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Upregulation of the Rab27a-dependent trafficking and secretory mechanisms improves lysosomal transport, alleviates endoplasmic reticulum stress, and reduces lysosome overload in cystinosis.

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Abstract

Cystinosis is a lysosomal storage disorder caused by the accumulation of the amino acid cystine due to genetic defects in the CTNS gene, which encodes cystinosin, the lysosomal cystine transporter. Although many cellular dysfunctions have been described in cystinosis, the mechanisms leading to these defects are not well understood. Here, we show that increased lysosomal overload induced by accumulated cystine leads to cellular abnormalities, including vesicular transport defects and increased endoplasmic reticulum (ER) stress, and that correction of lysosomal transport improves cellular function in cystinosis. We found that Rab27a was expressed in proximal tubular cells (PTCs) and partially colocalized with the lysosomal marker LAMP-1. The expression of Rab27a but not other small GTPases, including Rab3 and Rab7, was downregulated in kidneys from Ctns-/- mice and in human PTCs from cystinotic patients. Using total internal reflection fluorescence microscopy, we found that lysosomal transport is impaired in Ctns-/- cells. Ctns-/- cells showed significant ER expansion and a marked increase in the unfolded protein response-induced chaperones Grp78 and Grp94. Upregulation of the Rab27a-dependent vesicular trafficking mechanisms rescued the defective lysosomal transport phenotype and reduced ER stress in cystinotic cells. Importantly, reconstitution of lysosomal transport mediated by Rab27a led to decreased lysosomal overload, manifested as reduced cystine cellular content. Our data suggest that upregulation of the Rab27a-dependent lysosomal trafficking and secretory pathways contributes to the correction of some of the cellular defects induced by lysosomal overload in cystinosis, including ER stress.

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Cystinosis/pathology*
Down-Regulation
Endoplasmic Reticulum Stress*
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Humans
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Mice
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Substances

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