Derangements of amino acids in cachectic skeletal muscle are caused by mitochondrial dysfunction

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Introduction & Aim

Cachexia is the direct cause of at least 20% of cancer-associated deaths. Muscle wasting in skeletal muscle results in weakness, immobility, and death secondary to impaired respiratory muscle function. Muscle proteins are massively degraded in cachexia; nevertheless, the molecular mechanisms related to this process are poorly understood. Previous studies have reported conflicting results regarding the amino acid abundances in cachectic skeletal muscle tissues. There is a clear need to identify the molecular processes of muscle metabolism in the context of cachexia, especially how different types of molecules are involved in the muscle-wasting process.

Material and Methods

Molecular analysis in mice

Validation experiments for MALDI imaging results

Focusing mitochondria for cancer cachexia

Summary

Metabolic derangements in cachetic mouse muscle tissues were detected, with significantly increased quantities of lysine, arginine, proline, and tyrosine and significantly reduced quantities of glutamate and aspartate. A majority of altered amino acids was released by the breakdown of proteins involved in oxidative phosphorylation. Additionally, expression of the cationic amino acid transporter CAT1 was significantly decreased in the mitochondria of cachetic mouse muscles; this decrease may play an important role in the alternations of cationic amino acid metabolism and decreased quantity of glutamate observed in cachexia. Our results suggest that mitochondrial dysfunction has a substantial influence on amino acid metabolism in cachetic skeletal muscles, which appears to be triggered by diminished CAT1 expression, as well as the degradation of mitochondrial proteins. These findings provide new insights into the pathobiology of muscle wasting.

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