The Journal of Physiology

PERSPECTIVES

The role of satellite cells in activity-induced adaptations: breathing new life into the debate

Michael De Lisio[1] and Jean Farup[2]
[1]School of Human Kinetics, Regenerative Medicine Program, Centre for Neuromuscular Disease, and Brain and Mind Institute, University of Ottawa, Ottawa, Canada
[2]Research Laboratory for Biochemical Pathology, Department for Clinical Medicine, Aarhus University, Aarhus, Denmark
Email: mdelisio@uottawa.ca

Satellite cells are myogenic stem cells responsible for muscle regeneration throughout the lifespan. Given their capacity to expand, differentiate, and provide a new source of nuclei to growing myofibres, their role in muscle adaptation to exercise was inferred. Early work supported this hypothesis, as satellite cell ablation by irradiation prevented muscle hypertrophy in rodent models (Rosenblatt *et al.* 1994), and satellite cell content and expansion were positively correlated with muscle hypertrophy in human resistance training (Petrella *et al.* 2008). Recently, this mechanism of skeletal muscle adaptation to exercise has been called into question. Using a model of inducible satellite cell depletion, it has been shown that satellite cells are not necessary for muscle hypertrophy in fully mature mice (Murach *et al.* 2017*b*). As such, the precise role of satellite cells in muscle adaptation to exercise is an open topic, currently under debate.

In this issue of *The Journal of Physiology*, Murach and colleagues (2017*a*) provide novel insights into the role of satellite cells in running-induced adaptations in the diaphragm, a relatively understudied muscle in the context of exercise/physical activity and satellite cell biology. Using the $Pax7^{DTA}$ inducible satellite cell depletion model, the authors questioned the necessity of Pax7+ satellite cells for diaphragm adaptations following long-term exposure to a running wheel. Based on previous studies, which have shown that satellite cell turnover is higher in the diaphragm compared to hindlimb muscle (Keefe *et al.* 2015), the authors hypothesized that satellite cell depletion would impair running-induced adaptations. Although satellite cell depletion decreased physical activity levels and resulted in a modest but significant decrease in myonuclear density in aged mice, satellite cell depletion had no impact on fibre-type or functional adaptations following wheel-exposure in adult or aged mice. Interestingly, the authors observed an increased content of Pax3 mRNA+ (Pax3+) cells in satellite cell-depleted mice. This finding led them to speculate that increased Pax3+ cell content could compensate for the depletion of satellite cells, thus providing an alternative cell source for provision of new myonuclei.

The study is well done and the conclusions are in line with the results; however, some caveats are important to consider. First, the authors chose the voluntary wheel running model of activity in the present study. This model has a number of advantages such as free access to a running wheel, which permits unlimited amounts of activity that is not associated with the psychological stress of forced treadmill exercise. Despite these benefits, this model does not allow for a controlled, progressive application of exercise stress. This is important in the context of the present study as satellite cell-depleted mice were less active than control mice and one could speculate that equal activity levels would induce a more robust phenotype. Second, the limited literature evaluating the adaptations in the diaphragm to running have primarily shown improvements in oxidative and antioxidant potential, two phenotypes not traditionally associated with satellite cells. In the present study, the authors did not observe an expansion in outcomes traditionally linked to satellite cells such as increased satellite cell content, myonuclear number, or fibre hypertrophy in control mice. These findings further question the role and relevance of satellite cells in running-induced adaptations in the diaphragm under steady state conditions. Perhaps the additional stimulus induced on the diaphragm by voluntary wheel running is not sufficiently greater than the continuous contractile activity of the diaphragm at steady state to induce significant alterations in these outcomes. However, following acute atrophy, such as in conditions of prolonged mechanical ventilation, satellite cells may be more relevant in restoring healthy diaphragm architecture. More studies will be needed to address these issues.

Overall, this work creates an interesting conundrum. If satellite cell contribution to diaphragm is high in physiological conditions (Keefe *et al.* 2015), why does satellite cell depletion fail to have any deleterious functional or morphological consequences with age or increased physical activity? Although respiratory muscle failure can be a cause of death secondary to an underlying pathology, respiratory muscle failure is not a primary pathology commonly observed in healthy older adults. Thus, perhaps sufficient reserve capacity has accumulated in the diaphragm due to its continuous low-level contractile activity. This could also serve to explain the lack of fibrotic tissue accumulation in satellite cell-depleted mice. The authors propose compensation by other cell types, specifically Pax3+ cells, to maintain diaphragm function with depleted satellite cells. Although the authors were not able to determine the extent to which new nuclei were added to the diaphragm in their study, compensation by other cells to maintain diaphragm health is plausible given the prolonged duration of satellite cell depletion. Pax3+ cells are an interesting candidate cell given their capacity for myogenesis *in vitro* and *in vivo*. Although the maintenance of myonuclear density was not complete, the Pax3+ cell accumulation may explain why the decline in myonuclear density was not more dramatic. These observations suggest that future studies should examine the role of Pax3+ cells in normal diaphragm physiology, and the extent to which myonuclear addition is necessary for diaphragm maintenance. In sum, Murach and colleagues provide important information on the necessity of satellite cells in activity-induced adaptations in the diaphragm, an often neglected skeletal muscle in the exercise/physical activity literature. Their findings open novel research directions that could have important implications for basic muscle biology, and muscle health.

DOI: 10.1113/JP274969

References

Keefe AC, Lawson JA, Flygare SD, Fox ZD, Colasanto MP, Mathew SJ, Yandell M & Kardon G (2015). Muscle stem cells contribute to myofibres in sedentary adult mice. *Nat Commun* **6**, 7087.

Murach KA, Confides AL, Ho A, Jackson JR, Ghazala LS, Peterson CA & Dupont-Versteegden EE (2017*a*). Depletion of Pax7+ satellite cells does not affect diaphragm adaptations to running in young or aged mice. *J Physiol* **595**, 6299–6311.

Murach KA, White SH, Wen Y, Ho A, Dupont-Versteegden EE, McCarthy JJ & Peterson CA (2017*b*). Differential requirement for satellite cells during overload-induced muscle hypertrophy in growing *versus* mature mice. *Skelet Muscle* **7**, 14.

Petrella JK, Kim J-S, Mayhew DL, Cross JM & Bamman MM (2008). Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. *J Appl Physiol* **104**, 1736–1742.

Rosenblatt JD, Yong D & Parry DJ (1994). Satellite cell activity is required for hypertrophy of overloaded adult rat muscle. *Muscle Nerve* **17**, 608–613.

Additional information

Competing interests

Neither of the authors has any conflict of interest.

Funding

Funding is provided by the Natural Science and Engineering Research Council of Canada (RGPIN-2017-04320) to M.D., and The Danish Council for Independent Research (5053-00195) to J.F.