"Regulation of muscle protein degradation in physiological and pathological catabolic states"

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Abstract
Protein degradation in skeletal muscle is emerging as a homeostatic mechanism, the fine-tuning of which contributes to muscle health. On the one side, too high protein degradation flux can lead to muscle atrophy. On the other side, sufficient protein degradation activity is required for eliminating aberrantly folded proteins, providing alternative energy substrates and remodelling muscle fibre. The general purpose of the present work was to contribute to the understanding of the molecular mechanisms underlying the regulation of the ubiquitin-proteasome pathway (UPP) and the autophagy-lysosomal pathway (ALP) during catabolic states. In a first part of the work, the potential interest of proteasome inhibitors as therapeutic tools to prevent patho-physiological muscle atrophy in mice was questioned. In a second part of the thesis, the regulation of proteolytic systems in response to acute endurance exercise was studied. In a mouse model of disuse, intraperitoneal administration of a p...

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Summary

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The general purpose of the present work was to contribute to the understanding of the molecular mechanisms underlying the regulation of the ubiquitin-proteasome pathway (UPP) and the autophagy-lysosomal pathway (ALP) during catabolic states. In a first part of the work, the potential interest of proteasome inhibitors as therapeutic tools to prevent pathological muscle atrophy in mice was questioned. In a second part of the thesis, the regulation of proteolytic systems in response to acute endurance exercise was studied.

In a mouse model of disuse, intraperitoneal administration of a proteasome inhibitor was able to repress the atrophy of the gastrocnemius muscle. This protective effect was not related to an inhibition of proteasome activity, but rather to the repression of the increase in the mRNA expression of muscle specific ligase MuRF-1 and MAFbx. The inhibitory effect of proteasome inhibitors on muscle specific ligases was confirmed in a mouse model of sepsis.

The transcription of a subset of genes belonging to the UPP (MuRF-1, MAFbx, USP28, C2) and ALP (Gabarap1l, Bnip3, Bnip3L, LC3b) was increased in an extreme model of endurance exercise (ultra-marathon), in human skeletal muscle. In this model, the coordinated activation of UPP and ALP was mediated through a major repression of the insulin/Akt pathway, together with an increase in the phosphorylation state of AMPK. Mice that exercised on a treadmill at low intensity in the fasted state underwent a higher activation of both autophagy-related genes and autophagy-related proteins, as compared to mice that exercised in the fed state. This higher activation was related to a repression of the insulin/Akt pathway. Other signalling pathways as well as selective forms of autophagy are also likely to contribute to the increase in autophagy flux during endurance exercise. Future works should be undertaken to investigate how transient activation of autophagy in response to endurance exercise may contribute to promote muscle health.