Differential Gene Expression in Cell Types of the Human Skeletal Muscle: A Bioinformatics-Based Meta-Review

Kyung-Wan Baek^{1,3} PhD, So-Jeong Kim² BS, Ji-Seok Kim^{1,3} PhD, Sun-Ok Kwon¹ PhD

¹Department of Physical Education, Gyeongsang National University, Jinju; ²Department of Convergence Medical Science, Gyeongsang National University, Jinju;

³Research Institute of Pharmaceutical Sciences, Gyeongsang National University, Jinju, Korea

PURPOSE: This study evaluates the differences in the expression of genes frequently analyzed in the field of exercise science between the skeletal muscle tissue and various cell types that comprise the skeletal muscle tissue.

METHODS: We summarized the genes and proteins expressed in the skeletal muscle that were published in “*Exercise Science*” journal from 2015 to present. Thereafter, we selected 15 genes and proteins that were the most analyzed genes and proteins in the skeletal muscle. These genes and proteins were horizontally compared for expression differences in skeletal muscle components and cultured cells based on NCBI Gene Expression Omnibus DataSets.

RESULTS: The most analyzed genes (encoding analyzed proteins) in skeletal muscle tissues in “*Exercise Science*” were *PPARGC1A*, *PPARD*, *MTOR*, *MAP1LC3A*, *MAP1LC3B*, *PRKAA1*, *AKT1*, *SLC2A4*, *MAPK1*, *COX4I1*, *MAPK14*, *MEF2A*, *MAPK8*, *RPS6KB1*, and *SOD1*. Among them, *PPARGC1A*, *AKT1*, *SLC2A4*, *MAPK1*, and *COX4I1* were specifically expressed in the skeletal muscle. However, expression of other genes was found to be significantly affected in other cell types of the skeletal muscle tissue.

CONCLUSIONS: Genes such as *PPARGC1A*, which are specifically expressed in the skeletal muscle, may be analyzed without pre-treating (such as perfusion) the skeletal muscle tissue. However, expression of other genes may depend on the skeletal muscle cell type. Thus, in such instances, pretreatment, such as perfusion and isolation, should be considered.

Key words: Skeletal muscle, Gene, Gene expression, Bioinformatics, Exercise

INTRODUCTION

One of the main areas of interests in exercise science is investigating the role of exercise in regulating gene expression in the skeletal muscle, as it causes physiological changes to the skeletal muscle [1,2]. Therefore, it is important to accurately analyze gene expression in the skeletal muscle.

A tissue sample, obtained via a muscle biopsy that has not been subjected to an isolation process has different proportions of the formative cells [3,4]. This is because skeletal muscle mainly consists of muscle fibers; however, it also contains blood and lymph vessels, nerves, and immune cells. Each of these cell types can potentially respond to experimental conditions; therefore, it is difficult to decipher the exact role of

muscle cells in the overall tissue response. For example, the surface marker CD14 is expressed on circulating monocytes [5]. Thus, the mRNA expression of CD14 is higher in blood cells and primary macrophages than in other cell types [6]. In addition, it was demonstrated that endothelin expression is specific to endothelial cells and is much higher in these cells than in muscle or blood cells [6]. Conversely, the mRNA levels of myosin heavy chain 2 are substantially high in biopsied muscle tissues, fibers, and cells; however, it is rarely expressed in blood, immune, and endothelial cells [7].

Since the skeletal muscle is a mixture of different cell types, it is necessary to pretreat the biopsied muscle or develop a statistically accurate technique such that the expression of the gene of interest can be deter-

Corresponding author: Sun-Ok Kwon Tel +82-55-772-2297 Fax +82-55-772-2299 E-mail kwon502@gnu.ac.kr

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mined. Moreover, it is experimentally challenging to evaluate the differences in gene expression in various cell types. Nevertheless, prior to experimentally validating the differential expression of genes in the skeletal muscle, a quick preliminary analysis and prediction can be conducted using the genome database available in NCBI Gene Expression Omnibus (GEO) DataSets (<https://www.ncbi.nlm.nih.gov/gds/>). An open access genome analysis tool that determines the baseline expression levels of a gene has become recently accessible. Recently accessible open access gene expression analysis tool maintain and process only baseline/control conditions for each microarray uploaded in NCBI GEO DataSets [8].

In this paper, we discuss a rational approach to interpret the expression of genes and proteins most analyzed in the skeletal muscles in the journal “Exercise Science” using a genome dataset-based online analysis tool.

METHODS

1. Identifying the most analyzed genes and proteins in “Exercise Science”

We reviewed all the papers published in the journal “Exercise Science” from 2015 to present and identified all the genes and proteins analyzed in the skeletal muscle. Thereafter, we matched the identified genes to the species used in the experiment of each published papers by accessing the NCBI Gene database (<https://www.ncbi.nlm.nih.gov/gene/>). Similarly, we cross-referenced the identified proteins with the NCBI Gene database and identified the corresponding coding genes (Table 1). Among the identified genes, those that were homologous among species were considered as identical genes. All genes identified through the process described above were converted from mouse (*Mus musculus*) or rat (*Rattus norvegicus*) to human (*Homo sapiens*) gene symbols. Eventually, we ranked these analyzed genes, as shown in Table 2. Each publications within the “Exercise Science” journal included in this study contained one or more of the keywords “skeletal muscle”, “muscle”, “gene”, “gene expression” and “expression”.

2. Differential gene expression in cell types of the skeletal muscle

Expression levels of the converted genes were analyzed using the RNA expression analysis tool (<https://nicopillon.com/tools/muscle-atlas/>) based on the NCBI GEO DataSets. Subsequently, we compared the expression levels of genes in the muscle fibers, whole blood cells, endotheli-

al cells, fibroblasts, macrophages, muscle cells, and smooth muscle cells with those of genes expressed in tissues obtained from muscle biopsy. All of the analyzed genes were mentioned more than twice in the “Exercise Science”.

3. Statistical analysis

After calculating the relative gene expression values ($\log_2$) based on cellular characteristics, we performed one-way ANOVA and Dunnett’s multiple comparisons tests using GraphPad Prism (version 8.3.0, GraphPad Software, Inc., La Jolla, CA, USA). Statistical significance was set at $p < .05$.

RESULTS

1. Publications reporting gene and protein expression in skeletal muscle cells were analyzed in the “Exercise Science” journal from 2015 to present

Upon reviewing publications in the “Exercise Science” from 2015 to the present, we determined that 18 studies were interested in skeletal muscle genes or proteins. Of these, nine studies were conducted on mice, and seven were conducted on rats. In addition, one study was conducted in both mice and rats. Furthermore, one of the remaining studies was a genome meta-analysis. We found that the most analyzed skeletal muscle was the tibialis anterior, which was analyzed in six studies. In addition, the soleus, gastrocnemius, triceps, extensor digitorum longus, and flexor hallucis longus were the most frequently analyzed muscles in this order (Table 1).

2. Most analyzed genes and proteins in the “Exercise Science” journal from 2015 to the present

The most analyzed gene (or encoded protein) in the journal was *PPARGC1A* (encoding PPARG co-activator 1 alpha [PPAR β/δ]), which was identified in five publications. The next most analyzed gene was *PPARD* (encoding peroxisome proliferator activated receptor delta [PPAR β/δ]), which was analyzed in three publications. In addition, *MTOR* (encoding mechanistic target of rapamycin [mTOR]), *MAP1LC3A* (encoding microtubule associated protein 1 light chain 3 alpha [LC3]), *MAP1LC3B* (encoding microtubule associated protein 1 light chain 3 beta [LC3B]), *PRKAA1* (encoding protein kinase AMP-activated catalytic subunit alpha 1 [AMPK]), *AKT1* (encoding AKT serine/threonine kinase 1 [AKT]), *SLC2A4* (encoding solute carrier family 2 member

Table 1. Publications in which gene expression and protein expression in skeletal muscle were analyzed in the “Exercise Science” journal from 2015 to the present

Publications	Species	Materials	Analyzed muscle	Identified genes	Identified proteins (protein-coding gene)
Lee et al. [26]	<i>Mus musculus</i>	Gastrocnemius, tibialis anterior			CPT1B (<i>Cpt1b</i>), FAS (<i>Fas</i>), p-AMPK (<i>Pkkaa1</i>), AMPK (<i>Pkkaa1</i>)
Baek et al. [12]	<i>Homo sapiens</i>	#Meta-analysis of various muscles	METTL21C, COL1A1		
Lim and Kim [27]	<i>Rattus norvegicus</i>	Flexor hallucis longus			Akt (<i>Akt1</i>), mTOR (<i>Mtor</i>) p70 S6K (<i>Rps6kb1</i>), 4E-BP1 (<i>Eif4ebp1</i>), ERK (<i>Ephb1</i>), JNK (<i>Mapk8</i>), p38 (<i>Mapk14</i>)
Ahn [28]	<i>Mus musculus</i>	Tibialis anterior			HSP20 (<i>Hspb6</i>), SOD1 (<i>Sod1</i>)
Lim and Son [29]	<i>Rattus norvegicus</i>	Soleus			MyoD (<i>Mdfic</i>), myogenin (<i>Myog</i>)
Oh et al. [30]	<i>Rattus norvegicus</i>	Tibialis anterior			LC3-I (<i>Map1lc3a</i>), LC3-II (<i>Map1lc3b</i>), p62 (<i>Khdrrb1</i>), phospho-p70S6K (<i>Rps6kb1</i>)
Chang and Kim [31]	<i>Mus musculus</i>	Extensor digitorum longus, soleus			Wnt3a (<i>Wnt3a</i>), β -catenin (<i>Cttnb1</i>), LEF-1 (<i>Lef1</i>), p-GSK3 β (<i>Gsk3b</i>), Wnt7a (<i>Wnt7a</i>), Fzd7 (<i>Fzd7</i>), PKC (<i>Pkcg</i>), p-AKT (<i>Akt1</i>), p-mTOR (<i>Mtor</i>)
Lee et al. [32]	<i>Mus musculus</i>	Gastrocnemius		Nr4a3, Nr4a2, Btg2, Atf3, Otud1, Siki1, Fos, Mss51, Thbs1, Irs2, Maff, Mafk, Bcl6, Scd3, Il1rl2, Cish, Adh1, Gm2310, Hba-a2, Hba-a1, Tesc1, Ube2l6, Gm17482	
Namgoong et al. [33]	<i>Mus musculus</i>	Gastrocnemius, soleus		Fndc5, Ppargc1a, Ucp1	
Oh [34]	<i>Rattus norvegicus</i>	#Unspecified		Hp, Ahsg, Ambp, Timp1, Dscr1, Atf3, Hmox1, Egr1, Myh6, Mt1a, Igfbp1, Nr4a3, Gc, LOC259246, LOC298109, LOC259244, Ankrd1, ApoH, MGC72973, Fetub, Itih3, Mup4, Mup5, Slpi, Serpina1, Trfcsf12a, F2, Itih4, Myf6, Ucp3, NM 031628	
Hong et al. [35]	<i>Mus musculus</i>	Triceps			LC3 (<i>Map1lc3a</i>), p62 (<i>Gtf2h1</i>), LC3 II (<i>Map1lc3b</i>), Beclin-1 (<i>Becn1</i>), Bnip3 (<i>Bnip3</i>), Lamp1 (<i>Lamp1</i>), HDAC6 (<i>Hdac6</i>)
Koh et al. [36]	<i>Mus musculus, Rattus norvegicus</i>	Tibialis anterior		Ppargc1a, Ppard	
Kim et al. [37]	<i>Mus musculus</i>	#Unspecified			PGC1a (<i>Ppargc1a</i>), AMPK (<i>Pkkaa1</i>), SOD (<i>Sod1</i>)
Jung et al. [38]	<i>Rattus norvegicus</i>	#Unspecified			PPAR beta/delta (<i>Ppard</i>), PGC-1 alpha (<i>Ppargc1a</i>), cytochrome C (<i>Cycs</i>), COX1 (<i>mt-Co1</i>)
Koh et al. [39]	<i>Mus musculus</i>	Tibialis anterior			NRF-1 (<i>Nrf1</i>), PPAR beta/delta (<i>Ppard</i>), PGC-1a (<i>Ppargc1a</i>) MEF2A (<i>Mef2a</i>), GLUT4 (<i>Slc2a4</i>), Cytochrome C (<i>Cycs</i>), ATP synthase (<i>Papss2</i>)
Koh et al. [40]	<i>Mus musculus</i>	Tibialis anterior			COX IV (<i>Cox4i1</i>), SUO (<i>Sdh</i>)
Yoon et al. [41]	<i>Rattus norvegicus</i>	Soleus			ERK1/2 (<i>Mapk3</i>), p38 (<i>Mapk14</i>), JNK (<i>Mapk8</i>),
Kim et al. [42]	<i>Rattus norvegicus</i>	Triceps			PGC1a (<i>Ppargc1a</i>), PPAR delta (<i>Ppard</i>), GLUT4 (<i>Slc2a4</i>), MEF2A (<i>Mef2a</i>), COX IV (<i>Cox4i1</i>)

Table 2. Most analyzed genes in skeletal muscle in published “Exercise Science” journals

Rank	Gene symbol of <i>Homo sapiens</i>	Number of publications
1	<i>PPARGC1A</i>	5
2	<i>PPARD</i>	3
3	<i>MTOR</i>	2
3	<i>MAP1LC3A</i>	2
3	<i>MAP1LC3B</i>	2
3	<i>PRKAA1</i>	2
3	<i>AKT1</i>	2
3	<i>SLC2A4</i>	2
3	<i>MAPK1</i>	2
3	<i>COX4I1</i>	2
3	<i>MAPK14</i>	2
3	<i>MEF2A</i>	2
3	<i>MAPK8</i>	2
3	<i>RPS6KB1</i>	2
3	<i>SOD1</i>	2

4 [GLUT4]), *MAPK1* (encoding mitogen-activated protein kinase 1 [ERK]), *COX4I1* (encoding cytochrome c oxidase 4I1 [COX4]), *MAPK14* (encoding mitogen-activated protein kinase 14 [p38]), *MEF2A* (encoding myocyte enhance factor 2A [MEF2]), *MAPK8* (encoding mitogen-activated protein kinase 8 [JNK]), *RPS6KB1* (encoding ribosomal protein S6 kinase B1 [p70-S6K]), and *SOD1* (encoding superoxide dismutase 1 [SOD]) were analyzed in two publications each.

3. Cell-type based differential expression of the most studied genes in “Exercise Science”

We found that the expression of *PPARGC1A* did not differ substantially between muscle-biopsy obtained tissue samples and muscle fibers. However, the expression in *PPARGC1A* significantly differed in all other cell types ($p < .0001$; Fig. 1A). On the other hand, *PPARD* expression differed insignificantly between muscle-biopsy obtained tissue samples, muscle fibers, endothelial cells, and muscle cells. Nevertheless, we validated that *PPARD* expression significantly differed in whole blood cells ($p < .0001$), fibroblasts ($p < .0001$), macrophages ($p < .0001$), and smooth muscle cells ($p < .001$) compared to that in biopsied tissue samples (Fig. 1B). The expression of *MTOR* in muscle fibers ($p < .0001$), fibroblasts ($p < .01$), macrophages ($p < .0001$), and smooth muscle cells ($p < .05$) were significantly different from muscle biopsy-extracted tissues. However, there was no significant difference in expression between the biopsied tissue cells, whole blood cells, endothelial cells, and muscle cells (Fig. 1C). Furthermore, *MAP1LC3A* expression significantly differed among biopsied tissues and smooth muscle cells. However, *MAP1LC3A* expression

in all other cell types, differed significantly from that in biopsied tissues (Fig. 1D). On the other hand *MAP1LC3B* expression levels were similar in muscle fibers, macrophages, smooth muscle cells, biopsied tissues. However, whole blood cells, endothelial cells, fibroblasts, and muscle cells had significantly different *MAP1LC3B* expression compared to cells of the biopsied tissues ($p < .0001$; Fig. 1E). Moreover, *PRKAA1* expression in muscle fibers and macrophages was not significantly different from that in biopsied tissues. However, expression in whole blood cells, endothelial cells, fibroblasts, muscle cells, and smooth muscle cells differed significantly compared to that in biopsied tissue cells (Fig. 1F).

Notably, expression levels of *AKT1*, *SLC2A4*, *MAPK1*, and *COX4I1* in muscle fibers, whole blood cells, endothelial cells, fibroblasts, macrophages, muscle cells, and smooth muscle cells differed significantly from those in biopsied muscle tissues ($p < .0001$; Fig. 2A-D). Expression of *MAPK14* in muscle fibers ($p < .01$), whole blood cells ($p < .0001$), and fibroblasts ($p < .001$) was significantly different from that in biopsied tissues. However, *MAPK14* expression did not differ significantly among endothelial cells, macrophages, muscle cells, smooth muscle cells, and biopsied tissues (Fig. 2E). Additionally, we determined that *MEF2A* expression in macrophages and muscle cells was not significantly different from that in biopsied tissue cells. On the contrary, muscle fibers, whole blood cells, endothelial cells, fibroblasts, and smooth muscle cells exhibited significantly different expression of *MEF2A* compared with cells from biopsied tissues ($p < .001$; Fig. 2F). We observed that the difference in *MAPK8* expression was insignificant among muscle fibers, endothelial cells, fibroblasts, and biopsied tissue cells. However, whole blood cells ($p < .0001$), macrophages ($p < .0001$), muscle cells ($p < .05$), and smooth muscle cells ($p < .0001$) expressed *MAPK8* at significantly different levels compared with cells obtained from biopsied tissues (Fig. 2G). Moreover, *RPS6KB1* expression in whole blood cells and endothelial cells did not differ significantly from that in biopsied tissues. On the other hand, *RPS6KB1* in muscle fibers ($p < .05$), fibroblasts ($p < .001$), macrophages ($p < .0001$), muscle cells ($p < .0001$), and smooth muscle cells ($p < .001$) differed significantly from that in biopsied tissue samples (Fig. 2H). Eventually, we observed that difference in *SOD1* expression between smooth muscle cells and biopsied tissue cells was insignificant. However, *SOD1* expression in muscle fibers, whole blood, endothelial cells, fibroblasts, macrophages, and muscle cells was significantly different from that in biopsied tissues ($p < .0001$; Fig. 2I).

Fig. 1. Differences in expression of various genes analyzed in skeletal muscle according to cell types included in skeletal muscle among publication in the "Exercise Science" journal (Part 1). All data presented as the mean $\pm$ standard deviation; vs. muscle biopsy. * $p < .05$, ** $p < .01$, *** $p < .001$, and **** $p < .0001$. N.S. = no significant difference compared to muscle biopsy.

DISCUSSION

Since physical activity is the movement of skeletal muscles [9], gene or protein expression that are altered in response to physical activity or exercise is a major concern in modern exercise science. Gene and protein expression regulated by physical exercise are experimentally validated by molecular biology techniques such as polymerase chain reaction or

western blotting post animal-based experiments [10]. In addition, integrating microarray or RNA-sequencing data obtained from human tissues with meta-analysis can help gain insights on the effect of exercise in several diseases [11]. Thus, this can possibly explain the molecular mechanisms underlying the application of exercise as a treatment intervention for sarcopenia and muscle-related diseases in humans [12-14]. Moreover, it can also help in explaining skeletal muscles role as a primary secretory

Fig. 2. Differences in expression of various genes analyzed in skeletal muscle according to cell types included in skeletal muscle among publication in the "Exercise Science" journal (Part 2). All data presented as the mean ± standard deviation; vs. muscle biopsy. * $p < .05$, ** $p < .01$, *** $p < .001$, and **** $p < .0001$. N. S = no significant difference compared to muscle biopsy.

organ in metabolic disorders [15]. Nevertheless, previous studies have failed to block differential gene and protein expression in cells as intervening factors in the skeletal muscle. Therefore, we conducted this study to prevent any misinterpretations of the expression of genes mainly analyzed in the field of exercise science. We aimed for our data to be helpful in future studies.

Exercise affects gene expression in almost every cell type that makes up the human body [16]. In addition, the effect on gene expression may differ depending on the type of exercise and the intensity of exercise or cell type [17]. Therefore, in order to determine the effect of exercise on

skeletal muscle gene expression, it is necessary to conduct research by distinguishing the cell types constituting skeletal muscle. For example, hepatokines such as fetuin A may be released from the liver due to exercise [18], and the related gene expression may not be specific to skeletal muscle, it is because skeletal muscle contains blood. From a similar point of view, exercise may induce differences in macrophage polarization in some adipocytes in skeletal muscle in both acute and chronic exercise [19,20]. Therefore, based on various literature, finding the basis for whether there may be a difference in gene expression depending on the cell type and clarifying the target cell type will be the basis for the re-

search plan. At the same time, if exercise scientists predict the difference according to cell type at the in silico and then conduct the research, it is thought that it will help the progress of the study to analyze the change in gene expression in skeletal muscle due to exercise.

Notably, we found that the expression of *PPARGC1A*, which is the most analyzed gene in “*Exercise Science*”, did not differ significantly between biopsied muscle tissues and muscle fibers. However, we observed that it was differentially expressed in other cell types. This indicated that *PPARGC1A* is specifically expressed in skeletal muscle fibers. In addition, the significant difference in expression of *AKT1*, *SLC2A4*, *MAPK1*, and *COX4I1* between biopsied cells and other cell types, indicated that the biopsied muscle tissue could be analyzed without additional pre-treatment. Therefore, we determined that *PPARGC1A*, *AKT1*, *SLC2A4*, *MAPK1*, and *COX4I1* are genes specifically expressed in the skeletal muscle. PGC-1 α (encoded by the *PPARGC1A*) is a transcriptional coactivator that regulates genes involved in energy metabolism (the master regulator of mitochondrial biogenesis) [21-23]. It also appears to be of major interest in exercise physiology, as endurance exercise is well known to activate *PPARGC1A* in rodent and human skeletal muscle [24]. Several publications in the “*Exercise Science*” journal also appear to reflect the characteristics of *PPARGC1A*, which may be involved in muscle metabolism, increase in skeletal muscle due to obesity, blood pressure regulation, cellular cholesterol homeostasis regulation, and obesity [25].

Barring the aforementioned genes, various genes may have differential gene expression in other cell types of the skeletal muscle. Therefore, depending on the purpose of the study, perfusion before animal sacrifice or conducting a pre-treatment (e.g., isolation) of the tissue after biopsy may be required. For example, perfusion may be a suitable method to evaluate skeletal muscle-specific gene expression of *MTOR* and *RPS6KBI* that did not exhibit a significant difference in expression in whole blood cells. In addition, all other genes, including *MTOR* and *RPS6KBI* but excluding skeletal muscle-specific genes, had no significant differences in their expression levels among one or more cell types. Therefore, an appropriate cell isolation process may be required depending on the purpose of the study.

CONCLUSION

We analyzed skeletal muscle-specific gene expression of genes most analyzed in the “*Exercise Science*” journal in the following order: *PPARGC1A*, *PPARD*, *MTOR*, *MAPL1LC3A*, *MAPL1LC3B*, *PRKAA1*, *AKT1*,

SLC2A4, *MAPK1*, *COX4I1*, *MAPK14*, *MEF2A*, *MAPK8*, and *RPS6KBI*. We verified that *PPARGC1A*, *AKT1*, *SLC2A4*, *MAPK1*, and *COX4I1* were specifically expressed in muscle fibers or biopsied muscle tissues. However, other genes were found to have mixed gene expression levels in other cell types.

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CONFLICT OF INTEREST

The authors declare that they do not have conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: KW Baek, SO Kwon; Data curation: KW Baek, SJ Kim; Formal analysis: KW Baek; Funding acquisition: SO Kwon; Methodology: KW Baek, SJ Kim; Project administration: KW Baek, SO Kwon; Visualization: KW Baek; Writing-original draft: KW Baek; Writing-review & editing: KW Baek, JS Kim, SJ Kim, SO Kwon.

ORCID

Kyung-Wan Baek	https://orcid.org/0000-0002-8445-3773
So-Jeong Kim	https://orcid.org/0000-0001-6422-7595
Ji-Seok Kim	https://orcid.org/0000-0002-3023-1999
Sun-Ok Kwon	https://orcid.org/0000-0002-5181-8414

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