Molecular mechanism of the lysosomal transporter PQLC2,a rate-limiting step in cysteamine therapy of cystinosis

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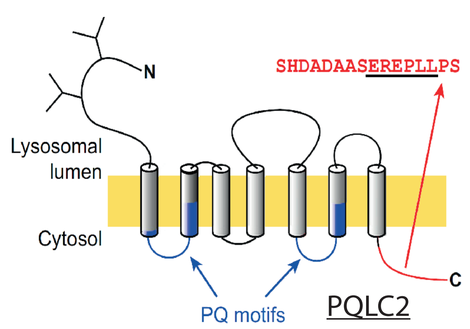
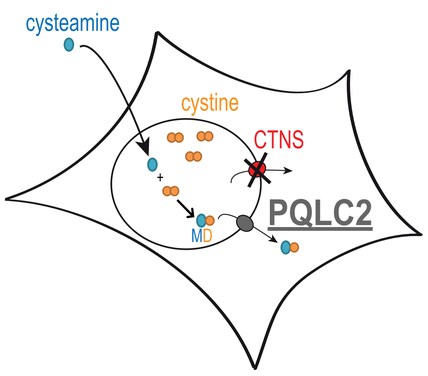


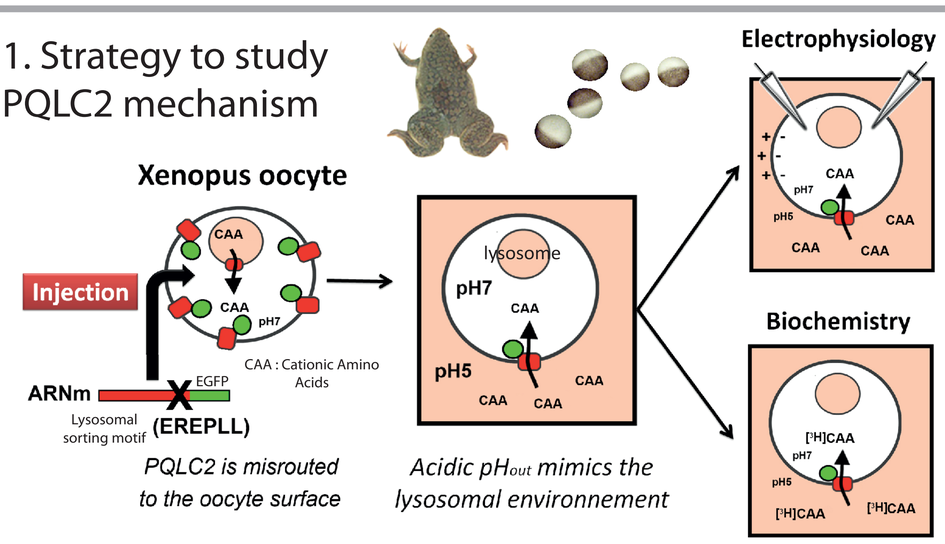
Recently, we used proteomics, yeast genetic and transport studies to identify and characterize a lysosomal transporter for cationic amino acids (**CAA**) termed PQLC2 (**Jezegou et al., PNAS 2012**). Interestingly, PQLC2 also transports a lysine-like mixed disulfide (**MD**) that is a chemical intermediate in cysteamine therapy of cystinosis.

In this study, we investigated the transport properties of PQLC2 and explored whether it might represent a therapeutic target to improve cysteamine therapy.

Taken together, our results suggest that PQLC2 mediates a rate-limiting step in lysosomal cystine clearance, that it is expressed at a suboptimal level and is modulated by the electrical potential of the lysosomal membrane. Thus, this study brings forwards novel ways to improve cystine depletion during cysteamine therapy.

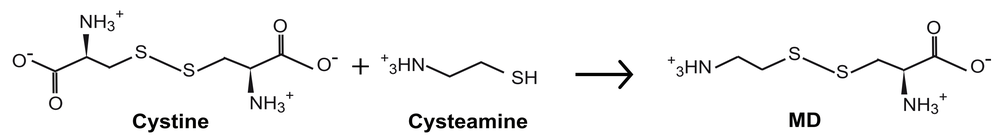


1. Strategy to study PQLC2 mechanism

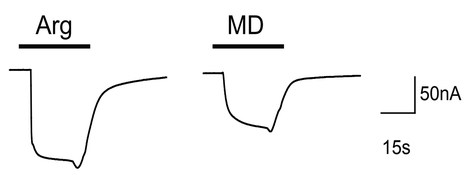


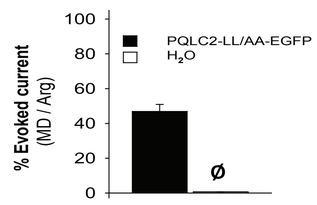
2. PQLC2 transports the mixed-disulfide (MD)

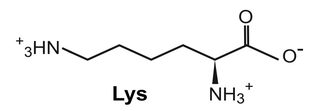
A. Cystinosis treatment



B. MD transport current carried by PQLC2



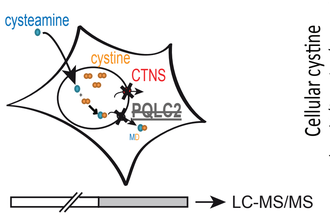


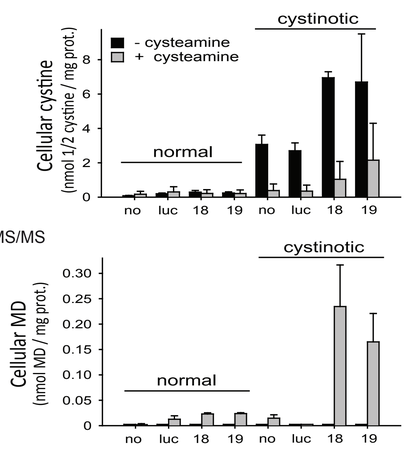


Jézégou et al., PNAS 2012

3. PQLC2 mediates the rate-limiting step in cysteamine therapy

A. PQLC2 knock-down traps MD in cysteamine-treated cystinotic cells





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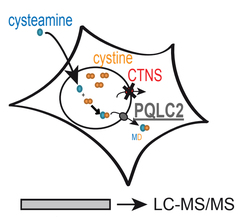
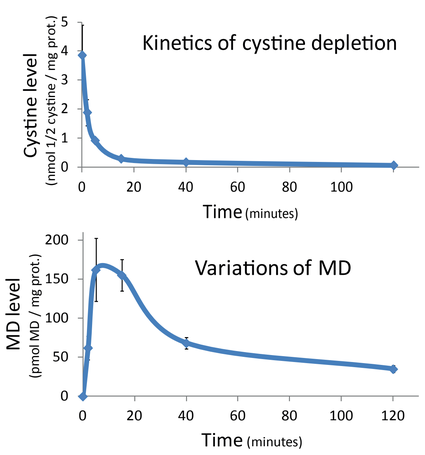
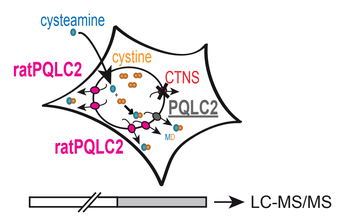
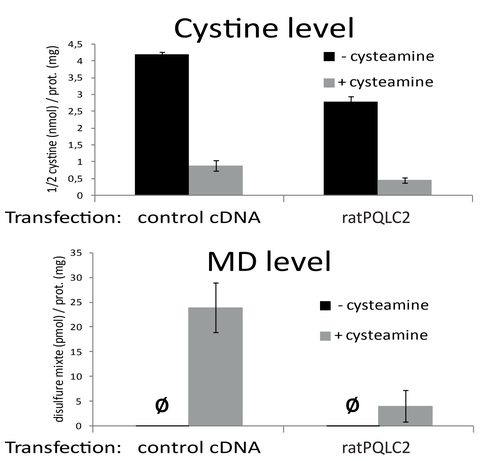
B. MD clearance is substantially slower than its synthesis





C. Over-expression of PQLC2 in patient fibroblasts increases MD clearance

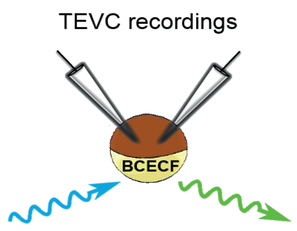




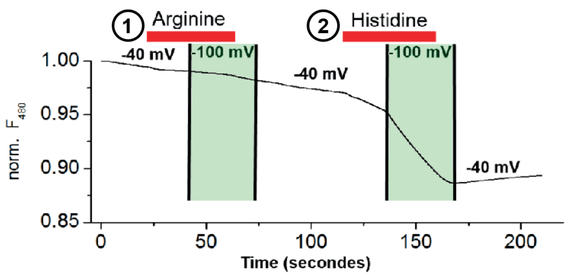
4. PQLC2 is putatively a uniporter driven solely by lysosomal voltage, suggesting that lysosomal ion channels may modulate the efficiency of cysteamine therapy

A. PQLC2 does not cotransport protons

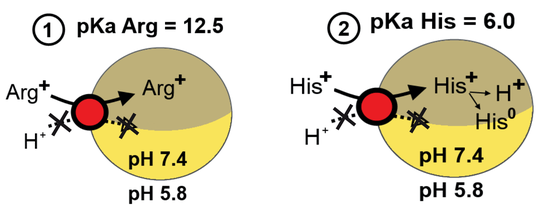
a) Experimental setup



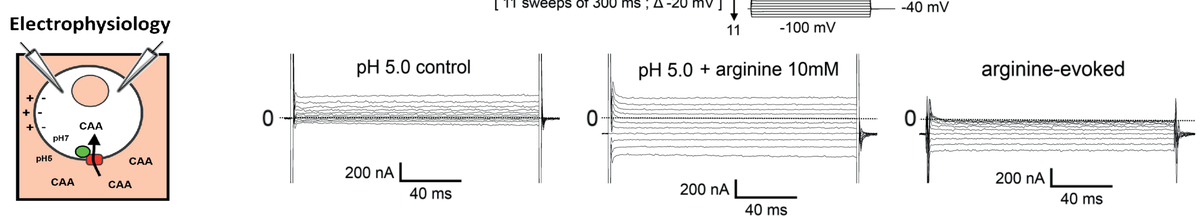
b) acidification measurements



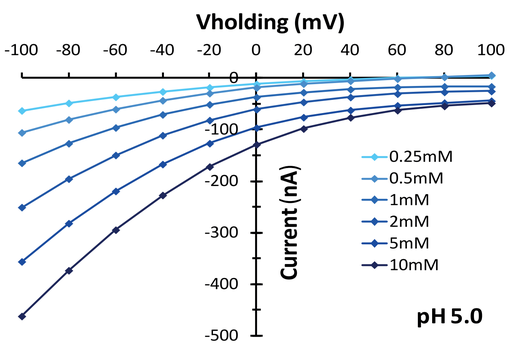
c) Interpretations



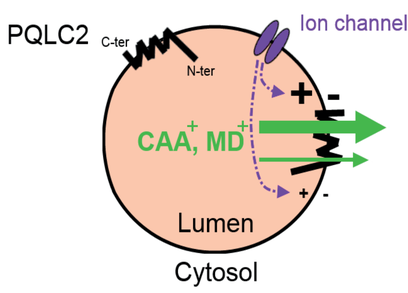
B. Voltage is the main driving force for CAA transport, despite the strong 2-Unit pH gradient under our experimental conditions



Current-voltage relationship of PQLC2-mediated arginine transport



Hypothesis : MD export from lysosomes may be improved by modification of the lysosomal membrane potential by acting on ion channels



Xavier Leray has a PhD fellowship from the Cystinosis Research Foundation.

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