

Post-Exercise Regulation of the AP-1 Transcriptional Program

BACKGROUND

- Much of what makes exercise beneficial for one's health is unknown
- A better understanding of how exercise affects human gene expression may provide insights into improving human health

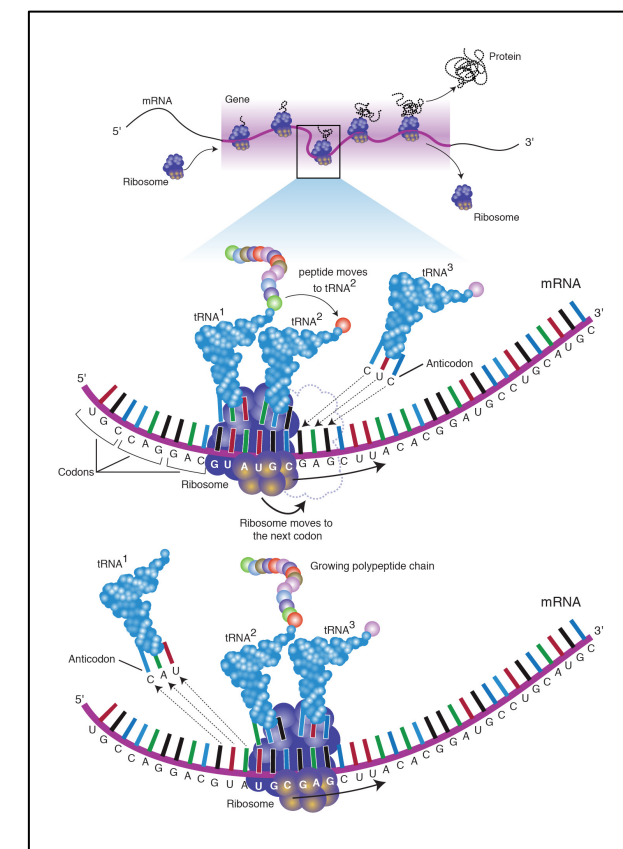


Figure 1. National Human Genome Research Institute

- Gene expression – the degree to which genes are transcribed into mRNA, which is translated into proteins (figure 1)
- RNA-seq analysis – Conducted to measure gene expression by measuring the mRNA strands present
- Transcription factors (TFs) – proteins that regulate the transcription of genes

GOALS

- Identify exercise-induced changes in gene expression
- Identify candidate transcription factors responsible for changes in gene expression



METHODS

- RNA-seq analysis using DESeq2 on MoTrPAC data (figure 2)
- Gene ontology analysis on DEGs using clusterProfiler
- Transcription factor motif analysis using MSigDB
- Pathway analysis using KEGG

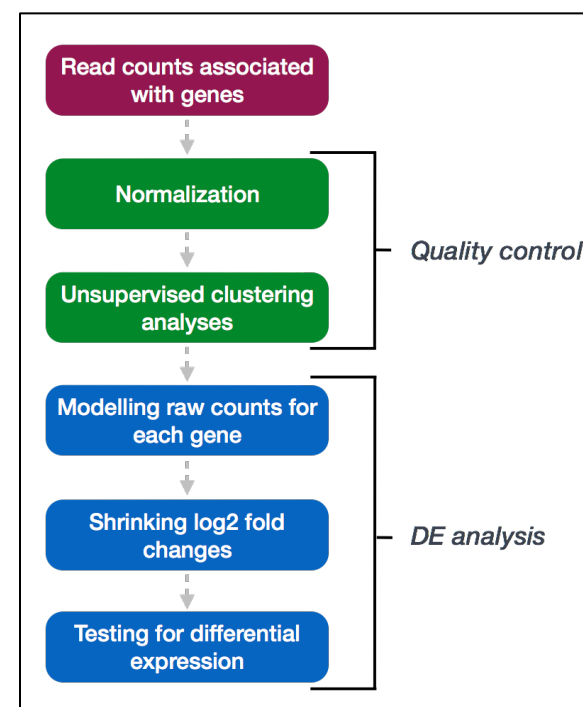
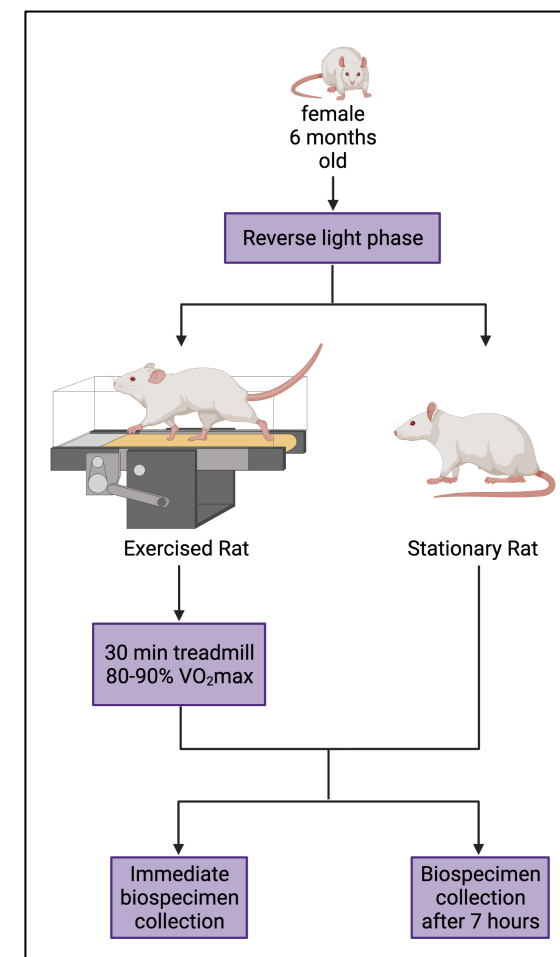


Figure 2. Harvard Chan Bioinformatics Core

RESULTS

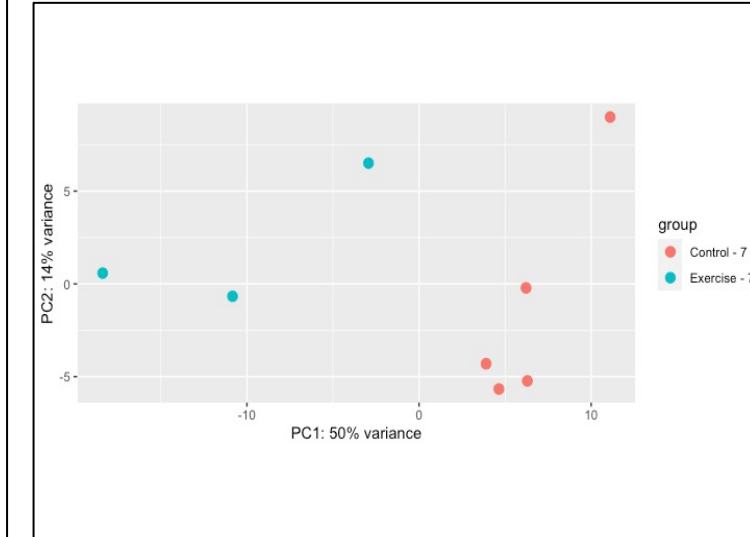


MoTrPAC Data Collection Protocol²

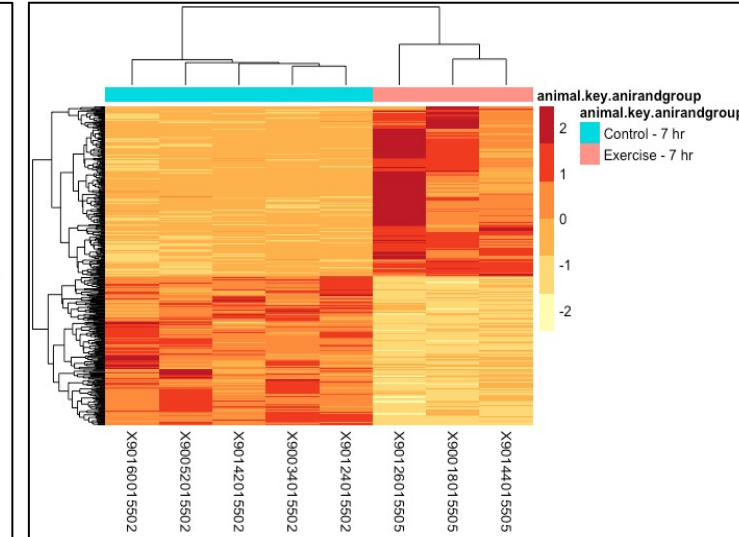
Gene Sets from the
Molecular Signatures
Database (MSigDB)

Exercise Causes Differential Expression

Principal Component Analysis



Heatmap



Experimental samples collected 7 hours post-exercise

TFs that Target 7-Hour DEGs

Gene Set Name	# Genes in Set (K)	# Genes in Overlap (k)	k/K	p-value
NFAT (TGGAAG)	1934	68	0.0352	3.07E-20
AP-1 (TGANTCA)	1139	47	0.0413	9.52E-17
NFY (GATTGGY)	1177	44	0.0374	3.17E-14
ERR-1 (TGACCTY)	1064	41	0.0385	9.50E-14
TATA (TATAAA)	1317	43	0.0326	5.56E-12

AP-1 Formation

- AP-1 tends to either be a Jun-Jun homodimer or a Jun-Fos heterodimer³ (figure 3)
- AP-1 targets the transcription of its own subunits (positive autoregulation)⁴

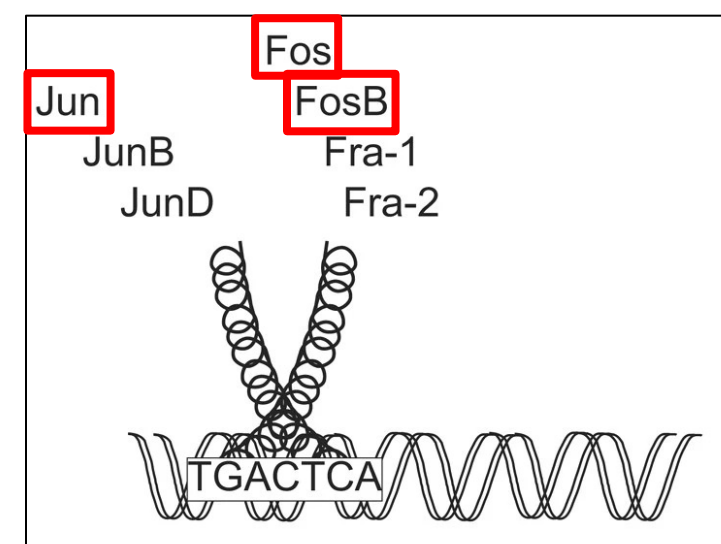
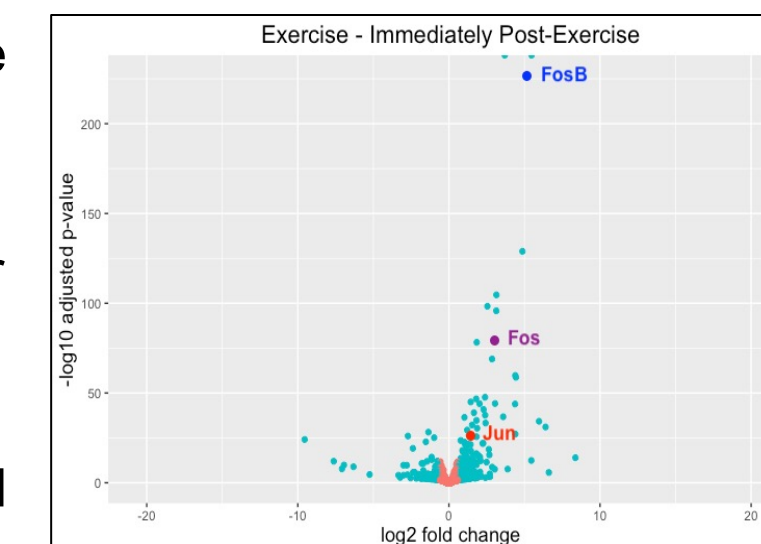


Figure 3. Zenz, R. et al.

Jun, Fos, & FosB Expression I.P.E.

- Jun, Fos, and FosB are highly upregulated
- This indicates that the AP-1 transcription factor is responsible for some DEGs 7 hrs. P.E.
- Due to positive autoregulation, AP-1 will be further produced as a result



Pathways that Activate AP-1

Significantly Positively Perturbed Signaling Pathways

Description	Enrichment Score	p-value
IL-17 signaling pathway	0.81652684	0.00296344
TNF signaling pathway	0.76734059	0.02067199
C-type lectin receptor signaling pathway	0.74474837	0.02478965
T cell receptor signaling pathway	0.72200212	0.04185286
MAPK signaling pathway	0.6618261	0.00296344
PI3K-Akt signaling pathway	0.61525874	0.00898963

Pathways from the Kyoto Encyclopedia of Genes and Genomes (KEGG)

Activation of AP-1

- MAPK signaling pathway results in the activation of AP-1⁵
 - Pathway that communicates signal from a ligand to the nucleus of the cell
 - JNK and p38 phosphorylates AP-1
- MAPK pathway is activated by pro-inflammatory cytokines⁵
 - IL-1 β , IL-6, TNF α

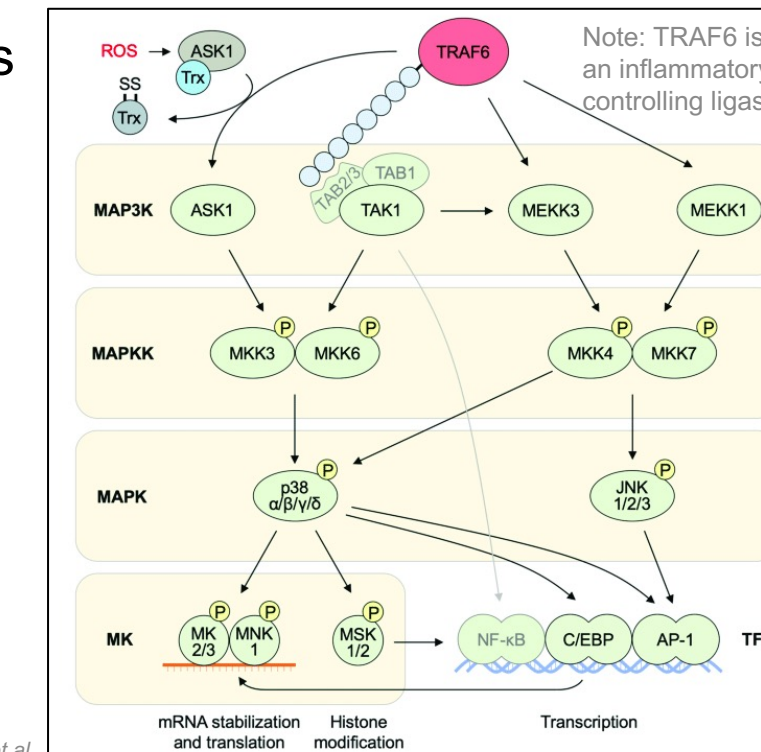


Figure 4. Dainichi, T. et al.

CONCLUSION

- Exercise causes 474 genes to be differentially expressed 7 hours later. This altered gene expression results in increased muscle development and muscular energy generation.
- The AP-1 transcription factor may cause some of this differential expression,
 - It binds to regulatory regions near the DEGs
 - Its subunit proteins are produced immediately post-exercise
 - It may be activated through the MAPK pathway

POTENTIAL FUTURE RESEARCH

- Does similar gene expression due to exercise occur in humans?
- Does similar gene expression happen tissue that is not skeletal muscle?
- Does production of the AP-1 transcription factor have any effects on cellular processes?
- How does cell expression differ in various skeletal muscle cell types (through single-cell RNA-seq)?
- How is exercise response affected without AP-1 (through gene knockout experiment)?

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SOURCES

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