Regulation of exercise performance and contractile function by the endoplasmic reticulum resident antioxidant Selenoprotein S (SEPS1)

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There is emerging interest into endoplasmic reticulum (ER) resident selenoproteins due to their potential to regulate redox homeostasis and intracellular Ca^{2+} signalling. Selenoproteins are important for skeletal muscle growth and development, and their role in regulating contractile function is increasingly recognised (Moghadaszadeh *et al.*, 2013). Selenoprotein S (SEPS1) is one of seven ER resident antioxidant selenoproteins. It is implicated in ER stress reduction and antioxidant defences *via* its interactions with the thioredoxin antioxidant system (Liu *et al*. 2013). The reduction of SEPS1 *via* siRNA amplifies the cellular and ER stress profile of C2C12 myoblasts subjected to excess lipid (palmitate), ultimately leading to reduced cell viability (Addinsall, unpublished data). *In vivo*, the genetic reduction or deletion of SEPS1 has a fibre type specific effect on muscle function and cellular stress responses, leading to impaired contractile function of isolated fast twitch EDL (but not slow twitch *soleus*) muscles and differential regulation of the thioredoxin antioxidant system between fast and slow twitch muscles. Here, our aim is to further characterize the role of SEPS1 in regulating skeletal muscle contractile function using a more physiological approach of strenuous endurance exercise and muscle function testing *in situ*, where the blood and nerve supply remain intact.

Adult male SEPS1 global homozygous ($SEPS1^{-/-}$), heterozygous ($SEPS1^{+/-}$) and wildtype ($SEPS1^{+/+}$) littermates generated by PGK-Cre were utilised to examine the how the loss of SEPS1 affects exercise performance and skeletal muscle contractile function following strenuous endurance exercise. The animal studies were approved by the Animal Ethics Committee at the La Trobe University, in accordance with NH&MRC guidelines. On 3 consecutive days, mice underwent a total of three bouts of incremental exercise starting at $5m/min^{-1}$ and increasing to $25m/min^{-1}$ for 5 minute increments or until voluntary cessation of physical activity. The distance (m) and time (min) run each day was calculated. Twenty-four hours following acute exercise, mice were anesthetised *via* intraperitoneal injection of Sodium pentobarbital (6mg/ml), such that they were unresponsive to tactile stimuli. *Tibialis anterior* (TA) muscle function was assessed *in situ*, where the distal tendon was attached to a force transducer (1300A Whole Mouse Test System, Aurora Scientific) allowing assessment of muscle force production, endurance and recovery from fatigue. Following functional testing, anaesthetized mice were humanely euthanised by cervical dislocation and tissues were collected for molecular and histological analysis.

The genetic deletion of SEPS1 was associated with reduced exercise capacity. Specifically, during the exercise bouts, SEPS1 knockout mice tended to run less than their wild type littermates. Analysis of TA muscle function data *in situ*, as well as muscle morphology and biochemical markers of cellular stress is ongoing to determine whether the decrease in exercise performance is related to impaired fast twitch muscle function or altered antioxidant defences.

Liu J, Li F, and Rozovsky S. (2013). The intrinsically disordered membrane protein selenoprotein S is a reductase *in vitro*. *Biochemistry* **287**, 26388–26399.

Moghadaszadeh B, Rider BE, Lawlor MW, Martin K. Childers, Grange RW, Gupta K, Boukedes SS, Owen CA, and Beggs AH. (2013). N deficiency in mice is associated with abnormal lung development. *FASEB J* **27(4)**, 1585–1599.