1 – INTRODUCTION

In recent years, much research has focused on the potential for high-intensity interval training (HIIT), defined as repeated intense work bouts separated by recovery periods (Laursen & Jenkins, 2002), to enhance exercise performance and improve cardiovascular and metabolic health. This scientific interest has been accompanied by an increased attention from the society, ranking HIIT among the top fitness trends worldwide.

HIIT promotes a number of physiological adaptations resembling those associated with traditional endurance exercise, including multiple changes within the skeletal muscle (MacInnis & Gibala, 2017). During the past 20 years, there has been a growing interest on specific forms of HIIT characterized by short-duration maximal/supramaximal efforts (Bishop et al., 2011; Hostrup & Bangsbo, 2017). Supramaximal-intensity HIIT has been shown to promote substantial skeletal muscle remodelling, including marked adaptive responses at the mitochondrial level (Roberts et al., 1982; Pilegaard et al., 1999; Barnett et al., 2004; Burgomaster et al., 2005; Burgomaster et al., 2006; Gibala et al., 2006; Burgomaster et al., 2007; Burgomaster et al., 2008; Little et al., 2010; Serpiello et al., 2012; Jacobs et al., 2013; Larsen et al., 2015; Hostrup et al., 2018). However, the mechanisms underlying such adaptive responses are still incompletely understood.

The term hormesis comes from the Greek hórmēsis, literally meaning “rapid motion”. In the fields of biology and medicine, the concept of hormesis, also known as “general adaptation syndrome”, refers to the process by which an organism adapts to a specific stress in an effort to return the body to normal homeostasis (Calabrese et al., 2013). Exercise may elicit hormetic responses via the multitude of biochemical and physiological changes occurring at the cellular level, with skeletal muscle being among the tissues displaying the greatest remodelling capacity in response to various hormetic agents, including metabolic, oxidative, hypoxic, thermal and mechanical stress. Recently, the concept of hormesis has been applied specifically to the mitochondria (Yun & Finkel, 2014), the cellular organelles providing most of the energy necessary to sustain prolonged muscle contraction. Accordingly, mitochondrial hormesis (mitohormesis) has been proposed as a key process coordinating the adaptive responses to exercise, with exercise-induced perturbations in mitochondrial homeostasis purportedly promoting nuclear and cytosolic adaptations to render the whole cell less susceptible to future challenges (Merry 2016).

Mitochondria are dynamic organelles undergoing a constant turnover coordinated by cellular pathways including biogenesis, remodelling dynamics and autophagy (Hood et al., 2015). Mitochondrial biogenesis is the process promoting mitochondrial protein synthesis ultimately leading to an expansion in mitochondrial volume density. Mitochondrial remodelling dynamics by fusion and fission cycles is crucial for mitochondrial quality control, with fusion events restoring the functionality of defective organelles through the formation of a reticular network with neighbouring undamaged mitochondria, while fission events promote the segregation of severely damaged mitochondria from the mitochondrial network. To complete the mitochondrial quality control axis, mitochondria-specific autophagy (mitophagy) selectively degrades and recycles damaged mitochondria segregated by fission events. Taken together,
effective mitochondrial turnover is essential for the maintenance of a high-quality and functional mitochondrial pool.

Early work from Holloszy demonstrated that rodents subjected to exercise training exhibited an increase in muscle mitochondrial enzyme activity along with a general increase in mitochondrial protein concentration following the training period (Holloszy, 1967). In addition, mitochondria from muscle of the trained rodents displayed higher capacity to oxidize pyruvate compared with muscle from untrained counterparts, indicating that exercise training promoted an increase in the capacity to produce ATP via oxidative phosphorylation. Notably, in view of earlier animal studies failing to detect substantial adaptive mitochondrial changes in response to moderate-intensity exercise training (Hearn & Wainio, 1956; Gould & Rawlinson, 1959), Holloszy (1967) adopted a strenuous exercise program including short vigorous efforts interspaced by longer periods at a relatively lower intensity with the purpose to induce a marked exercise stress. Overall, the findings form that study highlighted the importance of utilizing exercise stimuli of an adequate intensity to elicit significant hormetic responses at the muscle mitochondrial level.

The remarkable hormetic response of mitochondria to exercise training was later confirmed in human skeletal muscle (Morgan et al., 1971; Hoppeler et al., 1973; Hoppeler et al., 1985), paving the way for a multitude of human studies showing that the performance- and health-enhancing effects of physical exercise were accompanied by quantitative and qualitative changes in muscle mitochondria.

Thus, given that the nature of the mitochondrial hormetic responses to HIIT is still incompletely understood, the present PhD thesis elaborated on the acute and chronic effects of high-intensity exercise in human skeletal muscle and elucidated the potential role of mitochondria in the performance- and health-enhancing effects of HIIT.

The thesis includes the work conducted during a three-year PhD project, consisting of three research articles which aimed at answering the following questions:

1) Are the initial mitochondrial adaptive events elicited by high-intensity exercise mediated by the degree of exercise-induced metabolic stress? (Study I)

2) Are the performance-enhancing effects of high-intensity exercise training associated with improved muscle mitochondrial function in young healthy individuals? (Study II)

3) Are the health-enhancing effects of high-intensity exercise training associated with ameliorated muscle mitochondrial quality in middle aged/older individuals with essential hypertension? (Study III)