Healthy aging by muscle mitochondrial stress adaptation?
Susanne Klaus, German Institute of Human Nutrition in Potsdam (Germany)

As main organs of energy expenditure and storage, respectively, skeletal muscle (SM) and adipose tissue are major effectors of energy balance and metabolic health. Considering the dramatic increase in obesity and associated metabolic disorders this makes them interesting targets for strategies of obesity prevention and treatment. SM is responsible for about 20% of resting energy expenditure and over 90% of energy expenditure during physical exercise and alterations in its glucose and lipid metabolism are closely associated with obesity induced health impairments. Together, SM and adipose tissue comprise around 70% of body weight in healthy adults and a direct crosstalk between these two organs seems to be involved in regulation of metabolic health.

SM wasting, or atrophy, occurs as a physiological response to muscle disuse, fasting, starvation and aging, as well as in a wide range of systemic diseases, including cancer and diabetes. This is often connected to alterations in mitochondrial function such as mitochondrial respiratory chain (OXPHOS) dysfunction or formation of reactive oxygen species. Mitochondria are key dynamic organelles that not only provide energy (ATP) via oxidative phosphorylation but also are involved in the cellular integrated stress response and in mitohormesis, a molecular adaptation and retrograde response resulting in stress resistance.

Transgenic mice with ectopic expression of uncoupling protein 1 (UCP1) in SM show a muscle-specific decrease in mitochondrial efficiency through increased respiratory uncoupling. Surprisingly, despite a decreased muscle mass and compromised OXPHOS capacity these UCP1-Tg mice show robust metabolic adaptations such as increased insulin sensitivity and metabolic flexibility resulting in increased longevity especially on obesogenic diets. This is associated with the induction of “browning” in different depots of white adipose tissue, i.e. the appearance of clusters of brown-like adipocytes with increased UCP1 expression and mitochondrial activity. Exploration of the mechanisms showed that this “browning” is due to (and completely dependent on) the increased expression and secretion of fibroblast growth factor 21 (FGF21) from SM in UCP1-tg mice which functions as an endocrine acting myokine. Importantly, the decreased mitochondrial efficiency in SM of UCP1-tg mice induces a compensatory cytoprotective response, triggering an increased protein turnover and amino acid metabolism with increased biosynthetic pathways of serine, one-carbon and glycine (SOG). This is related to an increased oxidative stress tolerance as an adaptive mitohormetic response to preserve cellular survival of skeletal muscle. Part of this profound metabolic reprogramming is the induction of endocrine acting secreted factors (myokines) such as FGF21 and others.

Taken together, this supports the emerging idea that mild mitochondrial impairment drives retrograde cell-autonomous and cell-non-autonomous stress pathways to regulate mitochondrial protein homeostasis and extend life span.

References: