PGC1α protects against cisplatin-induced skeletal muscle dysfunction

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Background and Hypothesis:

We and others have shown that chemotherapy promotes skeletal muscle wasting and weakness (i.e., cachexia) by disrupting mitochondrial homeostasis and causing oxidative stress. Peroxisome proliferative-activated receptor gamma coactivator 1-alpha (PGC1α) is a pivotal regulator of mitochondrial biogenesis and is involved in reducing oxidative damage in skeletal muscle. Hence, in the present study we investigated whether overexpression of skeletal muscle PGC1α (mPGC1α) was sufficient to preserve skeletal muscle mass and function in young and old mice treated with cisplatin.

Experimental Design or Project Methods:

Young (2-month; *n* = 5) and old (18-month; *n* = 5-8) male wild type (WT) or mPGC1α transgenic mice were treated with cisplatin (2.5mg/kg), while age-matched WT mice received vehicle for 2 weeks. Animals were assessed for muscle force and motor unit number estimation (MUNE). Skeletal muscles were weighed and processed for molecular analyses, including assessment of mitochondrial protein content.

Results:

Young WT mice exposed to cisplatin showed evidence of cachexia, as indicated by reduced gastrocnemius size (-16%), plantarflexion force (-8%) and MUNE (-56%), whereas mPGC1α mice were only partially protected. Interestingly, despite exacerbated cachexia in aged WT mice treated with chemotherapy, as demonstrated by markedly decreased gastrocnemius size (-22%), plantarflexion force (-18%) and MUNE (-80%) compared to untreated WT, muscle mass, strength and innervation were fully preserved in age-matched mPGC1α mice. Follow-up molecular analyses revealed that WT animals exposed to chemotherapy present loss of muscle mitochondrial proteins PGC1α, OPA1 and CytochromeC, whereas their levels in mPGC1α mice were robustly increased.

Conclusion and Potential Impact:

Altogether, our data suggest that PGC1α plays a pivotal role in preserving skeletal muscle mass and function, usually impaired by anticancer treatments. These findings enforce developing mitochondria-targeting therapeutics to combat the negative consequences that chemotherapy has on skeletal muscle.