



## Mitochondrial Biogenesis Induced by Exercise and Nutrients: Implication for Performance and Health Benefits

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### ABSTRACTS

The skeletal muscle occupies about 40% of body mass, one of the largest organs in the body, and it has great plasticity in response to physiological stressors and then alters the contractile and metabolic properties of the muscles. Therefore, healthy status of muscle affects health status of whole body. Mitochondria are abundantly present in mammalian muscle cells, known as the power plants of the cell to generate adenosine triphosphate (ATP) with oxygen. The muscle health depends on the mitochondrial function. In aging and some of metabolic disease states, the mitochondrial function is defected. Some parts of this defect result from lower physical activity and nutritional status. The exercise is well-known as a major strategy to induce mitochondrial biogenesis and upregulation of the mitochondrial function. Recently some nutrients are also suggested as ligands for transcription of the mitochondrial proteins. We also recently found insight of protein interaction with mitochondria that will possibly augment mitochondrial respiratory potential. The present review article introduces some recent research evidences relating to mitochondrial quality control, mitochondrial biogenesis mediated by both exercise and nutrients and an interaction of protein with mitochondria to facilitate mitochondrial respiration.

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## 1. INTRODUCTION

The beneficial effects of exercise at the whole-body level are numerous, with adaptive responses occurring in many organs. Especially skeletal muscle mitochondrial respiration has a significant contribution on the whole body respiration and energy expenditure (Zurlo *et al.*, 1990). Then, lower aerobic capacity links a risk incidence for mortality (Myers *et al.*, 2002). Therefore, determinant of mitochondrial function in skeletal muscle has substantially impact for protecting against metabolic diseases, such as obesity and type 2 diabetes, leading to longevity. This review summarizes recent understanding of mitochondrial function in muscle relating to mitochondrial quality control, mitochondrial biogenesis mediated by both exercise and nutrients and an interaction of protein with mitochondria to facilitate mitochondrial respiration. The results show mitochondrial functions can invariably be overcome with exercise and nutrients.

## 2. MITOCHONDRIAL CHARACTERISTICS AND DYNAMIC CONTROL TO MAINTAIN ITS FUNCTIONS

### 2.1. Mitochondrial biogenesis and protein transport into mitochondria

Mitochondrial biogenesis can be defined as growth and division of existing mitochondria. Mitochondria has their own genome and a capacity for auto-replication. Mitochondrial proteins are encoded by the nuclear and the mitochondrial genomes (mtDNA), but mtDNA contains only 37 genes encoding 13 subunits of the electron transport chain (ETC) complexes I, II, III, IV, and V, 22 transfer RNAs, and 2 ribosomal RNAs necessary for the translation. Therefore, mammalian mitochondria have to import more than 1,500 proteins that are encoded by the nucleus from cytosol (Reichert & Neupert, 2004). These proteins are imported into mitochondria via the

translocase of the outer membrane complex (TOM; TOM40 complex) (Shiota *et al.*, 2015). After transfer across the outer membrane, certain precursors are directed through the import machinery of the inner membrane complex (TIM; TIM23 complex) into the mitochondrial matrix in a membrane potential-dependent manner (Truscott, 2001). Usually mitochondrial protein precursors contain typical pre-sequence on the N-terminal to associate TOM 40; however, majority of mitochondrial protein does not contain pre-sequence within their mature sequences. TOM 40 is focused if it has role on the import for proteins without pre-sequence.

### 2.2. Mitochondrial fusion and fission dynamics

Mitochondria keeps dynamic changes in their morphology driven by a cycle of fusion/fission and translocation (Bereiter-Hahn, 1990) the ability to undergo fusion/fission enables mitochondria to exchange contents including mitochondrial DNA (mtDNA) and helps to ensure proper organization of the mitochondrial network. Mitochondrial fission is driven by dynamin-related proteins 1 (DRP1) and optic atrophy 1 (OPA1), while mitochondrial fusion is controlled by Mitofusins (Mfn1/2) and mitochondrial GTPase (Westermann, 2010). Mitochondrial fusions are highly expressed in heart and skeletal muscle, and their expression is induced during myogenesis and physical exercise (Bach *et al.*, 2003; Soriano *et al.*, 2006). Chen *et al.* strongly suggested by the double mutant of Mfn1 and/or Mfn2 in hindlimb muscle that loss of the mitochondrial fusions causes severe mitochondrial dysfunction, mtDNA mutation, compensatory mitochondrial proliferation and muscle atrophy (Chen, *et al.*, 2010). In addition to the control of the mitochondrial network, Mfn2 also stimulates the mitochondrial oxidation of substrates, cell respiration, and mitochondrial membrane

potential, suggesting that this protein may play an important role in mitochondrial metabolism, and as a consequence, in energy balance. In contrast to the fusion function, fission depends on the DRP1 and OPA1. Drp1<sup>-/-</sup> mice revealed embryos had clearly enlarged mitochondria and meets embryonic lethal, suggested that Drp1 was required for embryonic development (Ishihara *et al.*, 2009). Furthermore, Yamada *et al.* suggested new oligomeric maturation model for Drp1 and that Drp1 oligomers move on mitochondria and, intriguingly, merge and become larger and more stationary prior to cutting the mitochondria, in the contrast to the previous concept that Drp1 is a cytosolic protein which is recruited to the surface of mitochondria via interactions with mitochondrial fission factor (Mff), mitochondrial dynamics proteins of 49 and 51 kDa (Mid49/51) and mitochondrial fission 1 protein (Fis1) (Roy *et al.*, 2015). Mfn1/2 and DRP1 expression increases in parallel with mitochondrial content and exercise capacity in human skeletal muscle (Garnier *et al.*, 2005), suggesting that fusion/fission processes are an integral part of mitochondrial biogenesis.

### 3. MITOCHONDRIAL BIOGENESIS INDUCED BY EXERCISE AND NUTRIENTS

#### 3.1. In response to exercise

Endurance exercise has a number of health benefits, including improvements in muscle metabolism and exercise tolerance. The improvement in exercise tolerance is a result of greater oxygen delivery and extraction by the exercising muscle. The increase in mitochondrial content is known as well-established adaptation within the exercised muscle as mitochondrial biogenesis.

One of signal cascades is an activation of Ca<sup>2+</sup>/calmodulin-dependent protein kinase (CaMK). Skeletal muscle contractile activity elevates intracellular [Ca<sup>2+</sup>]. This is a trigger

for CaMK to phosphorylate histone deacetylases (HDAC). The HDAC usually suppresses the activation of transcription factors such as MEF2 (myocyte enhancer factor 2) within nucleus. But once the HDAC is phosphorylated by CaMK, HDAC is released into the cytosol and herein MEF2 starts to activate (Liu *et al.*, 2005). MEF2 is a transcription factor for the peroxisome proliferated activated receptor gamma coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) and its activation upregulates an expression of PGC-1 $\alpha$  (Lin *et al.*, 2002). Another cascade induced by muscle activity is the enzyme called AMP-activated protein kinase (AMPK) serving as a metabolic sensor via elevation of cellular [AMP]/[ATP] ratio during muscle activity (Hood, 2001; Williams, 1986). The other cascade is cAMP axis. Several signal cascades directly influencing the activity of the PGC-1 $\alpha$  promoter have been identified, that is occurring through a proximal cAMP responsive element (CRE) via a CRE-binding protein (CREB). Activation of CREB via phosphorylation appears to be an important step in a cascade that results in the integration of several pathways leading to the execution of PGC-1 $\alpha$ -mediated actions in skeletal muscle (Hood, *et al.*, 2006). Since PGC-1 $\alpha$  is just a co-activator, it must co-activate with PPAR $\alpha$ , nuclear respiratory factor-1, -2 (NRF-1/2), estrogen-related receptor  $\alpha$  (ERR $\alpha$ ) to regulate mRNA for mitochondrial proteins (Lin *et al.*, 2002).

In mammals, the silent information regulator 2 ortholog, SIRT1 functionally interacts and deacetylates several protein. SIRT1 also deacetylates and functionally activates PGC-1 $\alpha$ . SIRT1 is required for PGC-1 $\alpha$ -induced upregulation of mitochondrial biogenesis in skeletal muscle. SIRT1 plays a role in muscle gene expression in the modulation of the cytosolic [NAD<sup>+</sup>]/[NADH]

ratio (reduced form of nicotinamide adenine dinucleotide). Because the cytosolic  $[NAD^+]/[NADH]$  ratio decreases during muscle contraction, it is possible that SIRT1 contributes to skeletal muscle adaptations with endurance exercise (Suwa *et al.*, 2008; Shibaguchi *et al.*, 2017). It is therefore very likely that increased SIRT1 protein expression by endurance exercise results in elevated SIRT1 deacetylase activity against PGC-1 $\alpha$  as well as causing an allosteric effect of an increased cytosolic  $NAD^+$ -to-NADH ratio and then at least in part contributes to the metabolic adaptations in skeletal muscle (Suwa *et al.*, 2008).

### 3.2. In response to nutrients

Over the past 10 years, polyphenols have been focused as antioxidant ligands preventing of various diseases associated with oxidative stress, such as cancer and cardiovascular diseases (Manach *et al.*, 2004; Middleton, 2000). Sirtuin1 is thought to play a role in regulation of mitochondrial biogenesis. It has been demonstrated in vitro, that polyphenolics, particularly resveratrol, can enhance the activity of the recombinant human sirtuin coded by SIRT1, apparently by a conformational change to the enzyme. Resveratrol at 10  $\mu$ M also extended the lifespan of yeast from ~23 to ~37 generations (Howitz *et al.*, 2003). Chemical derivatives of resveratrol appear to be even more effective (Yang H, *et al.*, 2007), suggesting that these compounds in some way decrease the DNA damage associated with aging. These enzyme-activation results have been questioned by subsequent studies on the grounds that resveratrol required highly supra-physiological concentrations (a 3-fold activation at 20  $\mu$ M) and a non-physiological substrate to have a measurable effect (Grubisha *et al.*, 2005; Kaeberlein *et al.*, 2005). Observations that the plasma concentration of resveratrol from a realistic dose is in the Nano molar range and that it exists in vivo almost entirely as conjugates,

rather than as free resveratrol (Goldberg, 2003). Hamidie *et al.* investigated the effect of fat-soluble polyphenol, curcumin, on mitochondrial biogenesis in rat hindlimb muscle (Hamidie *et al.*, 2015; Nandiyanto *et al.*, 2016). The intraperitoneal injection of curcumin for 28-day resulted increase in the expression of COX-IV, and OXPHOS subunits as well as increase in mtDNA copy number (Hamidie *et al.*, 2015). These change is augmented if endurance training is added and cAMP cascade through PGC-1 $\alpha$  was suggested to be possible mechanism on this adaptation. (Dallas *et al.*, 2008) also supported the evidences that polyphenol have ability to inhibit PDE in human body fat adipocytes to show strong lipolytic effect mediated by cAMP-PDE inhibitor.

## 4. INTERACTION OF MYOGLOBIN WITH MITOCHONDRIA AS OXYGEN MEDIATOR

Myoglobin (Mb) is known as O<sub>2</sub> store or O<sub>2</sub> transporter that expresses in skeletal and cardiac muscle cells. It is also the first protein to be determined in a three-dimensional structure, by X-ray analysis, and a typical globular protein with a heme. Many studies have striven to better understand Mb function *ex vivo* and *in vivo*, and have suggested that Mb stores O<sub>2</sub> and facilitates O<sub>2</sub> diffusion within muscle cells. The former function is of be particular importance to marine animals such as whales, seals and penguins (Guyton *et al.*, 2005; Ponganis *et al.*, 2002). The latter function remains a controversial issue regarding *in vivo* skeletal muscles. The fact is Mb-knockout mice showed no superficial physiological deficits, suggested a reassessment of Mb function *in vivo* (Flögel *et al.*, 2005; Garry *et al.*, 1998). The Mb knockout strategy, however, has fundamental technical issues, and thereby has brought several physiological compensatory adaptations such as homeostatic mechanisms, including increased capillary density that tends to

steepen the partial pressure of O<sub>2</sub> (PO<sub>2</sub>) gradient to the mitochondria, effectively shortening the diffusion path for oxygen (Gödecke *et al.*, 1999; Meeson *et al.*, 2001). Therefore, the contribution of Mb during muscle contraction is still in debate in the last two decades.

Detection of Mb desaturation and oxygenation is one of key measurements to understand physiological contribution of Mb to the mitochondrial respiration during contraction. Our hind limb perfusion experiment overcomes to detect Mb oxygenation excluding the interference of haemoglobin from the Near Infrared Spectroscopy signal *in vivo* (Masuda *et al.*, 2010; Takakura *et al.*, 2010). The technical advantage enables us to calculate the O<sub>2</sub> saturation of intracellular Mb (SmbO<sub>2</sub>) and the PO<sub>2</sub> in myocytes, and found an evidence that Mb supplies the immediate source of O<sub>2</sub> to mitochondria at the onset of contraction (Takakura *et al.*, 2010). This *in vivo* evidence supports the idea of Mb as facilitate O<sub>2</sub> transporter (Wittenberg & Wittenberg, 1989). There is, however, more debate how Mb provides O<sub>2</sub> to the mitochondria at immediately onset of contraction (increase in respiration) since the diffusivity of Mb *in vivo* estimated lower than it *in vitro* assessment (Lin *et al.*, 2007). Recently, we found Mb localized closely with mitochondria, and some of Mb interact with a mitochondrial protein (complex IV) (Yamada *et al.*, 2013). Furthermore, transient Mb overexpression in myoblast led to enhance respiratory capacities of muscle mitochondria through specifically increase in complex IV activity (Yamada *et al.*, 2016). Moreover, the increase in the expression of nuclear encoded mitochondrial genes correlates with Mb upregulation in both mRNA and protein (Garry *et al.*, 1996; Kim *et al.*, 1995), and Mb expression also links with the onset of differentiation (Kanatous & Mammen, 2010; Singh *et al.*, 2014). These new evidence

suggest that Mb is required for mitochondrial respiration during differentiation, and co-localization of Mb with/within the mitochondria contributes augmentation of mitochondrial respiration capacity via specifically regulated the activity of complex IV in skeletal muscles.

## 5. CONCLUSION

Muscle tissue has mitochondria which is responsive to acute change in contractile activity (i.e. exercise or inactivity) which initiate the signal leading to the mitochondrial biogenesis and improved organelle functions. Chronic exercise also promotes the degradation of poorly functioning mitochondria (i.e. mitophagy), thereby accelerating mitochondrial turnover, and preserving a pool of healthy organelles. In contrast, muscle disuse has strong negative implications for whole-body metabolic health and the preservation of muscle mass. A number of traditional, as well as novel regulatory pathways exist in muscle that control both mitochondrial biogenesis and mitophagy. Interestingly, Mb, traditional and unique protein expressing in muscle cell, is suggested as a protein which has direct interaction with mitochondrial protein to manipulate respiration potential. Understanding of molecular basis of evidence as for the mitochondrial functions can invariably be overcome with exercise and nutrients, signifying that exercise activates a multitude of pathways which can respond to restore mitochondrial health from the aging and metabolic disease state.

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## 8. REFERENCES

- Bach, D., Pich, S., Soriano, F. X., Vega, N., Baumgartner, B., Oriola, J., Daugaard J R, Lloberas J, Camps M, Zierath J R, & Rabasa-Lhoret, R. (2003). Mitofusin-2 determines mitochondrial network architecture and mitochondrial metabolism A novel regulatory mechanism altered in obesity. *Journal of Biological Chemistry*, 278(19), 17190-17197.
- Bereiter-Hahn, J. (1990). Behavior of mitochondria in the living cell. *International review of cytology*, 122, 1-63.
- Chen, H., Vermulst, M., Wang, Y. E., Chomyn, A., Prolla, T. A., McCaffery, J. M., & Chan, D. C. (2010). Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. *Cell*, 141(2), 280-289.
- Dallas, C., Gerbi, A., Tenca, G., Juchaux, F., & Bernard, F. X. (2008). Lipolytic effect of a polyphenolic citrus dry extract of red orange, grapefruit, orange (SINETROL) in human body fat adipocytes. Mechanism of action by inhibition of cAMP-phosphodiesterase (PDE). *Phytomedicine*, 15(10), 783-792.
- Flögel, U., Laussmann, T., Gödecke, A., Abanador, N., Schäfers, M., Fingas, C. D., Metzger S, Levkau B, Jacoby C, & Schrader, J. (2005). Lack of myoglobin causes a switch in cardiac substrate selection. *Circulation research*, 96(8), e68-e75.
- Garnier, A., Fortin, D., Zoll, J., N'Guessan, B., Mettauer, B., Lampert, E., Veksler V., & Ventura-Clapier, R. (2005). Coordinated changes in mitochondrial function and biogenesis in healthy and diseased human skeletal muscle. *The FASEB Journal*, 19(1), 43-52.
- Garry, D. J., Bassel-Duby, R. S., Richardson, J. A., Grayson, J., Neuffer, P. D., & Williams, R. S. (1996). Postnatal development and plasticity of specialized muscle fiber characteristics in the hindlimb. *Developmental genetics*, 19(2), 146-156.
- Garry, D. J., Ordway, G. A., Lorenz, J. N., Radford, N. B., Chin, E. R., Grange, R. W., Bassel-Duby R., & Williams, R. S. (1998). Mice without myoglobin. *Nature*, 395(6705), 905-908.
- Gödecke, A., Flögel, U., Zanger, K., Ding, Z., Hirchenhain, J., Decking, U. K., & Schrader, J. (1999). Disruption of myoglobin in mice induces multiple compensatory mechanisms. *Proceedings of the National Academy of Sciences*, 96(18), 10495-10500.

- Goldberg, D. M., Yan, J., & Soleas, G. J. (2003). Absorption of three wine-related polyphenols in three different matrices by healthy subjects. *Clinical biochemistry*, 36(1), 79-87.
- Grubisha, O., Smith, B. C., & Denu, J. M. (2005). Small molecule regulation of Sir2 protein deacetylases. *Febs Journal*, 272(18), 4607-4616.
- Guyton, G. P., Stanek, K. S., Schneider, R. C., Hochachka, P. W., Hurford, W. E., Zapol, D. G., Liggins, G. C., & Zapol, W. M. (1995). Myoglobin saturation in free-diving Weddell seals. *Journal of Applied Physiology*, 79(4), 1148-1155.
- Hood, D. A. (2001). Invited Review: contractile activity-induced mitochondrial biogenesis in skeletal muscle. *Journal of applied physiology*, 90(3), 1137-1157.
- Hood, D. A., Irrcher, I., Ljubcic, V., & Joseph, A. M. (2006). Coordination of metabolic plasticity in skeletal muscle. *Journal of experimental biology*, 209(12), 2265-2275.
- Howitz, K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W., Lavu, S., Wood, J. G., Zipkin, R. E., Chung, P., Kisielewski, A., Zhang, L. L., Scherer B., & Sinclair D. A. (2003). Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature*, 425(6954), 191-196.
- Ishihara, N., Nomura, M., Jofuku, A., Kato, H., Suzuki, S. O., Masuda, K., Otera, H., Nakanishi, Y., Nonaka, I., Goto, Y., Taguchi, N., Morinaga, H., Maeda, M., Takayanagi, R., Yokota, S., & Mihara, K. (2009). Mitochondrial fission factor Drp1 is essential for embryonic development and synapse formation in mice. *Nature cell biology*, 11(8), 958-966.
- Kaeberlein, M., McDonagh, T., Heltweg, B., Hixon, J., Westman, E. A., Caldwell, S. D., Napper, A., Curtis, R., DiStefano, P. S., Fields, S., Bedalov, A., & Kennedy B. K. (2005). Substrate-specific activation of sirtuins by resveratrol. *Journal of Biological Chemistry*, 280(17), 17038-17045.
- Kanatous, S. B., & Mammen, P. P. (2010). Regulation of myoglobin expression. *Journal of Experimental Biology*, 213(16), 2741-2747.
- Kim, K., Lecordier, A., & Bowman, L. H. (1995). Both nuclear and mitochondrial cytochrome c oxidase mRNA levels increase dramatically during mouse postnatal development. *Biochemical Journal*, 306(2), 353-358.
- Lin, J., Wu, H., Tarr, P. T., Zhang, C. Y., Wu, Z., Boss, O., Michael, L. F., Puigserver, P., Isotani, E., Olson, E. N., Lowell, B. B., Bassel-Duby, R., & Spiegelman, B. M. (2002) Transcriptional co-activator PGC-1 alpha drives the formation of slow-twitch muscle fibres. *Nature*, 418(6899), 797-801
- Lin, P. C., Kreuzer, U., & Jue, T. (2007). Anisotropy and temperature dependence of myoglobin translational diffusion in myocardium: implication for oxygen transport and cellular architecture. *Biophysical journal*, 92(7), 2608-2620.
- Liu, Y., Shen, T., Randall, W. R., & Schneider, M. F. (2005). Signaling pathways in activity-dependent fiber type plasticity in adult skeletal muscle. *Journal of Muscle Research & Cell Motility*, 26(1), 13-21.
- Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Polyphenols: food sources and bioavailability. *The American journal of clinical nutrition*, 79(5), 727-747.

- Masuda K, Takakura H, Furuichi Y, Iwase S and Jue T (2010) NIRS measurement of O<sub>2</sub> dynamics in contracting blood and buffer perfused hindlimb muscle. *Advanced Experimental Medical Biology*, 662, 323-8
- Meeson, A. P., Radford, N., Shelton, J. M., Mammen, P. P., DiMaio, J. M., Hutcheson, K., Kong, Y., Elterman, J., Williams, R. S., & Garry, D. J. (2001) Adaptive mechanisms that preserve cardiac function in mice without myoglobin *Circulation Research*, 88(7), 713-20
- Middleton, E., Kandaswami, C., & Theoharides, T. C. (2000). The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacological reviews*, 52(4), 673-751.
- Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise capacity and mortality among men referred for exercise testing. *New England Journal of Medicine*, 346(11), 793-801.
- Nandiyanto, A. B. D., Sofiani, D., Permatasari, N., Suchaya, T. N., Wiryani, A. S., Purnamasari, A., Rusli, A., & Prima, E. C. (2016). Photodecomposition Profile of Organic Material during the Partial Solar Eclipse of 9 March 2016 and Its Correlation with Organic Material Concentration and Photocatalyst Amount. *Indonesian Journal of Science and Technology*, 1(2), 132-155.
- Ponganis, P. J., Kreutzer, U., Sailasuta, N., Knowler, T., Hurd, R., & Jue, T. (2002). Detection of myoglobin desaturation in *Mirounga angustirostris* during apnea. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 282(1), R267-R272.
- Hamidie, R. D. R., Yamada, T., Ishizawa, R., Saito, Y., & Masuda, K. (2015). Curcumin treatment enhances the effect of exercise on mitochondrial biogenesis in skeletal muscle by increasing cAMP levels. *Metabolism*, 64(10), 1334-1347.
- Reichert, A. S., & Neupert, W. (2004). Mitochondriomics or what makes us breathe. *Trends in genetics*, 20(11), 555-562.
- Roy, M., Reddy, P. H., Iijima, M., & Sesaki, H. (2015). Mitochondrial division and fusion in metabolism. *Current opinion in cell biology*, 33, 111-118.
- Shibaguchi, T., Ishizawa, R., Tsuji, A., Yamazaki, Y., Matsui, K., & Masuda, K. (2017). Fermented Grain Beverage Supplementation Following Exercise Promotes Glycogen Supercompensation in Rodent Skeletal Muscle and Liver. *Indonesian Journal of Science and Technology*, 2(1), 1-7.
- Shiota, T., Imai, K., Qiu, J., Hewitt, V. L., Tan, K., Shen, H. H., Sakiyama, N., Fukasawa, Y., Hayat, S., Kamiya, M., Elofsson, A., Tomii, K., Horton, P., Wiedemann, N., Pfanner, N., Lithgow, T., & Endo, T. (2015). Molecular architecture of the active mitochondrial protein gate. *Science*, 349(6255), 1544-1548.
- Singh, S., Canseco, D. C., Manda, S. M., Shelton, J. M., Chirumamilla, R. R., Goetsch, S. C., Ye, Q., Gerard, R. D., Schneider, J. W., Richardson, J. A., Rothermel, B. A., & Mammen, P. P. (2014). Cytoglobin modulates myogenic progenitor cell viability and muscle regeneration. *Proceedings of the National Academy of Sciences*, 111(1), E129-E138.



- Soriano, F. X., Liesa, M., Bach, D., Chan, D. C., Palacín, M., & Zorzano, A. (2006). Evidence for a mitochondrial regulatory pathway defined by peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$ , estrogen-related receptor- $\alpha$ , and mitofusin 2. *Diabetes*, 55(6), 1783-1791.
- Suwa, M., Nakano, H., Radak, Z., & Kumagai, S. (2008). Endurance exercise increases the SIRT1 and peroxisome proliferator-activated receptor  $\gamma$  coactivator-1 $\alpha$  protein expressions in rat skeletal muscle. *Metabolism*, 57(7), 986-998.
- Takakura, H., Masuda, K., Hashimoto, T., Iwase, S., & Jue, T. (2010). Quantification of myoglobin deoxygenation and intracellular partial pressure of O<sub>2</sub> during muscle contraction during haemoglobin-free medium perfusion. *Experimental physiology*, 95(5), 630-640.
- Truscott, K. N., Kovermann, P., Geissler, A., Merlin, A., Meijer, M., Driessen, A. J., Rassow, J., Pfanner, N., & Wagner, R. (2001). A presequence-and voltage-sensitive channel of the mitochondrial preprotein translocase formed by Tim23. *Nature Structural & Molecular Biology*, 8(12), 1074-1082.
- Westermann, B. (2010). Mitochondrial fusion and fission in cell life and death. *Nature reviews Molecular cell biology*, 11(12), 872-884.
- Williams, R. S., Salmons, S., Newsholme, E. A., Kaufman, R. E., & Mellor, J. (1986). Regulation of nuclear and mitochondrial gene expression by contractile activity in skeletal muscle. *Journal of Biological Chemistry*, 261(1), 376-380.
- Wittenberg, B. A., & Wittenberg, J. B. (1989). Transport of oxygen in muscle. *Annual Review of Physiology*, 51(1), 857-878.
- Yamada, T., Furuichi, Y., Takakura, H., Hashimoto, T., Hanai, Y., Jue, T., & Masuda, K. (2013). Interaction between myoglobin and mitochondria in rat skeletal muscle. *Journal of Applied Physiology*, 114(4), 490-497.
- Yamada, T., Takakura, H., Jue, T., Hashimoto, T., Ishizawa, R., Furuichi, Y., Kato, Y., Iwanaka, N., & Masuda, K. (2016) Myoglobin and the regulation of mitochondrial respiratory chain complex IV. *The Journal of physiology*, 594(2), 483-495.
- Yang, H., Baur, J. A., Chen, A., Miller, C., & Sinclair, D. A. (2007). Design and synthesis of compounds that extend yeast replicative lifespan. *Aging cell*, 6(1), 35-43.
- Zurlo, F., Larson, K., Bogardus, C., & Ravussin, E. (1990). Skeletal muscle metabolism is a major determinant of resting energy expenditure. *Journal of Clinical Investigation*, 86(5), 1423.