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Plenary Abstract

New Pathogenetic Mechanisms that Link Autophagy to Pompe Disease

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BACKGROUND

Skeletal muscle is one of the tissues with the highest rate of autophagosome formation and degradation. A group of congenital myopathies, characterised by lysosomal alteration, are described by massive autophagic build-up and are named Autophagic Vacuolar Myopathies (AVM). Among these disorders, Danon disease (DD) and Pompe (GSD2) are characterised by the presence of large glycogen-filled lysosomes in the skeletal muscle. We have recently shown that autophagy impairment contributes to disease progression in GSD2 patients. However, the mechanism that leads to autophagy inhibition, and whether this impairment is shared in other AVM in humans is an open issue.

MATERIAL AND METHODS

We have analysed muscle biopsies of GSD2 and DD patients for markers of autophagy and signalling pathways related to lysosomal biogenesis and endosome trafficking by immunofluorescence, Western blotting and quantitative RT-PCR techniques.

RESULTS

Our findings underline that indeed autophagy is critical for maintenance of muscle mass in DD and GSD2 and that alterations of pathways related to endosome trafficking and lysosomal biogenesis are major pathogenetic mechanisms that contribute to muscle wasting and weakness in GSD2 and DD disease. In particular, alterations of VPS15/VPS34/beclin complex and TFEB transcription factor have been found in GSD2 and DD patients.

CONCLUSIONS

A new perspective emerges from our findings that is focused on signalling perturbation as a pathogenetic mechanism. Autophagosome build-up and lysosome dysfunction impact pathways that, once impaired, greatly contribute to weakness and resistance to therapy in GSD2 and DD patients. Understanding which pathways are the most critical and how to reactivate them are the next most important and challenging issues in order to optimise treatments and counteract disease progression.

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