Calcium aids protein folding as therapy for enzymes in types of lysosomal storage diseases

February 5 2008

Lysosomes are organelles that break down macromolecules in a cell, and this process is crucial for maintaining healthy cells. A lysosomal storage disease results from deficient activity of the hydrolytic enzymes, responsible for the breakdown of defunct molecules.

Currently, lysosomal storage diseases are treated by enzyme replacement therapy. This can be challenging because the enzyme has to find its proper way into cells and lysosomes to function. In neuropathic diseases, enzyme replacement is not useful because recombinant enzymes do not enter the brain.

This week in the open-access online journal PLoS Biology, Tingwei Mu, Douglas Fowler, and Jeffrey Kelly show that diltiazem and verapamil, potent FDA approved L-type Ca2+ channel blocking drugs, could restore the activity of mutant lysosomal enzymes associated with three distinct lysosomal storage diseases. The drugs acted by increasing the endoplasmic reticulum (ER) folding capacity and trafficking.

These compounds appear to function through a Ca2+ ion-mediated upregulation of a subset of cytoplasmic and ER lumenal chaperones, possibly by activating signaling pathways that lessen cellular stress. They have shown that increasing ER calcium levels appears to be a relatively selective strategy to partially restore mutant lysosomal enzyme homeostasis in diseases caused by the misfolding and degradation of

mutant enzymes. Since diltiazem crosses the blood-brain barrier, it may be useful for the treatment of neuropathic lysosomal storage diseases, and possibly other loss-of-function diseases, although efficacy needs to be demonstrated before this happens.

Citation: Mu TW, Fowler DM, Kelly JW (2008) Partial restoration of mutant enzyme homeostasis in three distinct lysosomal storage disease cell lines by altering calcium homeostasis PLoS Biol 6(2): e26. doi:10.1371/journal.pbio.0060026

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