



A Chimera Carrying the Functional Domain of the Orphan Protein SLC7A14 in the Backbone of SLC7A2 Mediates Trans-stimulated Arginine Transport*

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Capsule

Background: The molecular identity of the lysosomal transporter for cationic amino acids, system c, remains unknown.

Results: SLC7A14 is a lysosomal localized protein with a functional domain that mediates arginine transport.

Conclusion: SLC7A14 may mediate cationic amino acid transport across lysosomal membranes.

Significance: As system c represents a salvage pathway in the therapy of cystinosis, characterization of SLC7A14 might help to develop better drugs.

Abstract

In human skin fibroblasts, a lysosomal transport system specific for cationic amino acids has been described and named system c. We asked if SLC7A14 (solute carrier family 7 member A14), an orphan protein assigned to the SLC7 subfamily of cationic amino acid transporters (CATs) due to sequence homology, may represent system c. Fusion proteins between SLC7A14 and enhanced GFP localized to intracellular vesicles, co-staining with the lysosomal marker LysoTracker[®]. To perform transport studies, we first tried to redirect SLC7A14 to the plasma membrane (by mutating putative lysosomal targeting motifs) but without success. We then created a chimera carrying the backbone of human (h) CAT-2 and the protein domain of SLC7A14 corresponding to the so-called "functional domain" of the hCAT proteins, a protein stretch of 81 amino acids that determines the apparent substrate affinity, sensitivity to trans-stimulation, and (as revealed in this study) pH dependence. The chimera mediated arginine transport and exhibited characteristics similar but not identical to hCAT-2A (the low affinity hCAT-2 isoform). Western blot and microscopic analyses confirmed localization of the chimera in the plasma membrane of *Xenopus laevis* oocytes. Noticeably, arginine transport by the hCAT-2/SLC7A14 chimera was pH-dependent, trans-stimulated, and inhibited by α -trimethyl-L-lysine, properties assigned to lysosomal transport system c in human skin fibroblasts. Expression analysis showed strong expression of SLC7A14 mRNA in these cells. Taken together,

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these data strongly suggest that SLC7A14 is a lysosomal transporter for cationic amino acids.

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[SLC7A14](#)

[System c](#)

[Arginine Transport](#)

[Cystinosis](#)

[Human Cationic Amino Acid Transporter \(hCATs\)](#)

Footnotes

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↵ This article contains [supplemental Figs. 1-5 and Table I](#).

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