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Perspectives

PERSPECTIVES

Androgen-mediated Regulation of Skeletal Muscle Mass: A Ticking Clock

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A Perspective on "Sustained Accumulation of Molecular Clock Suppressors Period 1 and Period 2 Promotes C2C12 Myotube Atrophy Through an Autocrine-mediated Mechanism With Relevance to Androgen Deprivation-induced Limb Muscle Mass Loss"

Age-related changes in androgen metabolism, such as loss of testosterone (andropause) or estrogen (menopause), contribute to a decline in skeletal muscle function and health.[1] The underlying mechanisms of age-related muscle loss with androgen deprivation remain largely unknown, with previously published reports attempting to investigate the role of nuclear hormone receptors (eg, androgen receptors) proving futile.[2] There remains a need to identify androgen-sensitive molecular factors that contribute toward the regulation of skeletal muscle mass and function in order to develop therapeutic interventions for improving quality of life with advancing age.

The circadian clock has emerged as an important regulator of skeletal muscle homeostasis in response to various stimuli such as exercise and disease.[3,4] The molecular clock is a transcription-translation feedback loop, consisting of a positive arm in which BMAL1 and CLOCK form a heterodimer that activates the transcription of target genes (eg, *Per*, *Cry*) and a negative arm in which Per and Cry proteins accumulate and suppress the transcriptional activity of the BMAL1-CLOCK heterodimer.[4] The negative arm of the molecular clock requires deeper investigation, considering recent evidence in a *Per2* knockout mouse model highlighting changes in skeletal muscle metabolism (eg, glucose, amino acid) and function.[5] The recent paper in *Function* by Laskin et al.[6] sought to build upon previously published work on molecular clock disruption under androgen-deprivation conditions[7] by investigating the molecular mechanisms of *Per1* and *Per2* accumulation on skeletal muscle atrophy. As the authors had previously observed Per2 protein accumulation in an androgen-deprivation model,[7] the current study employed a series of experimental approaches to assess the function of *Per2* on skeletal muscle atrophy through overexpression, conditioned media, and knockout models. The authors observed significant atrophy with *Per2* overexpression in C_2C_{12} myotubes and in vivo preservation of *tibialis anterior* (TA) muscle mass with *Per2* deletion under androgen deprivation. The skeletal muscle sparing in only the TA muscle versus other hindlimb muscles (eg, *gastrocnemius*) is notable given that atrophy models, such as immobilization and hindlimb unloading, display varying degrees of reduced muscle mass between limb muscles (ie, atrophy-resistance versus atrophy-susceptible muscles).[8] This observation is an important consideration for developing strategies for mitigating skeletal muscle atrophy, where one size does not fit all. The authors also found *Per1* overexpression to induce skeletal muscle atrophy; thus, *Per1* and *Per2* appear to be pivotal negative regulators of skeletal muscle mass. The association between androgen and *Per1*/*Per2* levels on muscle mass is worth highlighting given the broader context that each is tightly controlled by negative feedback mechanisms. Like the diurnal regulation of the molecular clock by positive and negative arms, androgen levels are also diurnally regulated through negative feedback by gonadotropins.[9] It will

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be interesting for future studies to examine the interaction between the arms of each control system in the context of muscle mass regulation (ie, *BMAL1-CLOCK/Per-Cry* and androgens/gonadotropins).

To probe the mechanisms and consequences of *Per1* and *Per2* overexpression, Laskin and colleagues performed RNA sequencing analyses and identified a pro-inflammatory gene signature associated with the atrophy phenotype. The authors then collected conditioned media from *Per1* and *Per2* overexpressed myotubes and exposed control myotubes to the conditioned media, resulting in significant atrophy. These data are interesting given that inflammation has long been contemplated as a driver of the aging phenotype and may contribute to the development of age-related muscle loss.[1] Given the reported data by Laskin and colleagues, it would be prudent to explore the role of *Per1* and *Per2* in aging skeletal muscle as recent evidence has reported *Per2* to be disrupted in older individuals,[10] and mice targeted for *BMAL1* restoration display an improvement in lifespan and skeletal muscle strength.[11] In addition, the mechanisms for Per1 and Per2 protein stability warrant investigation, given that these proteins are tightly regulated via post-translational modifications, such as ubiquitination and phosphorylation, and that previous observations have reported ubiquitin ligases to regulate molecular clock protein degradation.[4] The study by Laskin et al. also raises the possibility of molecular clock proteins functioning in other models of androgen deprivation such as menopause and the consequence on age-related reductions in skeletal muscle function.

The intersection between circadian biology and muscle physiology continues to move into exciting areas and the study by Laskin et al. provides complementary data whilst highlighting many questions that remain to be pursued, including but not limited to:

- Is there an effect of *Per1* deletion in vivo on skeletal muscle metabolism and function?
- What is the impact of *Per1* and *Per2* overexpression/deletion on other clock components (eg, *BMAL1*, *CLOCK*, *Rev-erbα/β*, *Cry*)?
- Does *Per1* and *Per2* overexpression/deletion affect protein turnover?
- What is the impact of combined *Per1* and *Per2* overexpression and deletion on muscle morphology, function, and metabolism?
- What is the role of the positive arm of the muscle molecular clock on muscle mass in the context of androgen deprivation?
- In addition to the direct effects of androgen deprivation on *Per1*/*Per2* in muscle, are there also indirect contributions from disrupted endocrine feedback loops (eg, reduced pancreatic insulin production)?

Overall, the study published in *Function* by Laskin et al. expands our understanding of the role of *Per1* and *Per2* in skeletal muscle health and the influence of androgen metabolism on the negative regulators of the molecular clock. Future studies are warranted to explore the regulation of *Per1* and *Per2* in skeletal muscle function under aging and disease conditions.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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