The epigenetic basis of variable responses to exercise training - a novel study design

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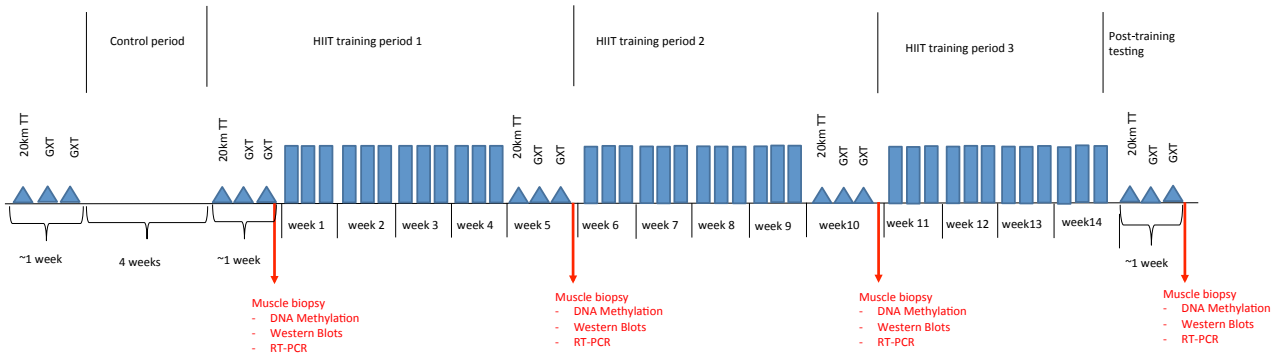
Background: There is considerable individual variability in the response to similar exercise training (Atkinson and Batterham, 2015; Hecksteden *et al.*, 2015). Indeed, some people are 'low/medium responders', while others are 'high-responders'(Bouchard *et al.*, 1998). To date, all exercise studies that claimed to identify "low-" or "high-responders" relied on the assumption that when the same training is prescribed to participants again, they would have the same adaptations. However, within- subject variability has never been tested. Moreover, those initially classified "low-responders" may respond to training if the length of training is extended. Recent evidence suggests that the response to exercise training may be influence by epigenetics signatures (Voisin *et al.*, 2015). Epigenetics is a reversible process that affects how genes are regulated in cells, and it interacts with environmental factors (*e.g.* diet, exercise) to create a cell memory of past events. However no study has yet tested whether the variable response to exercise could have an epigenetic basis.

Aims: 1) To investigate whether the "high-" or "low-response" to exercise training is consistent after a repeated intervention (quantify within-subject variability); and to accurately identify the high-and-low responders; 2) To test whether individuals who did not respond after a short intervention (4 weeks of training) will respond after a longer intervention (12 weeks of training), and 3) To test whether the epigenetic (methylation) changes are different between low-and high responders to exercise training.

Methods: This project is a continuation of the Gene SMART (Skeletal Muscle Adaptive Response to Training) study. A 4-week high-intensity interval training (HIIT) program will be repeated after a wash-out period of minimum 12 months (see figure). Following a similar, repeated intervention of 4 weeks, exercise training will continue for another 8 weeks. 20 participants will be recruited and tested pre- intervention (M0), after 4 weeks of training (M1), after 8 weeks of training (M2), and after 12 weeks of training (M3). Exercise testing will consist of a 20-km cycle Time Trial, and 2 graded-exercise tests (GXT) to determine power peak, lactate threshold and VO2max. Technical error will be used to classify individuals as "high-" and "low-responders" to the selected variables. Muscle biopsies will be taken from the *vastus lateralis* muscle at M0-M3. DNA Methylation assays using the Illumina Infinium Methylation EPIC chips will be conducted.



Conclusion: The overall aim of this study is to suggest a state-of the art, novel study design to accurately classify low-and-high responders to exercise training, with an estimate of within-subject variability. We will also test the hypothesis that response to exercise exists in every individual, but at different rates. Finally, we will explore epigenetic signatures (methylation changes) that may predict the rate of response to exercise training.

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