Cachexia and heart failure: metabolic reprogramming to counteract skeletal muscle impairment.

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Cachexia is the loss of more than 5% of body weight over 12 months occurring in the presence of a chronic illness such as cancer and chronic heart failure. Cachexia severely interferes with the responsiveness to the therapy of human patients and contributes to poor prognosis, reducing both quality of life and survival.

The lean mass loss in cachectic states is due to an excess of myofibrillar protein catabolism to a reduction of protein synthesis. More recently, altered autophagy and impaired myogenesis have also been evoked. The maintenance of the metabolic efficiency of the myofiber is also critical for maintaining muscle physiology and for avoiding skeletal muscle mass loss.

Some drugs acting as and defined “metabolic modulators” are able to enhance cell metabolic efficiency. Many of them have been studied for their effect on myocardium an approved for the treatment of cardiac disorders. Our group started investigating their almost unexplored effect on skeletal muscle. In particular, we studied the effect of Trimetazidine (TMZ) on skeletal muscle in conditions of sarcopenia and cachexia.

We have already demonstrated that this drug has a hypertrophic effect on cultured myotubes and that it improves exercise capability in patients suffering from chronic stable angina (Ferraro et al., 2013; Vitale et al., 2011). The metabolic modulator TMZ reduces fatty acid oxidation by inhibiting 3-ketoacyl Co-A thiolase and shifts ATP production from fatty acid oxidation toward glucose oxidation. This leads to an improvement of cell energy metabolism since ATP synthesis through fatty acid β-oxidation requires more oxygen compared to glucose oxidation; this accounts for TMZ’s cytoprotective role (Jaswal et al., 2011; Marazzi et al., 2009).

In order to study the effect of TMZ on skeletal muscle in conditions of sarcopenia and cachexia, we used 22-months old mice as model of sarcopenia and mice bearing the C26 coloncarcinoma as a model of cancer cachexia. Mice received 5mg/kg TMZ (i.p.) once a day for 12 consecutive days. A forelimb grip strength test was performed and tibialis anterior and gastrocnemius muscles were excised for analysis. Ex-vivo measurement of skeletal muscle contractile properties was also

performed. We showed that TMZ induces some effects typically achieved through exercise, among which is an enhanced fast-to slow myofiber phenotype shift, reduced glycemia, PGC1α up-regulation, oxidative metabolism, mitochondrial biogenesis and grip strength increase (Ferraro et al, 2016; Molinari et al., submitted). Our experiments revealed that TMZ administration induces some of the benefits achieved through exercise, therefore acting like an 'exercise mimetic' possibly enhancing the mechanisms of adaptation to stress in sarcopenia and cachexia.

Ferraro et al. (2013). FEBS J. 280(20):5094-108.

Vitale et al. (2011). Pharmacological research. 63(4):278-83.

Jaswal et al. (2011). Biochimica et biophysica acta. 1813(7):1333-50.

Marazzi et al. (2009). Advances in therapy. 26(4):455-61.

Ferraro et al. (2016). Journal of cachexia, sarcopenia and muscle. 7(4):449-57.