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The Role of PRMT1 in Skeletal Muscle Hypertrophy: A Research Protocol

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Abstract

Introduction: Protein arginine methyltransferases (PRMTs) are an important class of enzymes that catalyze post-translational modification of arginine residues on histone or nonhistone substrates. In skeletal muscle, PRMT1 expression has been linked to muscle homeostasis, regeneration, metabolism, and synthesis. The expression of PRMT1 in skeletal muscle has already been shown to be induced by treadmill exercise, however, the relationship between PRMT1 and skeletal muscle hypertrophy remains unexplored. This study aims to determine the significance of PRMT1 in muscle hypertrophy by identifying whether wild-type mice (WT) experience elevated levels of exercise-induced muscle hypertrophy compared to PRMT1-knockout mice (KO).

Methods: 12-month-old mice will be split into male (M) and female (F) groups. Both M and F groups will then be randomly distributed to WT and KO groups. WT M, KO M, WT F, and KO F groups will be further randomly divided into sedentary (SED) and exercise (EX) groups. EX groups will undergo a resistance training program for 8 weeks while SED groups will be at rest. All mice will be euthanized by cervical dislocation while at rest by the end of the 8 weeks, and their tissue samples will be collected. The progression of muscle hypertrophy between groups will be assessed weekly using Bioseb grip strength tests in grams normalized to body mass in grams (g/g). Following the 3 months, muscle biopsies of the gastrocnemius (GAS) muscle will be taken to perform fluorescence staining of the myofibers. Primary and secondary antibodies against myosin heavy chains I, IIa, IIx, and IIb will be used to stain cross-sectional areas (CSA). The CSA of the fast-glycolytic fibers will be measured to quantify muscle hypertrophy between WT and KO groups.

Anticipated Results: The Bioseb grip strength tests and GAS immunostaining should demonstrate that WT mice have greater grip strength and myofibers with larger CSAs compared to KO mice.

Conclusion: These results would demonstrate the importance of PRMT1 in facilitating exercise-induced muscle hypertrophy. Future directions may involve exploring downstream signaling molecules of PRMT1 to identify potential PRMT1 up regulators, accelerating muscle hypertrophy and combating pathological muscle atrophy.

Keywords: post-translational modification, arginine methylation, hypertrophy, skeletal muscle, exercise

Introduction

Arginine methylation is a post-translational modification that regulates histone and nonhistone substrates in several cellular processes [1]. PRMT1 is the most abundant among 9 identified protein arginine methyltransferases (PRMTs) and is responsible for at least ~85% of all arginine methylation in human cells [2]. PRMT1 involves diverse biological processes, including cell survival, gene transcription, DNA damage responses and hepatic glucose metabolism [3]. Removal of this enzyme causes embryonic lethality, emphasizing its importance in cell maintenance. Investigations in non-muscle cell types discovered that PRMT1 regulates nonhistone substrates such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), estrogen receptor, and forkhead box O1, which collectively regulate muscle phenotype determination and remodeling [4-6]. PRMT1 is also expressed in skeletal muscle and muscle progenitors. A recent report has revealed a critical role for PRMT1 in muscle regeneration by using a satellite cell-specific PRMT1 deletion mouse model [7]. Subsequently, a study by Choi et al., using a myosin, light polypeptide 1 (Myosin Light Chain 1/Fast-type Myosin Light Chains)-Cre driven PRMT1-deletion mouse model, demonstrated that PRMT1 regulates skeletal muscle function. They illustrated that this enzyme is critical for muscle maintenance and that deficiency leads to muscle atrophy [8].

Skeletal muscle hypertrophy is characterized as an increase in myofibers' size and levels of protein synthesis [9]. While many stimuli induce skeletal muscle hypertrophy, mechanical signals are arguably the most

intuitive. The proposed downstream hypertrophy signaling mechanism is controlled by rapamycin complex 1, which stimulates protein synthesis and initiates a hypertrophic response [10]. Previous studies have established the relationship between mechanical stimuli and muscle hypertrophy in 3 ways [10]. Firstly, skeletal muscle undergoes atrophy when it becomes immobilized, suggesting that a threshold level of mechanical stimuli is required to maintain a baseline muscle mass. Secondly, it has been shown that mechanical overload of skeletal muscle can induce hypertrophy. Lastly, low-load endurance exercises cause little or no hypertrophy, while high-load resistance exercises lead to comparably more elevated levels of hypertrophy [10]. Although resistance training has been linked to the development of muscle strength and size, many factors can affect the robustness of this relationship [11]. One such variable is sex, as previous studies have demonstrated that following procedural resistance training, the muscle mass of male mice increased comparably more than that of female mice [11].

While past research has begun to reveal the role PRMT1 plays in the maintenance of muscle mass and atrophy, research has yet to explore whether skeletal muscle hypertrophy is PRMT1-dependent. Using a PRMT1 skeletal muscle-specific knockout mouse model, our study seeks to demonstrate that the exercise-induced alterations in this enzyme are compulsory in the process of skeletal muscle hypertrophy and that its absence prevents the undertaking of the hypertrophic processes. Additionally, we will explore sex-based differences in WT and KO mice, furthering our understanding of the role PRMT1 plays in skeletal muscle. By comparing the degree of skeletal muscle hypertrophy following a resistance training program, our study will be the first to ascertain that this enzyme is necessary for chronic resistance training-induced skeletal muscle hypertrophy and how sex affects these animals' response to an exercise stimulus.

Methods

Mouse Model & Genotype

This experiment requires mice to adapt to an exercise routine and regularly perform physical exercise over a period of 8 weeks. C57BL/6 mice are a suitable mouse strain for these conditions as they are physically active and capable of learning various tasks. [12] Additionally, Vanlieshout et al. have also selected this mouse strain in an experiment involving exercise-induced skeletal muscle PRMT1 expression. [13]

Mice will be generated as per previous experiments [8]. KO mice will be created using a Cre-loxP system. Prmt1flox/flox mice will be crossbred with mice that express the Cre gene with a MyL1 promoter [8]. Their offspring will possess both Cre recombinase and Prmt1flox/flox, allowing the Cre recombinase to bind to loxP sites and cleave out the PRMT1 gene, resulting in PRMT1-knockout mice [8,14]. According to Choi et al., the presence of the MyL1 promoter acts as a control mechanism which restricts the Cre-loxP system to function only within skeletal muscle, as this promoter is mainly active in postmitotic type II myofibers [8].

In this study, 12-month-old WT and KO mice will be housed in an environmentally controlled room and be provided with food and water ad libitum [15]. All protocols will be approved by the University Animal Research Ethics Board, operating under the auspices of the Canadian Council for Animal Care.

Experimental Groups

For resistance training, 12-month-old mice will be separated into two groups according to sex. According to Choi et al., the body weights of KO mice become significantly different at 12 months following the knockout [8]. The M and F groups will be further divided into WT or KO mice. Each of the four groups (WT M, KO M, WT F, KO F) will then be randomly assigned to one of the following experimental groups: 1) sedentary (SED) animals, or 2) mice challenged with a resistance training program for 8 weeks (EX). Overall, the 12-month-old mice should be split into 8 groups: WT SED M, WT EX M, KO SED M, KO EX M, WT SED F, WT EX F, KO SED F, and KO EX F. All mice will be provided food and water ad libitum [15].

Training Apparatus & Procedure

The training regimen will be adapted as previously described [15]. The exercise group will be individually placed in a modified version of the resistance training apparatus for mice [16]. Each mouse will be placed in a 275cm x 437cm x 225cm Plexiglas box with aluminum flooring. A 150mm glass rod fitted with a light source that can be toggled off/on is attached to one side of the box, 50 mm above the floor. This will be referred to as the low bar. On the opposite wall, another 150mm glass rod fitted with a light source that can be toggled off/on is attached to the side of the wall, 200mm above the floor. This will be referred to as the high bar. If downward pressure is applied to the high or low bar while illuminated, it will toggle the light source off [15].

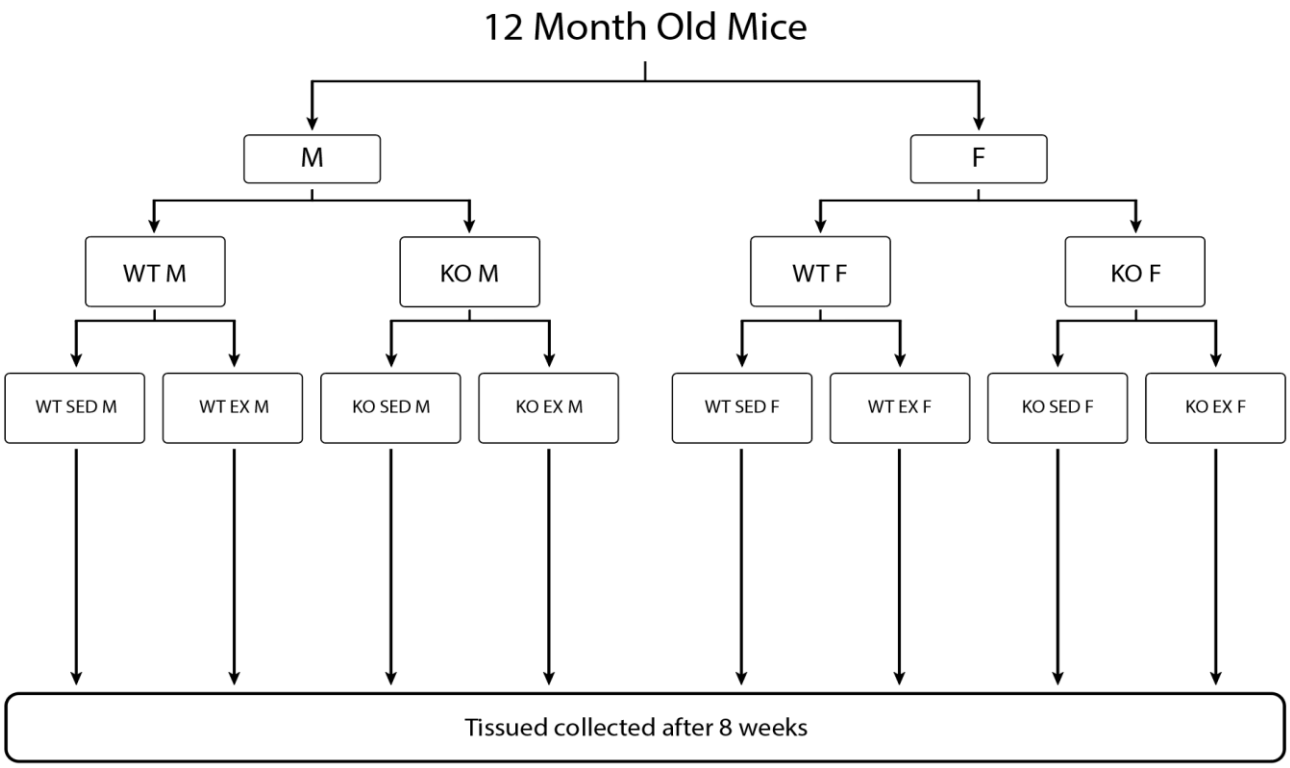

Figure 1. Flow diagram of study design**.** 12-month-old mice will be split into male (M) and female (F) groups. Both M and F groups will then be randomly distributed to wild-type (WT) and knockout (KO) groups. WT M, KO M, WT F, and KO F groups will be further randomly divided into sedentary (SED) and exercise (EX) groups. EX groups will undergo a resistance training program for 8 weeks while SED groups will be at rest. All mice will be euthanized by cervical dislocation while at rest by the end of the 8 weeks, and their tissue samples will be collected. Figure created with Adobe Illustrator.

The mice will undergo an entrainment process where either the low bar or high bar will be illuminated, and they will have 5 seconds to press on the illuminated bar to avoid an electric shock (1 mA, 60 Hz) [16]. The low and high bars will be illuminated sequentially to facilitate body movements requiring the mice to fully extend their hindlimbs. Each mouse will undergo four different 30-minute entrainment sessions, with each session separated by 72 hours [16]. Upon successful entrainment, a Velcro vest will be fitted onto the exercise group. Weights can be attached to the Velcro vest to create resistance [16].

The training procedure will be adapted from previous experiments [15-16]. 24 hours after the final entrainment session, the mice will begin the resistance exercise protocol [15]. During the 8-week training period, the exercise group will be individually placed into a training apparatus. A weight of around 10% of the mouse's current body mass will be attached to its Velcro vest to create resistance [15]. Similar to the entrainment process, the low bar and high bar will be illuminated sequentially, and the mice will have 5 seconds to press on the illuminated bar to avoid being shocked (1 mA, 60 Hz). During each training session, the mice will perform 3 sets of 8 reps, each consisting of a low bar press followed by a high bar press. Training sessions will be separated by 24 hours of rest. At the 2/4/6-week mark, the weights attached to the Velcro vests will be raised to 12.5%/15%/17.5% of the mouse's current body mass, respectively [16].

Bioseb Grip Strength

To compare the progression of muscle hypertrophy between the KO and WT mice, a Bioseb forelimb and hindlimb grip strength test will be performed before training and at the end of each week of the 8-week exercise program. Before training, the mice will undergo an acclimatization process, where they will perform 5 pulls in 1 set. During the test, the mice will be held by their tails, allowing their limbs to grasp the grid [17]. The mice are then gently pulled backwards by their tail until they let go of the grid [17]. Each test will be performed 3 times in 15 sets, with the average recorded in grams per gram of body weight for statistical analysis [17].

Isolation of Gastrocnemius Muscle

Following completion of the exercise program, the mice will be euthanized under anesthesia according to the University Animal Research Ethics Board regulations at least 48 hours following completion of the resistance training program [18]. Tissues from SED groups will be collected simultaneously as those from EX groups. Each mouse's GAS muscle will be isolated immediately after euthanization, as it is a muscle that reflects the training regimen's emphasis on plantar flexion. The whole muscle will be snap-frozen at optimal cutting temperature and then sectioned into 7-µm thick fragments using a cryostat microtome before immunostaining [8].

Immunostaining

A muscle section will be fixed, permeabilized, and incubated with appropriate antibodies. Antibodies against myosin heavy chain I, IIa, IIx, and IIb myofibers and their respective secondary antibodies will be used [19]. Images will be captured under Nikon ECLIPS TE-2000U and NIS-Elements F software (Nikon, Tokyo, Japan). Myofibers will be traced using a multi-color immunofluorescence analysis, and their area will be measured using NIS-Elements F software (Nikon). Each of the 4 myofibers in this study will be marked independently [19]. The CSA in units of μm^2 will be measured to quantify muscle hypertrophy between groups [8].

Statistical Analysis

Values are expressed as means ±SEM. As appropriate, the statistical significance will be calculated using an ANOVA with Tukey's post hoc test. Differences will be considered statistically significant at or under values of $p < 0.05$ [20].

Anticipated Results

After 8 weeks of exercise training, we anticipate the Bioseb Grip Strength tests to show varying results between experimental groups. Based on past literature, we expect M to be stronger than F, and overall, KO animals should display decreased strength [8,11]. This also suggests that KO SED and EX groups will experience less skeletal muscle hypertrophy compared to WT SED and EX groups, respectively [8].

Immunostaining provides information on the CSA of type IIb myofibers [19]. IIb will be the myofiber in focus, as previous work has revealed that these fibers undergo the most extreme alterations in response to resistance training [21]. Previous literature states that the CSA of myofibers is generally larger in EX groups than in SED groups due to hypertrophy. It is also reasonable to assume a noticeable increase of CSA in WT EX groups as to KO EX groups, while WT SED groups should maintain IIb CSA slightly better than KO SED groups despite the lack of exercise [22]. F groups should also have less IIb CSA with respect to their M counterparts [11].

Discussion

The anticipated results section was established after careful consideration of previous scientific literature, as skeletal muscle hypertrophy has been correlated with increased grip strength and IIb CSA [8]. It has been well-established from past literature that exercise induces skeletal muscle hypertrophy, therefore, EX groups should experience more skeletal muscle hypertrophy compared to their respective SED groups [9]. A previous paper by Choi et al. stated that PRMT1 KO mice experience increased muscle atrophy compared to WT mice at rest [8]. It is reasonable to assume that under hypertrophic conditions, atrophy would remain higher in KO than WT mice as past research has shown that resistance training decreases atrophy [23]. Therefore, KO SED groups should have lower grip strength and type II myofiber CSA compared to WT SED groups, as these measures are decreased during elevated atrophic conditions. Moreover, WT EX groups are expected to show increased skeletal muscle hypertrophy compared to KO EX groups [8,21-22]. We came to this conclusion after assessing previous studies which stated that in humans, PRMT1 could affect various molecules that regulate skeletal muscle plasticity, including PGC-1α, E2F transcription factor 1, receptor-interacting protein 140, and tumor-suppressing protein p53 [24]. We anticipate that KO EX mice will have impaired ability to regulate these molecules due to lower levels of PRMT1 expression, thus, resulting in decreased skeletal muscle hypertrophy. Lastly, regarding gender differences, F groups were shown to have blunted muscle hypertrophy compared to their M counterparts [11].

This study will reveal if PRMT1 is necessary for chronic resistance training-induced skeletal muscle hypertrophy. Future explorations examining downstream intracellular molecules and pathways would aid in understanding this enzyme's role in skeletal muscle. For example, changes in PRMT1 expression have been shown to have downstream effects on the levels of adenosine monophosphate-activated protein kinase, lipid-modified microtubule-associated proteins 1A/1B light chain 3B, and forkhead box O3 [8]. Thus, exploring these molecules in the context of a chronic exercise program would be worthwhile. Additional work exploring protein levels of PRMT1 and the above-mentioned downstream molecules in response to the chronic exercise program would also reveal PRMT1s role in hypertrophy. Moreover, if a distinct pathway for PRMT1 in skeletal muscle hypertrophy is identified, the findings can be compared to pathological skeletal muscle pathways in neuromuscular diseases to see if there is any convergence. A shared pathway of PRMT1 and neuromuscular diseases would allow for the development of PRMT1-based therapeutics for neuromuscular diseases, where PRMT1 upregulation in damaged tissue may initiate or accelerate tissue remodeling.

It is important to note that there are some limitations to the proposed research protocol. Firstly, the proposed methods do not measure the amount of PRMT1 or

determine its precise location during or after exercise. Secondly, this study will not look at downstream molecules of PRMT1 that may also be affected by chronic exercise, even though previous research suggests PRMT1 plays a role in various molecular pathways that may be altered by exercise training [8]. Lastly, this study only looked at the GAS muscle for immunostaining as opposed to a variety of hindlimb muscles, ignoring the potential of different levels of exercise-induced hypertrophy in various muscles across the body.

Conclusion

This study proposes a protocol to identify the role of PRMT1 in exercise-induced hypertrophy. Using the bioseb grip strength, immunostaining and CSA results, this study will demonstrate the significance of PRMT1 in exercise-induced muscle hypertrophy. In general, we expect more hypertrophy in WT, EX, and M mice groups as opposed to KO, SED, and F mice groups, respectively [8,11,21-22]. Overall, this work will illustrate the importance of PRMT1, exercise, and gender as essential factors in skeletal muscle hypertrophy.

List of Abbreviations Used

CSA: cross-sectional area
EX: exercise
GAS: gastrocnemius
KO: knockout
PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PRMT: protein arginine methyltransferases
SED: sedentary
SEM: standard error of the mean
WT: wildtype

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

All experimentation will be conducted in accordance with the Canadian Council for Animal Care (CCAC).

Authors' Contributions

AS: Contributed to the design, planning, and methods of the study, reviewed background information, revised the manuscript, and gave final approval of the version to be published.
NH: Contributed to the design, planning, and methods of the study, reviewed background information, revised the manuscript, and gave final approval of the version to be published.
KY: Contributed to the design, planning, and methods of the study, reviewed background information, revised the manuscript, and gave final approval of the version to be published.

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