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Viewpoint

Genetic background, endurance performance and muscle capillarization: lessons from the 'mini mice'

Olivier Birot

Email: birot@yorku.ca

Genetic background contributes to endurance performance in humans. This has also been well established in rodent models by selecting lines of mice for their high exercise capacity. The 'mini mice' used in the study by Audet *et al.* (2011) in this issue of *Experimental Physiology* came from the 54th generation of mouse lines selected since the early 1990s for their exercise capacity in wheel-running cages (Swallow *et al.* 1998). These mice run 2.7–3 times further than the control lines and have an increased mitochondrial enzymatic activity, as well as increased maximal oxygen consumption, when tested in hypoxia. This selection process over the years has also led to an unexpected 'mini-muscle' phenotype due to a single Mendelian recessive allele and characterized by a 50% reduction of the hindlimb muscle mass and a lower body weight. When compared with control lines, certain hindlimb muscles, such as the gastrocnemius, have a decreased weight relative to body weight and a higher proportion of slow oxidative fibres (Audet *et al.* 2011).

Skeletal muscle angio-adaptation refers to the ability of capillaries to regress, stabilize or grow in order to match blood and oxygen supply with the metabolic needs of the myofibres. These processes are tightly regulated by a balance between pro- and anti-angiogenic factors, such as vascular endothelial growth factor-A (VEGF-A) and thrombospondin-1 (TSP-1), respectively.

By determining the oxygen conductance to myofibres, the capillary-to-fibre interface appears to be a crucial component of skeletal muscle function and endurance exercise performance. There are two ways to improve the capillary-to-fibre interface. As observed in response to endurance training, the growth of capillaries by the process of angiogenesis leads to an increase in the capillary-to-fibre ratio (C/F), thus enhancing the capillary-to-fibre interface. Alternatively, in the case of fixed C/F but decreased myofibre cross-sectional area, as observed in the muscles of bats or humminbirds, capillary density will increase as a direct consequence of alteration of the myofibres, resulting in a higher capillary-to-fibre interface; in this situation, however, there is no *de novo* capillary formation (i.e. angiogenesis).

Since 'mini mice' have a significantly increased exercise capacity, Wong *et al.* (2009) have recently analysed the level of capillarization in the medial gastrocnemius muscle from these animals. Interestingly, the capillary-to-fibre interface was increased by region-specific mechanisms within the same muscle. In the superficial part of the medial gastrocnemius, a reduction in the myofibre size was responsible for an increased capillary density, whereas elsewhere angiogenesis around individual fibres increased the capillary-to-fibre ratio. Overall, muscle capillarization was improved and was suggested to contribute to the high exercise capacity of 'mini mice'.

As a natural follow-up step, Audet *et al.* (2011) hypothesized that the expression of VEGF-A and TSP-1, the key pro- and anti-angiogenic factors regulating skeletal muscle angio-adaptation, would be altered in 'mini mouse' skeletal muscles.

They first confirmed that gastrocnemius and plantaris muscles from 'mini mice' taken at rest indeed had higher C/F and capillary density than control muscles. As expected, these muscles also expressed higher basal levels of VEGF-A compared with control animals. More interesting, however, was the VEGF-A expression level in response to one bout of intense running exercise. Exercise is a well-established stimulus for VEGF-A expression in human and rodent skeletal muscle. Here, the authors proposed two interesting hypotheses. First, VEGF-A levels were already higher in mini-muscles than in control muscles in resting conditions. In addition, because of their higher level of capillarization, mini-muscles would be less sensitive to exercise-induced hypoxic stress. As VEGF-A expression is highly regulated at the transcriptional level by hypoxia and hypoxia-inducible factor-1α, one would therefore expect a lack of VEGF-A responsiveness to exercise stimulus in mini-muscles, and thus an increase in exercised control animals only. Second, mini-muscles have higher VEGF-A and capillarization levels at rest, but they also have higher oxidative activity compared with control muscles. Exercise would then stimulate VEGF-A expression in both control and mini-muscles to a similar relative extent. I will keep some suspense here and encourage the reader to find the answer in the article by Audet *et al.* (2011).

Regarding the expression of the anti-angiogenic TSP-1, the results are less clear and seem to be muscle-type specific. At rest, TSP-1 levels were similar in gastrocnemius muscles from control and 'mini mice'. In response to one bout of acute exercise, however, TSP-1 level was dramatically decreased in exercised mini-muscles. In the plantaris muscle, basal TSP-1 level was lower in 'mini mice' than in control mice, but exercise stimulated TSP-1 expression to a similar extent in both control and 'mini mice'.

Taken together, the results of Audet *et al.* (2011) illustrated that the angio-adaptive balance is altered in favour of some pro-angiogenic activity in mice selectively bred for high exercise capacity. This is a novel and interesting finding about the influence of the genetic background on muscle physiology and exercise performance.

This study also brings exciting questions. Why is basal VEGF-A expression higher in skeletal muscles from 'mini mice'? Could it be due to some genetic influences affecting VEGF-A gene directly? For example, Prior *et al.* (2006) have recently described that certain polymorphisms in VEGF-A DNA sequence were correlated with higher maximal oxygen consumption in human subjects. We could also not exclude the possibility that some genetic influences might indirectly affect VEGF-A expression. Prior *et al.* (2003) have shown DNA sequence variations for hypoxia-inducible factor-1α that were also correlated with maximal oxygen consumption in human subjects. To what extent could these alterations affect hypoxia-inducible factor-1α function towards its targets, such as VEGF-A?

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There is no doubt that Audet *et al.* (2011) have open a bit wider the door of an exciting but unfortunately understudied aspect of muscle angio-adaptation to exercise.

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