Role of selenoprotein S (SEPS1) in regulating skeletal muscle metabolic stress responses

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Selenoprotein S (SEPS1) is protective against oxidative and ER stress in various cultured cell lines. In humans, SEPS1 gene polymorphisms are associated with type 2 diabetes, suggesting a role in metabolic stress responses. The physiological implication of these two observations is unknown. Here we show that SEPS1 expression in skeletal muscle is regulated by nutrient availability *in vivo* and by saturated fatty acids (palmitate) *in vitro*. The effect of fasting and re-feeding on SEPS1 expression was examined in C57BL/6 wild type mice. All animal maintenance and procedures were performed in accordance with the Animal Ethics Committee Guidelines, approved by the Austin and Repatriation Medical Centre (AEC#: A2007/02766). The C57BL/6 mice were randomly allocated into the following 3 groups, *ad libitum* chow fed (fed), fasted overnight for 16 hours (fasted), and fasted overnight and then re-fed for 6 h (re-fed). Mice were anaesthetised with an intraperitoneal injection of Pentobarbitone Sodium (60 mg/kg), blood was collected by cardiac puncture and the liver, pancreas and white quadriceps muscles were excised and snap frozen in liquid nitrogen and stored at −80°C until gene and protein expression analysis. SEPS1 mRNA and protein levels in the liver and pancreas were not affected by nutrient availability. However, following 16 h of overnight fasting, SEPS1 protein levels in gastrocnemius muscles were increased compared with *ad libitum* chow fed mice and further increased following 6 h of re-feeding ($P<0.05$), whilst SEPS1 gene expression was not altered by fasting or re-feeding. The increase in lipid metabolism following fasting and re-feeding can increase oxidative stress due to electron transport chain flux and SEPS1 upregulation may be an adaptive response to counter this stress. Indeed, SEPS1 gene expression was increased 2-fold when C2C12 myotubes were treated for 24 h with 0.2 mM or 0.35 mM palmitate compared with vehicle ($P < 0.01$). A significant increase (184%) in SEPS1 protein expression was observed only in myotubes treated with 0.35 mM palmitate ($P < 0.01$). To further investigate whether SEPS1 is protective against lipid stress and required for metabolic function in skeletal muscle, SEPS1 expression was suppressed in C2C12 muscle cells using siRNA. Following palmitate treatment, SEPS1 expression was increased in siRNA and scramble control treated cells. Despite this, SEPS1 knockdown exacerbated oxidative and ER stress responses to excess lipid, as indicated by additional increases in H_2O_2 production, CHOP and GRP78 mRNA transcripts. Mitochondrial function, specifically maximal and spare respiratory capacity, was also decreased following SEPS1 gene suppression. This was not unexpected as SEPS1 was to shown to co-localize with mitochondria in C2C12 myoblasts. Therefore, in skeletal muscle SEPS1 is regulated in response to metabolic stress, has a role in oxidative and ER stress responses, and is important in maintaining mitochondrial function.