Sphingolipids Accumulate in Wasted Skeletal Muscles in Ageing and Cachexia

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Disclosures: None.

Introduction. Skeletal muscle (SKM) wasting, including weight loss and loss of function, occurs in chronic and age-related diseases, dramatically impairing quality of life. The mechanistic and metabolic reprogramming, including lipid rearrangements, linked with the SKM functional decline, is unknown.

Methods. Two studies were conducted in C57BL/6 mice. Since females have inherently higher fatty acid desaturation rates, we conducted this study in male mice only to address the general landscape of sphingolipidome rewiring in SKM wasting. A genetically inducible model of frailty (FRA), i.e., accelerated ageing, was validated by inducing high systemic interleukin-6 levels in adult animals through the 5-day food-based administration of doxycycline [1]. FRA mice experienced 30% wasting in the gastrocnemius, but not the soleus [1]. Next, a model of chemotherapy-induced SKM dysfunction (i.e., cachexia; CAC) was carried over by administering cisplatin to young (2 months) and old (18 months) mice, either wild type or genetically modified to overexpress PGC1α in SKM, the latter counteracting cisplatin-induced SKM wasting and neuromuscular defects in the quadriceps of old mice [2]. Using LC-MS/MS, we applied untargeted and quantitative lipidomics in the SKM and other metabolic tissues. The experiments were approved by the IACUCs at the UA and IU. Computational analyses were done using R packages, MetaboAnalyst 5.0, and LipidSuite 1.0.

Results. In FRA animals, we saw 1225 lipid events belonging to 25 lipid classes in the sarcopenic gastrocnemius. Only in the gastrocnemius (but not soleus), untargeted lipidomics indicated 2-fold changes in ceramides and di- and triglycerides, compared to the adult controls. Quantitative analyses confirmed the accumulation of complex sphingolipids, specifically hexosylceramides, in gastrocnemius, but not soleus (Figure 1, Upper panel), driven by C16-, C18-, C24-, C24:1-glucosyl, and C16-, C18-, and C24:1-lactosyl features only in the FRA group. Lipid shifts in plasma and subcutaneous adipose tissue paralleled gastrocnemius and soleus, respectively. Quantitative enrichment analyses (QEA) in plasma confirmed sphingolipid metabolism as 3rd most enriched pathway in FRA. Next, in the CAC study, the discovery approach in cachectic quadriceps revealed 233 lipid features belonging to carnitines, sphingolipids, cardiolipin, and phosphatidic acid classes. Lipidomic fingerprints showed the upregulation of hexosylceramides in cisplatin-induced cachexia in old animals only; however, the trend was reversed in the presence of PGC1α (Figure 1, Lower panel). The QEA showed β-oxidation as the 4th most enriched pathway, also in the presence of PGC1α, indicating the role of mitochondrial biogenesis in intracellular protection in cachexia. All the findings were present in the quadriceps, but not plasma, pointing out SKM-specific regulation in cisplatin-induced cachexia.

Discussion. Intramyocellular hexosylceramides-driven lipid accumulation in the gastrocnemius in accelerated ageing, and quadriceps in cisplatin-induced wasting, underpins SKM wasting in frailty and cachexia. Reportedly, FRA animals experienced higher PGC1α levels in the sarcopenic gastrocnemius [1], the same mitochondrial regulator that acts protectively in CAC [2], indicative of mitochondrial adaptive reparative mechanisms in lipotoxicity-driven SKM wasting.

Clinical Relevance. Accumulation of hexosylceramides might be a lipotoxic mechanism underlying SKM wasting in frailty-linked sarcopenia and cisplatin-induced cachexia, similar to what is already proposed in age-related sarcopenia [3]. Pharmacological inhibition of hexosylceramide synthase by eliglustat/miglustat will be tested for alleviating SKM wasting in chronic disease.

References. [1] Jergović, M et al. (2021). IL-6 can single-handedly drive many features of frailty in mice. Gerosc, 43, 539-549. [2] Huot et al. (2022). PGC1α overexpression preserves muscle mass and function in cisplatin-induced cachexia. J Cachexia Sarcopenia Muscle, 13(5), 2480-2491. [3] Laurila PP, et al. (2022). Sphingolipids accumulate in aged muscle, and their reduction counteracts sarcopenia. Nat Aging, 2(12), 1159-1175.

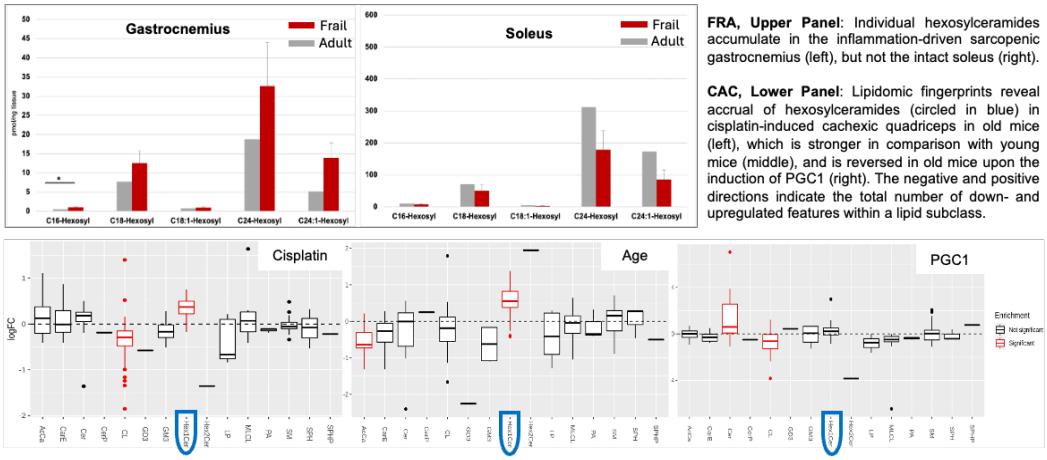

Figure 1. Accumulation of hexosylceramides in muscle wasting linked with ageing (upper panel) and cisplatin-induced cachexia (lower panel).