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Exercise-Induced MYC as an Epigenetic Reprogramming Factor That Combats Skeletal Muscle Aging

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[1]Exercise Science Research Center, Molecular Muscle Mass Regulation Laboratory, Department of Health, Human Performance, and Recreation, University of Arkansas, Fayetteville, AR; and [2]Neuropediatrics, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

JONES, R.G., F. VON WALDEN, and K.A. MURACH. Exercise-Induced myc as an epigenetic reprogramming factor that combats skeletal muscle aging. *Exerc. Sport Sci. Rev.*, Vol. 52, No. 2, pp. 63–67, 2024. *Of the "Yamanaka factors"* Oct3/4, Sox2, Klf4, and c-Myc (OSKM), the transcription factor c-Myc (*Myc*) is the most responsive to exercise in skeletal muscle and is enriched within the muscle fiber. We hypothesize that the pulsatile induction of MYC protein after bouts of exercise can serve to epigenetically reprogram skeletal muscle toward a more resilient and functional state. **Key Words:** Yamanaka factors, hypertrophy, Geroscience, DNA methylation, biological age

KEY POINTS

- Myc is a Yamanaka "epigenetic reprogramming" factor and oncogene that controls transcription, cell proliferation, ribosome biogenesis, protein synthesis, circadian rhythm, and metabolism, among other things.
- Differentiated multinuclear skeletal muscle fibers are resistant to tumorigenesis, and Myc gene and protein increases acutely but dramatically in skeletal muscle after exercise across species, including in humans.
- With aging, several hallmark adaptations to exercise training such as muscle hypertrophy are attenuated or delayed, as is Myc's responsiveness to an exercise bout.
- A controlled pulse of Myc in skeletal muscle fibers regulates more than 1300 genes and recapitulates molecular aspects of the skeletal muscle response to exercise.
- Through its role as an epigenetic reprogramming factor, pulsatile expression of Myc in skeletal muscle throughout the lifespan and/or late in life could be leveraged to cause a shift toward a more youthful and "rejuvenated" state.

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Accepted for publication: December 14, 2023.
Editor: Kimberly Huey, Ph.D., FACSM

0091-6331/5202/63–67
Exercise and Sport Sciences Reviews
DOI: 10.1249/JES.0000000000000333

INTRODUCTION

Skeletal muscle mass and function declines with aging, leading to loss of independence and mortality. This inevitable deterioration, termed "sarcopenia," is elusive in its precise definition and etiology, but the deleterious ramifications are well documented and understood (1). Exercise, and specifically hypertrophic resistance exercise, is the most widely accessible and effective therapy for combatting sarcopenia (1). Exercise is relatively simple to deploy and confers numerous benefits including increased muscle mass, strength, power, and quality throughout the lifespan (2). Unfortunately, aspects of the potency of exercise may decline in the later years of life. A dysregulated molecular response to resistance exercise characterizes aging (3), and the anabolic effects of resistance training may be attenuated or delayed beyond age 80 in both men and women (4,5). An improved understanding of what exercise-induced signals control muscle mass and function throughout the lifespan, and how those signals are altered by aging, could lead to therapeutic approaches that prevent sarcopenia and boost the efficacy of physical training.

The Geroscience field has matured over the last decade in conjunction with the identification of the hallmarks (or pillars) of aging (6–8). The list of hallmarks has expanded and evolved (8), but the overarching goal of Geroscience remains the same: accelerate research on the mechanisms of aging, in part by studying the hallmarks of aging, to find interventions that extend healthspan and potentially prolong lifespan (7). Numerous therapeutic strategies may accomplish these goals. Among them are caloric restriction and "antiaging" drug therapies such as senolytics, metformin, and rapamycin (9). Some of these interventions may modify the epigenome — that is, a layer of regulation that controls gene expression in the absence of a

modification to the DNA sequence. Recent efforts to leverage epigenetic "rejuvenation" to slow or reverse aging in preclinical models have become increasingly popular. One key epigenetic modification is the methylation of cytosines in a CpG context that can repress or promote gene transcription, known as DNA methylation. In broad strokes, relative hypomethylation of promoter regions can promote transcription while hypermethylation can repress it. DNA methylation profiling across tissues and species reveals systematic epigenetic changes throughout the lifespan that can accurately predict chronological age (10,11). Lower DNA methylation "clock" age relative to chronological age is thought to reflect younger biological age which could translate to improved health and delayed mortality.

One intervention that reverses DNA methylation age and promotes cellular youthfulness and resiliency is the induction of Yamanaka factors to elicit partial epigenetic reprogramming (10,12). Yamanaka factors were initially discovered as a strategy to induce pluripotent stem cells from differentiated somatic cells via epigenetic reprogramming (13). This discovery earned Shinya Yamanaka the Nobel Prize in Physiology or Medicine in 2012 (shared with Sir John B. Gurdon). Consistent with their function, brief systemic induction of Yamanaka factors (*Oct3/4*, *Sox2*, *Klf4*, and *Myc*, or OSKM) in mice ameliorates several hallmarks of aging *in vivo* including the age-associated impairment in skeletal muscle recovery time following injury (14). Exercise training also restores muscle regenerative capacity after injury in aged animals (15,16). Exercise is arguably the most powerful anti-aging "drug" available, yet it is still underprescribed (17,18). The extent to which Yamanaka factor induction and exercise share common mechanisms for promoting muscle health is an open area of inquiry.

Essentially all forms of exercise, either acute or chronic in rodents and humans, alter the skeletal muscle DNA methylome to influence gene expression (19). Our laboratory recently showed that late-life combined resistance and endurance exercise in mice reduced DNA methylation age in skeletal muscle (20,21). Compatible conclusions were reached in human muscle tissue with aerobic, high-intensity interval, and resistance exercise training throughout the lifespan (22). Our work showed that reduced methylation age coincided with elevated *Myc* levels (21), an altered DNA methylome specifically in skeletal muscle fiber nuclei (myonuclei), higher muscle mass, and greater *in vivo* muscle function than aged (24 months) sedentary mice (23). *Myc* is the Yamanaka factor that is most responsive to exercise in skeletal muscle (21) and is made by myonuclei during muscle loading (24). The sustained induction of *Myc* is linked to tumorigenesis, but differentiated syncytial muscle fibers are resistant to developing tumors (25,26). MYC can remain elevated in hypertrophying skeletal muscle tissue of rodents for up to 14 d without overt adverse consequence (27). We hypothesize that pulses of *Myc* transcript and subsequent MYC protein in muscle fibers serve as an epigenetic reprogramming stimulus that facilitates adaptability and a more youthful phenotype throughout the lifespan in the muscle of aged organisms. We also hypothesize that a blunted *Myc* response to resistance exercise may contribute to reduced muscle plasticity with training as aging progresses.

CURRENT UNDERSTANDING OF THE ROLE OF MYC IN SKELETAL MUSCLE

MYC is a transcription factor that regulates around 15% of the genome (28). It dimerizes with MAX and other proteins to bind DNA and regulate cell cycle, apoptosis, metabolism, circadian rhythm, ribosome biogenesis, protein synthesis, miRNA and extracellular vesicle biogenesis, and a variety of other cellular functions (28,29). Recent evidence suggests that MYC is a universal amplifier of transcription (30) and can directly bind RNA to control gene expression (31). Chronic upregulation of MYC is typically oncogenic, but overexpression in certain tissues such as the liver can serve beneficial roles such as preventing obesity and insulin resistance (32). Postdevelopmental systemic knockout of *Myc* in mice causes a premature aging phenotype characterized by low muscle mass, albeit with extended lifespan due to lower incidence of cancer in nonmuscle tissues (33). Its role as a Yamanaka factor points to its function in regulating the epigenome, and specifically DNA methylation. MYC can influence DNA methylation via its interactions with DNA methyltransferases and ten-eleven translocase enzymes that control methylation status (34–36).

The effects of MYC are well characterized in numerous tissues and in the context of cancer, but our understanding of its role in skeletal muscle is somewhat limited. MYC protein is generally not abundant in resting adult skeletal muscle but is elevated during developmental muscle growth (37,38). MYC protein is strongly upregulated in rodent muscle during surgical mechanical overload (38) and localizes to myonuclei during muscle loading in birds and rodents (39,40). *MYC* transcript peaks 3 h after acute resistance exercise in skeletal muscle of humans, remains elevated by 12 h, and returns to resting levels by 24 h (41). *MYC* is also elevated by endurance exercise in muscle, but to a lesser extent than resistance exercise (41). MYC protein is induced by resistance exercise in human muscle (42,43) and its levels associate with the magnitude of hypertrophic adaptation to resistance training in humans (44). A disproportionately higher MYC response with hypertrophic versus endurance stimuli is likely a result of MYC's influence on processes known to associate with growth, such as ribosome biogenesis. Enhanced ribosome biogenesis is a hallmark response to resistance exercise (41,45–47). The majority of studies on MYC in skeletal muscle focus on its role in driving ribosome biogenesis, translational capacity, and protein synthesis during loading-induced hypertrophy (*e.g.*, synergist ablation in rodents or resistance training in humans) (48). Despite MYC's well-documented ability to drive rDNA transcription in skeletal muscle and other tissues, it is currently unknown whether MYC induction is necessary or sufficient for adult muscle hypertrophy *in vivo*.

To provide a more detailed understanding of the role of MYC across skeletal muscles *in vivo*, our laboratory developed a genetically modified muscle-specific reverse tetracycline transactivator mouse model of pulsatile MYC induction that is controlled by the delivery of doxycycline in water (21,24). We can control the expression of MYC at will specifically in all skeletal muscle fibers *in vivo* at any point in the lifespan of the mouse using this tool. In our hands, overnight doxycycline in drinking water causes an accumulation of MYC protein in skeletal muscle 12 h after the removal of doxycycline. When MYC protein is high in skeletal muscle, we observe changes in the transcriptome that are greatest in the soleus (mixed slow- and fast-twitch, similar to human *vastus lateralis*), intermediate in the plantaris (primarily fast-twitch), and lowest in the quadriceps (mixed fiber types) (21,24). In the soleus muscle, a single

pulse of MYC altered approximately 1400 genes (21). Ribosome biogenesis-related genes were most induced by MYC, and skeletal muscle identity genes were repressed; the latter is indicative of a transient cellular reprogramming response toward "stemness," which is characteristic of Yamanaka factor expression (13).

Among ribosomal genes that were altered by MYC in muscle was Ribosomal protein large 3 (*Rpl3*) and muscle-specific Ribosomal protein large 3 like (*Rpl3l*). The induction of *Rpl3* and repression of *Rpl3l* is characteristic of muscle growth and could be related to ribosome biogenesis as well as ribosome specialization. Both processes can support the translational and metabolic demands of muscle adaptation (24). In addition to an alteration of myosin heavy chain transcripts in all muscles by MYC, it also repressed circadian rhythm genes such as *Reverbα*? and *Reverbβ*. MYC strongly influences the circadian rhythm in cancerous cells (49). Circadian clock transcription factors bind E-boxes the same as MYC. Exercise is known to affect circadian rhythms in skeletal muscle (50). Perhaps exercise-induced MYC competes with clock genes at E-boxes to affect the muscle circadian rhythm. In the plantaris muscle, the transcriptome signature from a brief pulse of MYC overlapped with the myonuclear transcriptome response to short-term mechanical overload in mice (24). MYC was also predicted as one of the most influential transcription factors controlling the myonuclear transcriptome during mechanical overload in mice, in addition to being highly enriched in myonuclei (24). These data, in context with the literature, collectively point to MYC playing a key role in regulating exercise adaptation in skeletal muscle.

MYC AND PARTIAL EPIGENETIC REPROGRAMMING IN SKELETAL MUSCLE WITH EXERCISE DURING AGING

The beneficial effects of exercise in aged skeletal muscle are numerous and should not be underestimated (18). Exercise improves muscle strength and power-producing capacity, insulin sensitivity and metabolic health, as well as muscle mass, all of which can contribute to a more youthful phenotype. Indeed, high muscle function and health is negatively associated with mortality (17,51). The functional benefits of exercise throughout the lifespan are well understood, but the mechanisms for how these benefits are controlled is unclear. We therefore hypothesized that late-life hypertrophic/endurance exercise in aged animals would share molecular features of partial epigenetic reprogramming by Yamanaka factors in skeletal muscle, as well as the induction of *Myc* (21).

To begin to address our hypothesis, we first developed an exercise training model for mice called progressive weighted wheel running, or PoWeR. This approach elicits muscle hypertrophy and faster-to-slower fiber type switching across various hind limb muscles in young (4–6 months) and aged (22–24 months) mice (23,52,53). Since Yamanaka factor induction reduces DNA methylation clock age (10), we corroborated that exercise has a similar effect on the muscle DNA methylome after 2 months of late-life PoWeR in mice (20,21). We then compared the muscle transcriptome after late-life PoWeR (21,23) to the transcriptome after brief muscle fiber-specific Yamanaka factor-mediated partial reprogramming (54). A quarter of the genes that were downregulated by late-life exercise were shared with partial reprogramming (21). These data suggest that exercise and Yamanaka factors elicit a common molecular signature in skeletal muscle. Next, we overlapped the late-life exercise transcriptome with Yamanaka factor induction as well as a pulse of MYC in muscle to further define a potentially age-mitigating molecular program. Our rationale for overexpressing *Myc* is that it is the Yamanaka factor that is most responsive to any form of exercise, but particularly hypertrophy-inducing exercise (21,41). All three interventions were associated with lower *Ndufb11* and *Romo1*; both are implicated in aging-associated dysregulation such as excessive reactive oxygen species (ROS) production and senescence (21). Finally, we profiled the muscle DNA methylome after a single pulse of MYC and found a shift in the epigenetic landscape (21). MYC altering the muscle methylome is consistent with its role as an epigenetic reprogramming factor in other cell types (34,35) and points to MYC as a regulator of the DNA methylation machinery in muscle with exercise. Since several metabolic intermediates are necessary for DNA methylation changes to ensue (55), epigenetic alterations may also be enabled by changes in cellular metabolism caused by MYC (56).

In the soleus muscle of aged mice, *Myc* is approximately 60% higher following 2 months of PoWeR when compared to the soleus of untrained controls (21,23). The mice began running 6–8 km/night beginning at 22 months of age, which is equivalent to approximately 65 y of age in humans, and the muscle was harvested 24 h after the final wheel running bout. Although *Myc* gene and protein is highly responsive to muscle loading (*e.g.*, exercise) in young adult rodents and humans, there is evidence to suggest that *Myc* in muscle is less responsive to resistance exercise in old age. Relative to young participants, MYC gene and protein in muscle is not higher at rest (57,58) but is less responsive after a bout of resistance exercise in people approximately 70 y of age (59,60). These data dovetail with classic work by Alway showing blunted MYC with mechanical loading of wing muscles in aged versus young birds (39). Unfortunately, aspects of human skeletal muscle biology can become refractory to resistance training beyond 80 y of age (4,5). We propose that pulses of MYC in muscle is a central mediator of the exercise training response throughout the lifespan and may mimic aspects of exercise to promote muscle health and curtail sarcopenia. Furthermore, periodic expression of MYC late in life could restore muscle adaptability that is reduced in old age and promote longevity and healthspan (Fig.).

CONCLUSION

MYC is a powerful transcription factor whose role in skeletal muscle is still being defined. It is highly responsive to resistance exercise in young adult rodent and human skeletal muscle and is implicated in various facets of adaptation including ribosome biogenesis and specialization, metabolism, and circadian rhythm. In its role as a Yamanaka factor, pulses of MYC may facilitate epigenetic reprogramming and contribute to exercise's ability to improve muscle health throughout the lifespan. MYC pulses combined with exercise may "supercharge" the adaptive response whereas depletion of MYC may blunt hypertrophic exercise adaptations, but more work is needed in this area. Furthermore, understanding whether MYC has muscle-specific, fiber type-specific, and/or sex-specific effects will provide further insights into how MYC influences muscle biology. Since MYC responsiveness to resistance exercise in muscle can decline later in life, restoring youthful regulation of MYC could improve muscle plasticity during aging. A deeper understanding of how MYC affects

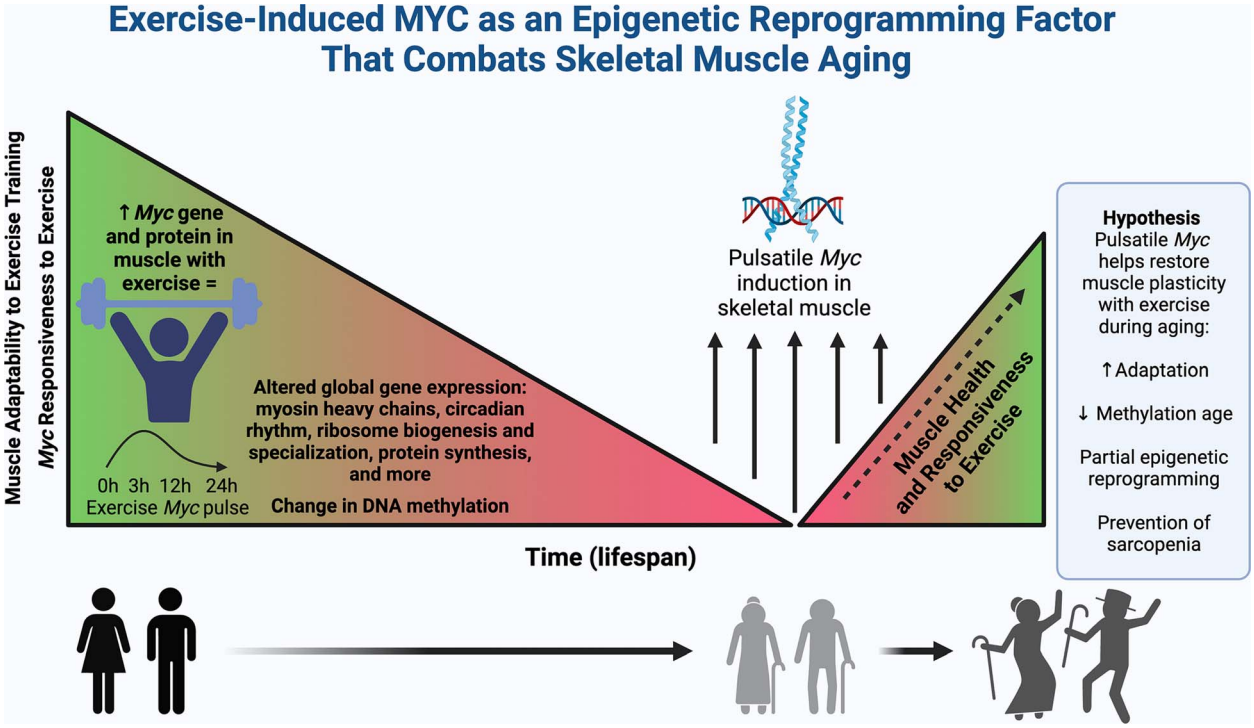

Figure. Summary of hypotheses about *Myc* in muscle with exercise and aging. *Myc* gene and protein increases acutely after exercise, and particularly hypertrophic resistance exercise, in young healthy skeletal muscle. MYC performs a variety of key functions in skeletal muscle cells and influences DNA methylation. With aging, skeletal muscle becomes smaller and weaker (*i.e.*, sarcopenia), and exercise adaptive potential declines concomitant with reduced *Myc* responsiveness to exercise. Pulses of *Myc*/MYC throughout the lifespan and late in life may attenuate sarcopenia and/or restore skeletal muscle adaptability to training. The benefits of MYC pulses in muscle may be related to partial epigenetic reprogramming (The figure was generated using BioRender).

muscle biology will help inform therapeutic approaches that ameliorate muscle wasting with aging and other conditions and clarify the mechanisms through which exercise serves as a "fountain of youth" (18).

Acknowledgments

The authors declare that they have no conflicts of interest. This work was supported by National Institutes of Health R00 AG063994 and R01 AG080047 to KAM. This research was conducted while Kevin A. Murach, PhD, was a Glenn Foundation for Medical Research and AFAR Grant for Junior Faculty awardee. The Swedish Research Council for Sport Science #2020/3 and The Swedish Research Council #2022-01392 supported FvW. Thank you to our collaborators and friends at the University of Kentucky Center for Muscle Biology and beyond that contributed to the work summarized in this article. The figure was generated using BioRender.

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