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Muscle Metabolic Modulation by Chronic Hypoxia

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Abstract: De Palma *et al.* published a research paper in which they describe the effect of chronic hypoxia on rat skeletal muscle metabolism by means of a comparative proteomic analysis (*J. Proteome Res.* **2007**, *6*(5), 1974–1984). For this, relatively young animals were used. In our communication, we note that, based on other literature, it is likely that the adaptive response of skeletal muscle to hypoxia attenuates with age.

Keywords: skeletal muscles • hypoxia • muscle fiber types • energy metabolism • hypoxia inducible factor 1 α (HIF1 α)

In the May issue of this year, De Palma *et al.* published a research paper in which they describe the effect of chronic hypoxia on rat skeletal muscle metabolism by means of a comparative proteomic analysis.¹ Their results comply with what is regarded as the “Pasteur effect”: a hypoxia-induced shifting from oxidative toward glycolytic metabolism.² The authors state that muscle tissue provides a good model of *in vivo* hypoxia adaptation. This is probably true, but the conditions under which the muscle tissue is exposed to hypoxia should not be overlooked. For example, hypoxia causes very distinct muscular adaptations when muscles are simultaneously exercised as compared to non-exercised muscles.³ The adaptive response to hypoxia may also differ between postnatal developing and matured muscles. Indeed, hypoxia-induced fiber type I to II shifts have been observed in young (3-week old) rats⁴ but not in adult (10-week old) rats.⁵ This is quite a consistent finding, and therefore Ishihara *et al.* postulated that chronic hypoxia inhibits the growth-related II to I fiber type shift that occurs during normal musculoskeletal development.⁶ In growing postnatal muscles, satellite cells (myogenic stem cells) become myoblasts that differentiate and fuse with existing myofibers. There are indications that type II myosin heavy chain isoform is expressed by “default” and that depending on various external stimuli, expression shifts toward the type I myosin heavy chain isoform.⁷ Because type I fibers are more oxidative as compared to type II fibers, the growth-related increase in protein levels associated with oxidative metabolism is likely also inhibited by hypoxia exposure. Many genes encoding for the enzymes involved in glycolytic metabolism

are under the transcriptional control of the hypoxia inducible factor 1 α (HIF1 α) (for review, see ref 8), which was also found to be upregulated by De Palma *et al.* Interestingly, muscular angiogenesis in response to hypoxia is also impaired with aging as the result of reduced DNA binding of HIF1 α and the subsequent downregulation of its target gene vascular endothelial growth factor.^{9,10} De Palma *et al.* studied 5-week old rats, which can be considered as relatively young animals whose muscles are still developing and in which hypoxia may have inhibited the shift from type II toward the more oxidative type I phenotype. It is not unlikely that the observed muscle metabolic modulation will be less pronounced in older rats with full-grown muscles when being exposed to hypoxia. This is a very intriguing question that deserves more attention. It is also interesting from a pathological point of view. Loss of muscle oxidative phenotype is common in disorders such as chronic obstructive pulmonary disease and chronic heart failure.¹¹ Muscle hypoxia is a potential cause, but it is unclear in what phase (satellite cell, myoblast, myofiber) skeletal muscle cells are most responsive to hypoxia in exhibiting the Pasteur effect. The comparative proteomic analysis used by the De Palma *et al.* would provide just the right tool to shed more light on this matter.

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