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The Role of p53 in Skeletal Muscle Adaptation During Exercise: A Literature Review

Amber Lu, BKin Student [1]*

[1] School of Kinesiology, University of British Columbia, Vancouver, British Columbia, Canada V6T 1Z1

*Corresponding Author: alu10@student.ubc.ca

Abstract

Introduction: Due to its natural relationship with physiological health, skeletal muscle has been studied in a variety of contexts. Most commonly, it is analyzed during exercise to determine the adaptations caused by specific homeostatic imbalances. These imbalances pushed for more research in p53, a tumour suppressor known for regulating cellular stability.

Methods: This literature review will be a narrative review using primary studies to determine the role of p53 in hypertrophy, mitochondrial biogenesis, and angiogenesis of skeletal muscles during exercise.

Results: Differences in gene expression related to hypertrophy, mitochondrial biogenesis, and angiogenesis were observed during skeletal muscle adaptations dependent on p53 content and activity during and after exercise.

Discussion: p53 content level was shown to contribute to skeletal muscle atrophy immediately following exercise, while having minimal effect on mitochondrial biogenesis. Rather, p53 activity was seen to be a more likely effector of mitochondrial levels. Moreover, through indirect pathways, p53 appears to negatively correlate with increases of angiogenesis in skeletal muscle.

Conclusion: Research on p53 continues to express the importance of the protein beyond its role as a tumour suppressor. This review highlights alternative roles of p53 by analyzing its interactions in relation to exercise-induced adaptations of skeletal muscle.

Keywords: p53; skeletal muscle; hypertrophy; mitochondrial biogenesis; angiogenesis; exercise

Introduction

Skeletal muscle is one of the largest organs of the human body, contributing to 40% of total body mass and comprising 50-75% of the body's total number of proteins [1]. Human skeletal muscle consists of three different fibre types (type I, type IIa, and type IIx) each associated with different size, contractile and metabolic phenotype, and capillarization [2,3]. Skeletal muscle plays a direct role in human health by regulating blood glucose levels; dictating basal energy metabolism; and producing locomotion for individual mobility [1].

Exercise is a well-established stimulus to promote skeletal muscle adaptation, with certain modalities eliciting specific adaptations. Resistance exercise, for instance, is an anaerobic activity involving muscle overload, causing adaptations such as hypertrophy [4]. In contrast, endurance exercise involves prolonged aerobic movement to enhance oxidative capacity through mitochondrial biogenesis and angiogenesis [5]. Hypertrophy is a process typically associated with resistance exercise, where cellular proteins such as myofibrillar or sarcoplasmic proteins are increased in pre-existing muscle fibre resulting in an overall increase in muscle mass [6]. This is significant as the increased mass promotes increased resting metabolic rate, decreased body fat, and stabilized physical ability while aging [7]. Mitochondrial biogenesis is the creation of new components of the mitochondrial retinaculum to promote an increase in skeletal muscle oxidative capacity and metabolism [8,9]. Angiogenesis is the growth of new capillaries from pre-existing blood vessels leading to an expansion of the microvascular network to increase oxygen and nutrient transport into active skeletal muscle [10].

Protein 53 (p53) is a well-known tumour suppressor protein primarily studied for its ability to prevent cancerous tumours. The gene is present on chromosome 17 of human deoxyribonucleic acid (DNA) and is made up of 393 amino acids, 5 conserved regions, and a loop-helix structure [11]. As a tumour suppressor, p53 has many cellular niches, notably DNA repair and apoptosis [12]. This process begins with p53 acting as a transcription factor which binds to the promoter of target genes to trigger cell cycle arrest [11]. After that, p53 either undergoes DNA repair of the cell or apoptosis to fix or prevent possible tumour growth [12]. The p53 gene usually remains inactive, only activating when the cell experiences stress or undergoes continuous cell division and proliferation [11]. Because of its relation to cell stress,

p53 has also been found to have a role in skeletal muscle adaptability in response to exercise-related cell stress.

The aim of this review is to expand on previous knowledge about p53 by investigating studies that analyze beyond its function as a tumour suppressor. This is in hopes to further understand the complex roles of p53 in bodily health. As such, this review will discuss findings on p53 in relation to skeletal muscle adaptation. Specifically, it will focus on the role of p53 in hypertrophy, mitochondrial biogenesis, and angiogenesis in response to exercise.

Methods

A narrative literature review was conducted using relevant articles under the topic. The articles included primary studies sourced from PubMed. Key words in the initial search included "hypertrophy" OR "mitochondrial biogenesis" OR "angiogenesis" AND "skeletal muscle" AND "exercise" AND "p53". As well, further searches included broader terms such as "mitochondria", "atrophy", "capillary", or "endothelial cells". Articles including alternative methods for skeletal muscle adaptation were included to support key findings. However, articles were excluded if p53 was mutated, such as through Li Fraumeni Syndrome.

Results

Hypertrophy

Hypertrophy is the elevation of protein synthesis and muscle mass resulting from repeated overload stress [13]. In opposition, atrophy is the weakening and decrease in muscle mass and fibre cross-sectional area following muscle disuse [14]. Exercise has been extensively studied to both combat muscle atrophy and promote hypertrophy, particularly through resistance training. As well, previous research has already established a possible relationship between p53 and sarcopenia [15]. Thus, there is a natural role p53 can play when analyzing its activity during exercise-induced hypertrophy.

In a study done by Zolfaghari et al. (2022) analyzing treadmill running on diabetic Wistar rats, p53 content was found to be lower following 8 weeks of endurance training compared to the control [15]. However, within the same study, resistance training through weighted climbing did not have any observed effects on p53 levels, suggesting training modality specificity in relation to p53 protein content. This conclusion differed from Chen et al. (2002) who also tested resistance training on Wistar rats and found that, compared to the control, p53 content levels were greater 1 hour post-exercise than 6 hours post-exercise [16,17]. This adheres to a similar finding from Siu and Alway (2005), where the p53 content of unloaded wings of Japanese Coturnix quails were analyzed and found to undergo atrophy following 14 days of unloading [13]. During this, no significant difference in nuclear or cytoplasmic p53 levels was identified in the aged quails, whereas the younger quails had greater nuclear and cytoplasmic p53 content at 7 days of unloading compared to the control group [13]. At 14 days of wing unloading, the younger quail wing p53 levels were like that of the controls [13]. This gradual decrease in p53 following hypertrophy is comparable to the decrease in content seen by Chen et al. (2002) [16]. Within both studies, p53 content following stimulation increased above control levels and slowly decreased with time.

The mechanism of p53's regulation of muscle atrophy has also been suggested. It has been elucidated that p53's role as a mediator of apoptosis-regulatory factors [13], particularly involving mitochondrial quality control [18], results in muscle atrophy regulation. Cytochrome c is a protein released in response to mitochondria apoptosis [18]. Under basal conditions, cytochrome c release was greater in subsarcolemmal mitochondria of p53 knock-out (KO) mice skeletal muscle than in p53 wildtype (WT) mice [18,19]. Alternatively, intermyofibrillar mitochondria had a reduction in cytochrome c release in knock-out mice compared to wildtype mice at basal conditions [18,19]. Following endurance training, skeletal muscle displayed an increase in hypertrophy while cytochrome c release rate in subsarcolemmal mitochondria fractions was demonstrated to decrease along with DNA fragmentation, genetic damage commonly occurring during apoptosis. As well, this correlated with an increase in p53 phosphorylation [18,19] which was seen to also attenuate Bax, a downstream, pro-apoptotic effector protein, levels [19]. Conversely, p53 content levels were seen to have a positive correlation with the Bax protein during both muscle atrophy from disuse and muscle hypertrophy from aerobic training [20,21]. Furthermore, research carried out by Rezaee et al. (2021) found that during the decline of p53 and Bax with training, Bcl-2, an anti-apoptotic protein, increased [21]. This resulted in a decrease in the Bax/Bcl-2 ratio which has been found to activate apoptotic reactions through the release of cytochrome c [21].

Mitochondrial Biogenesis

It is a well-known fact that mitochondria are the primary source of energy for cellular activity [22]. During exercise, mitochondria support skeletal muscle through ATP synthesis, metabolic exchange, and calcium ion regulation. However, due to the elevation of needed support, more mitochondria are created through mitochondrial biogenesis [23]. Mitochondrial biogenesis refers to the growth and division of pre-existing mitochondria, increasing mitochondrial volume density [24]. In research, biomarkers are typically used to analyze changes in mitochondrial biogenesis. Notable markers in this section include mitochondrial transcription factor A (TFAM), peroxisome proliferator-activated receptor-gamma coactivator–1 alpha (PGC-1a), and cyclooxygenase (COX) for their established relationships with p53 [24].

Transgenic models have allowed for the elucidation of the role of p53 with respect to exercise training and

mitochondrial adaptation. In studies comparing p53 wildtype and knock-out mice, no difference has been described regarding improvements of endurance capacity between genotypes. In many reports, a decrease in subsarcolemmal and intermyofibrillar mitochondria [18,25] or mitochondrial regulator levels [19] in untrained KO mice is mentioned providing evidence that p53 does have some effect on mitochondrial content levels. Saleem et al. (2009) analyzed a similar trend where WT p53 mice had a greater trained endurance capacity compared to knockout mice indicated by a longer developed running distance [18]. During these trials, COX activity in both WT and KO mice displayed an increase in mitochondrial activity while having similar increases in mitochondrial content levels [18]. = This differed from Park et al. (2009) who found lower levels of mitochondrial content within p53 KO animals [25]. Moreover, Park et al. (2009) also described decrements in skeletal muscle mitochondrial respiration and VO2max [25]. In accordance with this attenuated oxidative capacity in KO animals, Park et al. (2009) reported submaximal exercise to induce three times more blood lactate in p53 KO mice [25].

Along with p53 content levels, p53 phosphorylation has also been studied during exercise. Previously, phosphorylation of p53 on Ser15 has been seen to increase with acute contractile activity via electrical stimulation of the gastrocnemius muscle occurring concurrently with increases in AMPK and p38 phosphorylation [18]. This was supported by BeyFuss et al. (2018) that found an increase in mitochondrial S15-p53 following an acute bout of exercise in trained animals [19]. Despite this, mRNA transcripts of genes involved in mitochondrial biogenesis were not determined to have differed significantly between trained WT and p53 KO mice. Furthermore, training had no effect on TFAM or PGC-1a which is comparable to Park et al. (2009) findings [25]. Many of these findings can be supported when studying CHCHD4, a mediator of p53 mitochondrial translocation. Overexpression of the gene has been seen to increase translocation of p53 into the mitochondria 60 minutes post endurance exercise, decreasing levels in the nucleus [26]. Zhuang et al. (2016) found that p53-induced genes increase with time post-exercise, correlating with CHCHD4 mRNA expression [26].

Angiogenesis

Angiogenesis, the formation of new blood vessels from pre-existing vessels, is critical for supplying oxygen and nutrients to body tissues. Particularly during exercise, when muscle homeostasis is disrupted, angiogenesis is vital to reestablish the balance between metabolic activity and blood supply in skeletal muscle [27]. This is carried out through two processes, either 'sprouting' or 'intussusceptive' angiogenesis. Sprouting occurs in response to muscle activity while splitting occurs in response to increased blow flow [28]. In previous research, angiogenesis has been commonly identified through increases in vascular endothelial growth factor A (VEGF-A) or decreases in thrombospondin-1 (TSP-1) [29]. Consequently, the VEGF-A/TSP-1 ratio has also been an accurate tool to determine changes in angiogenesis [27]. Unlike other muscle adaptations to exercise, murine double minute 2 (MDM2) is emphasized over p53 as a gene of interest due to the previous studies connecting MDM2 with VEGF and other pro-angiogenic genes in sedentary conditions [30]. However, p53 is still considered due to its interaction with MDM2 and anti-angiogenic functioning [30].

In a study conducted by Roudier et al. (2010) where capillary regression was seen following hindlimb unloading, female Wistar rats displayed two significant increases in p53 expression [27]. Initially, p53 acutely increased at 12 hours of unloading, followed by a gradual increase from day 3 to 9 of unloading. Moreover, TSP-1 expression also elevated during hindlimb unloading, however, this was not determined to be significant until day 5. From there, TSP-1 continued to increase until day 7, when it peaked, and a decrease was seen from day 7 to 9 [27]. This study saw an elevation in p53 followed by similar elevation patterns in TSP-1 and the capillary-to-fibre ratio in the soleus muscle [27]. In the same study, the soleus muscle of the female Wister rat did not show any change in TSP-1 expression and had an increase in the pro-angiogenic VEGFA/TSP-1 ratio during hindlimb unloading, which indicated possible differences in angiogenic adaptations for glycolytic and oxidative muscle types [27]. However, p53 expression was unnoted for the plantaris. leaving room for further research on p53's role in muscle-specific angiogenesis based on fibre type distributions or contractile phenotypes of respective muscles.

Following previous research, Roudier et al. (2012) completed another study analyzing the relationship between p53, MDM2, and exercise-induced adaptations of angiogenesis [30]. Within female Sprague Dawley rats, endurance training enhanced MDM2 protein and skeletal muscle angiogenesis in the plantaris [30]. However, when observing mice with mice with ~30% MDM2 and enhanced p53 activity, p53 was found to have no effect on capillarization levels [30].

Discussion

With the various roles skeletal muscle has in exercise, mobility, and health, it is understandable why it receives considerable attention in research. Exercise is a natural way to provide information about bodily health through its ability to promote cellular adaptations. P53 is typically studied in cancer research as a tumour suppressor for its ability to regulate DNA repair and apoptosis [12]. However, through this review, p53 was also shown to have a significant role in skeletal muscle adaptations during exercise.

Hypertrophy

Through further interpretation, the observed differences could be attributed to a couple factors. Firstly, the momentary increase in p53 that slowly decreased post-exercise, seen by Chen et al. (2002), was caused by a single session of tetanic contractions [16]. This differed from the study by Zolfaghari et al. (2022) which involved 8 weeks of adaptation and 72 hours of recovery before the muscle biopsy [15]. As such, it is possible that with a longer timeframe for adaptation, Chen et al. (2002) would have also lacked any observable changes in p53 post-resistance training. Additionally, certain differences in findings could be due to sex differences as Chen et al. (2002) tested male Wistar rats while Zolfaghari et al. (2022) tested female Wister rats [15,16]. Furthermore, it is possible that differences in the metabolic health of the two models could represent a variable confounding the experimental results. For instance, diabetic Wistar rats have been found to have more pronounced muscle hypertrophy due to an increase in activation and expression of associated genes which could thus alter the cellular milieu and affect p53 expression [17]. Another possibility causing the differences in p53 content following resistance training includes the ages of the rats tested. Zolfaghari et al. (2022) tested older rats (with an average age of 21 months), while Chen et al. (2022) tested younger rats (around 6-7 weeks) [15,16].

Despite these differences, other studies have determined a correlation between p53 and skeletal muscle atrophy [19,21]. As well, it is likely that p53 also regulates atrophy through apoptosis and mitochondrial quality control [19,21]. Given the findings, it is possible to suggest that p53 content levels decrease during aerobic and endurance exercise, resulting in Bcl-2 protein increasing while Bax protein decreases [20,21]. Then, following muscle disuse post-training, atrophy occurs as p53 increases Bax levels, releasing cytochrome c, causing DNA fragmentation [18,19].

Mitochondrial Biogenesis

While studies have seen altered mitochondrial content levels while studying KO and WT mice, the exact relationship between p53 and exercise training adaptations is still unclear [18,19,25]. The study done by Saleem et al. (2009) suggested that p53 content levels do not have a direct effect on mitochondrial biogenesis, but rather a role in influencing mitochondrial function [18]. Despite this, p53 may still have its role in mitochondrial biogenesis. Studies analyzing p53 phosphorylation on Ser15 found that an increase in p53 phosphorylation also elevated genes associated with mitochondrial biogenesis [19].

Angiogenesis

Research by Roudier et al. (2010) found similar elevation patterns in TSP-1 and the capillary-to-fibre ratio following p53 increases [27]. Given this finding, and research supporting p53 as an indirect regulator of TSP-1 through co-factors [31], p53 was determined as an indirect inhibitor of angiogenesis during muscle-induced adaptations [27]. However, this contrasted with Roudier et al. (2012) who observed that MDM2's role in angiogenesis is p53 independent [30]. Possible distinctions could be attributed to the fact that this study [30] examined sedentary mice with reduced MDM2 expression and p53 activity, while the previous study [27], analyzed hindlimb unloading and p53 expression in rats.

Conclusions

Skeletal muscle is a commonly studied field within a multitude of areas. As a primary muscle group, it has a multitude of applications in health, metabolism, and mobility. Most commonly, it is significant when analyzing the intersections of exercise and physiological health. These have been studied by comparing active and sedentary animals and using various exercise modalities and artificial simulations, such as electrical stimulation and unloading. In this review, skeletal muscle is targeted specifically for its natural relationship with exercise-induced adaptations. Due to previous research correlating increased exercise capacity with lowered cancer induction, the role of cancer-related genes such as p53 has been analyzed during exercise. p53 is typically studied as a tumour suppressor involved in processes such as DNA repair and apoptosis. However, the responsibilities of p53 expand beyond the roles, including involvement in metabolism, microenvironment, and aerobic capacity.

Considering this, a narrative review was conducted to analyze the role of p53 during skeletal muscle adaptations involving mitochondrial biogenesis, hypertrophy, and angiogenesis in various exercise contexts. Within the papers examined, certain results can be noted. Similar to during sarcopenia, p53 has been found to display regulation of apoptosis during atrophy of skeletal muscle. P53 appears to increase immediately following a bout of exercise, regulating apoptotic proteins cytochrome C and Bax. Moreover, while certain experiments have displayed slight significance, it is unclear whether p53 content levels have a relationship with genes regulating mitochondrial biogenesis. p53 activity, however, does appear to occur with increases in tests promoting skeletal muscle adaptation. Finally, p53 could also be seen to have a role in regulating angiogenesis through indirect TSP-1 interactions. The relationship involving MDM2 with p53 may further elucidate the possible pathway for this adaptation.

Future areas of research involving p53 and exercise points to further analysis of the p53 interactions with Bax and Bcl-2 can solidify its role in encouraging muscle atrophy. Furthermore, deeper investigations into p53 phosphorylation will continue to clarify its contributions to both mitochondrial function and biogenesis. Finally, with the limited studies involving p53/MDM2 and exercise, further research will be beneficial in examining whether

and how it affects angiogenesis. Particularly, analyzing the human analog of MDM2 might provide further insight as it is rarely studied in exercise contexts.

In conclusion, we identify that p53 does indeed have a role during exercise-induced adaptations in skeletal muscle. Specifically, p53 has probable evidence supporting its regulations of genes involved in muscle atrophy, mitochondrial upkeep, and capillary growth. Furthermore, the research examined in this review suggests that p53 plays a significant role in facilitating adaptations during homeostatic changes, especially in the context of exercise.

Further research surrounding this topic will continue to elucidate the metabolic and regulatory roles of p53 within skeletal muscle and physiological health.

List of Abbreviations Used

p53: protein 53
DNA: deoxyribonucleic acid
Bax: Bcl-2-associated X
Bcl-2: B cell lymphoma 2
TFAM: mitochondrial transcription factor A
PGC-1a: peroxisome proliferator-activated receptor-gamma coactivator – 1 alpha
COX: cyclooxygenase
WT: wildtype
KO: knock-out
NRF-1: nuclear respiratory factor 1
AMPK: adenosine monophosphate-activated protein kinase
p38: protein 38
CHCHD4: coiled-coil-helix-coiled-coil-helix domain-containing protein 4
mRNA: messenger ribonucleic acid
VEGF-A: vascular endothelial growth factor A
TSP-1: thrombospondin-1
MDM2: murine double minute 2

Conflicts of Interest

The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent

This article is a literature review and therefore did not require an ethics approval.

Authors' Contributions

AL: performed all literature search and wrote the manuscript.

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