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Commentary

Response to: The mitochondria-targeted antioxidant MitoQ attenuates exercise-induced mitochondrial DNA damage (Williamson et al., available online 6 August 2020, 101,673)

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ABSTRACT

Williamson and colleagues present important data on the effects of MitoQ - an antioxidant compound targeted to mitochondria - on mtDNA damage following exercise. Future studies are needed to elucidate, whether or not the observed prevention of MitoQ on DNA damage is beneficial with regard to functional outcomes in healthy, exercising humans in dependence of the exercise stimulus and individual characteristics of the person.

We read with great interest the study of Williamson and colleagues [1], in which the authors demonstrate that chronic ingestion of MitoQ mitigates exercise-induced nuclear and mitochondrial DNA (mtDNA) damage. MitoQ is composed of coenzyme Q10 linked via a 10-carbon alkyl chain to tetraphenylphosphonium cation (TPP) that enables the construct's localization to mitochondria, where it expectedly exerts direct antioxidant functions but also appears to upregulate intrinsic antioxidant systems [2,3].

The novel insights of Williamson and colleagues [1] on the effects of MitoQ that is targeted to mitochondria – and thus presumably also primarily acts on mitochondria – on DNA damage following exercise are of great importance. Their results disclose valuable bioavailability features of MitoQ that will aid the optimization of the design of future studies.

Moreover, the study adds to our understanding of molecular adaptations in exercising humans. It is well established that chronic exercise induces a number of adaptations of skeletal muscles and other tissues, which contribute to the reported vast beneficial effects of exercise. Reactive oxygen species (ROS), including ROS derived from mitochondria, are integral for these adaptations, as reviewed in a recent article collection [4] in this journal [5,6]. While generally assumed to be beneficial following moderate exercise in healthy individuals, the consequences of ROS-signalling and associated DNA damage strongly depend on various factors, including characteristics of the exercise stimulus (type, frequency, duration, intensity) and the individual (including health status, age, gender, etc.) performing exercise [7]. ROS-signalling may be damaging in excessive exercise, lead to overtraining [8] and can exert detrimental effects in pathological conditions, such as type 2 diabetes [9]. In this context it is important to point out that while MitoQ has been demonstrated to be beneficial in several disease models [2], Williamson and colleagues [1] investigated physiological mechanisms following exercise interventions, without targeting disease mechanisms. Although associated with potentially harmful oxidative bursts and consequently with oxidative modifications including of mtDNA, exercise is generally associated with a multitude of highly beneficial effects, such as increased performance, preventive potential for numerous diseases and reduced mortality [8,10].

An urgent open question for future studies is; how are acute exercise responses or chronic adaptation outcomes affected by the disruption of ROS-signalling following MitoQ supplementation, especially due to the ambiguous results from previous studies on coenzymeQ/MitoQ supplementation [11]? These responses comprise for example performance, blood flow and angiogenesis, muscle function and growth, mitochondrial adaptations, such as particularly oxidative phosphorylation, biogenesis and quality control. Currently it is unclear, whether the reduction of mtDNA damage is independent of beneficial molecular and physiological exercise adaptations under conditions of reduced ROS-signaling, and if there are consequences for example on muscle

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fatigue and muscle damage [12].

In conclusion, the authors of the discussed article [1] provide valuable characterizations of the potentially beneficial actions of MitoQ in exercising humans and will certainly stimulate further research on that topic. Future studies will be particularly important to address the current knowledge gap on whether or not the observed prevention of MitoQ on DNA damage is beneficial with regard to functional outcomes in healthy, exercising humans in dependence of the exercise stimulus and individual characteristics of the person.

Declaration of competing interest

None.

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