In the hematopoietic system, STAT3 plays a key role in stem cell homeostasis as well as in the production and maturation of different types of immune cells, including granulocytes (reviewed in [Hankey, 2009](#)). Interestingly, STAT3 is required for increasing and accelerating granulocyte production during emergency granulopoiesis ([Zhang et al., 2010](#)). Similarly, constitutively activated Stat3 promotes hematopoietic stem cell expansion but only under regenerative, and not homeostatic, conditions (reviewed in [Hankey, 2009](#)). Thus, a compendium of publications now highlights STAT3 as a crucial mediator of cell regeneration under severe stress conditions. In this line, IL6-STAT3 signaling has been recently shown to enhance the regeneration of airway epithelium after inhalation injury ([Tadokoro et al., 2014](#)).

Further investigations should integrate the specific role of STAT3 signaling with those of Wnt and Notch, which are crucial

in the regulation of muscle stem cell homeostasis and also subjected to alteration with age (Yin et al., 2013). A deregulated (activated) JAK-STAT signaling in stem cells from aged or diseased muscles exemplifies the tight links between environmental cues and stem-cell-autonomous defects. As shown by the GO analysis in the paper by Price et al. (2014), satellite cells from 18-month-old mice mainly display the expression of genes associated with immune response, vasculature development, and wound healing, which are all characteristics of inflamm-aging. Ultimately, the goal of such efforts is to define therapeutic targets by dissecting the specific environmental cues leading to altered cell-autonomous signaling pathways and particularly the epigenetic alterations triggered by a prolonged exposure to an inflammatory envi-

ronment. The papers by the Sacco and Rudnicki groups show that STAT3 mediates proinflammatory signals that shift the balance of muscle stem cell activity toward their differentiation under the chronic inflammatory conditions established during aging and therefore reduces their regenerative potential. These studies pave the way toward pharmacological intervention targeting STAT3 activity to improve muscle regeneration in sarcopenia or muscular dystrophies.

REFERENCES

- Brack, A.S., and Rando, T.A. (2012). *Cell Stem Cell* 10, 504–514.
- Hankey, P.A. (2009). *Front Biosci (Landmark Ed)* 14, 5273–5290.
- Mounier, R., Chrétien, F., and Chazaud, B. (2011). *Curr. Top. Dev. Biol.* 96, 121–138.
- Paylor, B., Natarajan, A., Zhang, R.H., and Rossi, F. (2011). *Curr. Top. Dev. Biol.* 96, 139–165.
- Price, F.D., von Maltzahn, J., Bentzinger, C.F., Dumont, N.A., Yin, H., Chang, N.C., Wilson, D.H., Frenette, J., and Rudnicki, M.A. (2014). *Nat. Med.*, in press. Published online September 7, 2014. <http://dx.doi.org/10.1038/nm.3655>.
- Raz, R., Lee, C.K., Cannizzaro, L.A., d'Eustachio, P., and Levy, D.E. (1999). *Proc. Natl. Acad. Sci. USA* 96, 2846–2851.
- Tadokoro, T., Wang, Y., Barak, L.S., Bai, Y., Randell, S.H., and Hogan, B.L. (2014). *Proc. Natl. Acad. Sci. USA* 111, E3641–E3649.
- Tierney, M.T., Aydogdu, T., Sala, D., Malecova, B., Gatto, S., Puri, P.L., Latella, L., and Sacco, A. (2014). *Nat. Med.*, in press. Published online September 7, 2014. <http://dx.doi.org/10.1038/nm.3656>.
- Yin, H., Price, F., and Rudnicki, M.A. (2013). *Physiol. Rev.* 93, 23–67.
- Zhang, H., Nguyen-Jackson, H., Panopoulos, A.D., Li, H.S., Murray, P.J., and Watowich, S.S. (2010). *Blood* 116, 2462–2471.