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microRNA–SIRT-1 interactions: key regulators of adult skeletal muscle homeostasis?

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Skeletal muscle homeostasis is a balance between muscle hypertrophy, atrophy and regeneration. During ageing and cachexia, this balance is disrupted. Age-related loss of muscle mass and function is associated with frailty and an increase in co-mortalities and co-morbidities. Age-related muscle wasting is of particular importance in our ageing society, with significant impact on the quality of life of older people and healthcare costs. As muscle hypertrophy is often associated with increased muscle force, exercise training is used to stimulate muscle hypertrophy and strength, and therefore enhance performance and to improve quality of life. However, exercise interventions designed to improve muscle function in older subjects aim to improve the function of the residual muscle fibres but do not address the mechanistic changes occurring during age-related muscle loss.

Sirtuins are a conserved family of NAD^+-dependent deacetylases involved in the control of muscle homeostasis and the ageing process. A member of this family, SIRT-1, has been reported to regulate mitochondrial biogenesis, atrophy and myogenesis in skeletal muscle. SIRT-1 resides mostly in the nucleus, where it acts as a functional transcriptional repressor through histone deacetylation but can also directly regulate target proteins by deacetylation. Interest in SIRT-1 begun a decade ago, when activators of SIRT-1 were shown to extend the lifespan (Gomes *et al.* 2013). Since then, the beneficial role of SIRT-1 in regulating skeletal muscle mass and satellite cell metabolism, proliferation and differentiation have been demonstrated by many authors. Moreover, SIRT-1 has been proposed as part of the mechanisms associated with loss of muscle mass and function during ageing (Donghoon & Goldberg, 2013; Gomes *et al.* 2013).

A paper by Koltai *et al.* in this issue of *The Journal of Physiology* adds a new layer of information to the potential involvement of SIRT-1 in regulating muscle homeostasis by controlling muscle hypertrophy (Koltai *et al.* 2017). The authors demonstrate that overload-induced hypertrophy of the plantaris muscle is accompanied by an increase in SIRT-1 expression and SIRT-1 activity. SIRT-1-mediated regulation of muscle hypertrophy/atrophy has been previously suggested (Gomes *et al.* 2013); however, the downstream mechanisms of SIRT-1 regulation of muscle homeostasis are only partially understood. Koltai *et al.* propose a direct role of SIRT-1 in compensatory hypertrophy of skeletal muscle. The authors show that the changes in SIRT-1 levels and activity during muscle hypertrophy are accompanied by an increase in AKT levels, which regulates protein synthesis, and a decrease in FOXO1, which regulates protein degradation. The authors also suggest that SIRT-1 may contribute to muscle hypertrophy via regulating satellite cell function, which is in agreement with data showing regulation of satellite cell metabolism via SIRT-1-mediated control of autophagy (Tang & Rando, 2014). Furthermore, changes in SIRT-1 expression during plantaris hypertrophy were associated with an increase in target protein endothelial nitric oxide synthase, but an overall decrease in reactive oxygen species (ROS), suggesting a signalling role for low levels of ROS in regulating the balance between muscle hypertrophy and atrophy.

The authors further investigate epigenetic mechanisms that may regulate SIRT-1 expression in muscle during hypertrophy, focusing on small non-coding RNAs, microRNAs: emerging potent regulators of muscle homeostasis. The authors demonstrate that changes in SIRT-1 expression are concomitant with downregulation of miR-133 and miR-1 expression. This is in agreement with previously suggested roles of miR-133a and miR-1 in the inhibition of muscle hypertrophy. Changes in other microRNAs: miR-23a, miR-34a, miR-125b and miR-214, previously reported to regulate muscle atrophy, hypertrophy and/or regeneration, were also measured.

The expression of SIRT-1 has been previously shown to be controlled by microRNAs (Soriano *et al.* 2016). Our group has shown that changes in miR-181a levels in the muscle of old mice is associated with changes in SIRT-1 expression, and indeed that SIRT-1 is a direct miR-181a target gene (Soriano *et al.* 2016). Moreover, overexpression of miR-181a in C2C12 myotubes led to decreased myotube size, a phenotype probably regulated by changes in SIRT-1 expression (Soriano *et al.* 2016). Interestingly, the levels of miR-181 are downregulated in muscle from old mice, whereas SIRT-1 expression is upregulated, suggesting a compensatory mechanism occurring in muscle during ageing. This is consistent with published data suggesting a compensatory, rather than mechanistic, role of microRNAs in muscle wasting during ageing and disease. It has also been widely reported that the activity of SIRT-1 is regulated by modifications induced by ROS. However, it is likely that changes in SIRT-1 expression during muscle hypertrophy are preceded by changes in the expression of microRNAs, upstream regulators of gene expression. As a single microRNA can regulate the expression of multiple genes and SIRT-1 has been reported to be regulated by multiple microRNAs, changes in microRNA expression could be more influential than the changes in SIRT-1 alone.

In summary, the study by Koltai *et al.* opens new avenues for functional studies of molecular mechanisms regulating skeletal muscle hypertrophy, atrophy and regeneration – balance between which is disrupted during ageing. It remains to be established to what extent SIRT-1 regulates these processes, whether microRNAs, potentially through regulation of SIRT-1 expression, play a key role in controlling muscle mass and function in adulthood and ageing, or whether microRNA-regulated mechanisms are mechanistic or rather compensatory. These functional studies are necessary for design of novel, effective interventions and/or therapeutics against loss of muscle mass and function.

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Additional information

Competing interests

None declared.