Last Word on Viewpoint: Does SIRT1 determine exercise-induced skeletal muscle mitochondrial biogenesis: differences between in vitro and in vivo experiments?

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TO THE EDITOR: The proposal that SIRT1 may regulate phenotypic fiber type remodeling (from less to more oxidative) is an attempt to reconcile the substantial evidence in cell culture demonstrating a positive relationship between SIRT1 and mitochondrial biogenesis and the in vivo evidence, which has largely failed to report any such observation (1, 3, 5).

Although the commentary by Schenk and Philip (see Ref. 4) highlights the controversies that have been raised by in vivo work examining the role of SIRT1 in skeletal muscle, we suggest caution before a role for SIRT1 is discarded entirely. Interpretations of experiments performed in KO mice must consider that many KO models adapt via collateral or “redundant” mechanisms permitting a normal increase in mitochondrial content and “function” in response to exercise training. Thus these models demonstrate whether the gene of interest is essential for a normal response to exercise but do little to reveal whether the gene contributes to the response in a normal organism. This distinction is often underappreciated. To extend beyond a KO approach in vivo will be challenging but may include exercise training of mice with skeletal muscle-specific overexpression of SIRT1. In fact, the lack of an increase in mitochondrial content following (considerable) increases in SIRT1 protein via transfection is relevant strictly to basal or nonexercising conditions (3); it remains to be determined if greater SIRT1 protein facilitates a larger biogenic response following exercise.

Rather than taking a black and white approach to dismiss the ample cell culture literature in its entirety based on recent in vivo findings discussed above (1, 3, 5) we believe the divergent findings between these models may provide a broader insight into the true role of SIRT1. Despite limitations to this proposal, as discussed in our initial Viewpoint (2), one approach that may provide further insight is to view SIRT1 content across a metabolic continuum from highly glycolytic (muscle cell culture) to more oxidative (in vivo) and also in relation to the degree of responsiveness of mitochondrial biogenesis following exercise in each muscle fiber type.

Furthermore, as suggested in the commentaries by Hood et al. and Braga (see Ref. 4) there is a need for future work to approach SIRT1 research in a creative manner with an integrative focus on in vitro, cell culture, and in vivo studies designed to examine SIRT1 deacetylation of target proteins and the impact of specific SIRT1 activators, specifically those related to exercise (e.g., NAD+/NAMPT, AMPK), on downstream programs of gene transcription. More specifically, creative approaches geared towards reconciling the substantial cell culture and growing in vivo literature may suggest these apparent discrepancies are actually clues to a larger revelation—one that may unveil the specific roles (if any) of SIRT1 in human skeletal muscle.

DISCLOSURES
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AUTHOR CONTRIBUTIONS

REFERENCES

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