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Enrichment Analysis of the Most Differentially Expressed Genes

(using KEGG and GO Databases)

# Annotations found using GeneSCF (Gene Set Clustering based on Functional annotation)

## KEGG Database

### mmu04024~cAMP\_signaling\_pathway

The transcription factor CREB (cAMP response element-binding protein) activates the transcription of PGC-1alpha. PGC-1alpha (PPARGC1A), one of the master regulators of mitochondrial biosynthesis.

### mmu04152~AMPK\_signaling\_pathway

The transcription factor AMPK is the central component of a cellular signaling system that monitors cellular energy change, acting as ‘metabolic master switch’ to regulate ATP concentrations in the face of energy depletion (e.g. fasting, exercise). Energy depletion causes a reduction in ATP and an increase in AMP which activ ates AMPK. AMPK in turn phosphorylates the coactivator PGC-1alpha (PPARGC1A), one of the master regulators of mitochondrial biogenesis.

### mmu03320~PPAR\_signaling\_pathway

Please refer to: Gianluca Miglio, Arianna C. Rosa, Lorenza Rattazzi, Massimo Collino, Grazia Lombardi, Roberto Fantozzi, PPARγ stimulation promotes mitochondrial biogenesis and prevents glucose deprivation-induced neuronal cell loss, Neurochemistry International, Volume 55, Issue 7, 2009, Pages 496-504, ISSN 0197-0186, <http://dx.doi.org/10.1016/j.neuint.2009.05.001>.

### mmu04010~MAPK\_signaling\_pathway

Please refer to: Minghui Gao, Junjian Wang, Na Lu, Fang Fang, Jinsong Liu, Chi-Wai Wong, Mitogen activated protein kinase kinases promote mitochondrial biogenesis in part through inducing peroxisome proliferator-activated receptor γ coactivator-1β expression, Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, Volume 1813, Issue 6, 2011, Pages 1239-1244, ISSN 0167-4889, <http://dx.doi.org/10.1016/j.bbamcr.2011.03.017>.

### mmu04020~Calcium\_signaling\_pathway

It is hypothesized that calcium influx is a signal that initiate changes in gene expression leading to new mitochondrial proteins.. p38 MAPK is activated by muscle contraction (possibly via calcium and CaMKII) and phosphorylates PGC-1alpha. CaMKIV responds to intracellular calcium by phosphorylation **CREB** (**cAMP response element-binding protein**), which activates expression of PGC-1alpha. PGC-1alpha is one of the master regulators of mitochondrial biogenesis.

Please refer to: Wright DC. Mechanisms of calcium-induced mitochondrial biogenesis and GLUT4 synthesis. Appl Physiol Nutr Metab. 2007 Oct;32(5):840-5. Review. PubMed PMID:18059607.

### mmu04022~cGMP-PKG\_signaling\_pathway

Please refer to: Whitaker RM, Wills LP, Stallons LJ, Schnellmann RG. cGMP-Selective Phosphodiesterase Inhibitors Stimulate Mitochondrial Biogenesis and Promote Recovery from Acute Kidney Injury. The Journal of Pharmacology and Experimental Therapeutics. 2013;347(3):626-634. doi:10.1124/jpet.113.

### mmu04068~FoxO\_signaling\_pathway

Please refer to: Olmos Y, Valle I, Borniquel S, Tierrez A, Soria E, Lamas S, Monsalve M. Mutual dependence of Foxo3a and PGC-1alpha in the induction of oxidative stress genes. J Biol Chem. 2009 May 22;284(21):14476-84. doi: 10.1074/jbc.M807397200. Epub 2009 Mar 26. PubMed PMID: 19324885; PubMed Central PMCID: PMC2682896.

## GO Database

### GO:0004383~guanylate cyclase activity

More recently, NO has been shown to be involved in mitochondrial biogenesis. HeLA cells expressing eNOS (endothelial NO synthase) display an increase in mtDNA content, cytochrome *c* and COX IV protein expression levels, as well as PGC-1α, NRF-1 and Tfam mRNA expression [[26](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3883043/" \l "R26)]. Moreover, the NO produced by eNOS activates guanylate cyclase to increase the amount of cGMP present, which transmits a signal to the nucleus through an unknown mechanism, leading to the induction of PGC-1α gene transcription and mitochondrial biogenesis as a consequence [1].

# Annotations found using DAVID

## Endocrine and other factor-regulated calcium reabsorption.

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## mitogen-activated protein kinase kinase kinase kinase 4 (Map4k4)

Map4k4 was among the first cluster of the most enriched genes (Enrichment Score: 2.08). Calcium signaling modulates mitochondrial biogenesis through the calciualmodulin-dependent protein kinase II (CaMKII), p38 mitogen activated protein kinase (MAPK) and PGC-1*α* [3]*.* MAP4K4 has also been reported to regulate MAPK/ERK1/2 pathway and MAPK/p38 pathway in few biological systems [2].

## GO:0071840 cellular component organization or biogenesis

QuickGO defines the term “A process that results in the biosynthesis of constituent macromolecules, assembly, arrangement of constituent parts, or disassembly of a cellular component”. I hypothesize that the mitochondria could be such a constituent part that undergoes biogenesis.

# References

[1] Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays in biochemistry. 2010;47:10.1042/bse0470069. doi:10.1042/bse0470069.

[2] Xuan Gao et al., “MAP4K4: an emerging therapeutic target in cancer”, Cell Biosci. 2016; doi: 10.1186/s13578016-0121-7.

[3] Palikaras,K. et al. RrBalancing mitochondrial biogenesis and mitophagy to maintain energy metabolism homeostasis, Cell Death Differ, 2015 - GO:0071840 cellular component organization or biogenesis 10.1038/cdd.2015.8

[4] Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays in biochemistry. 2010;47:10.1042/bse0470069. doi:10.1042/bse0470069.