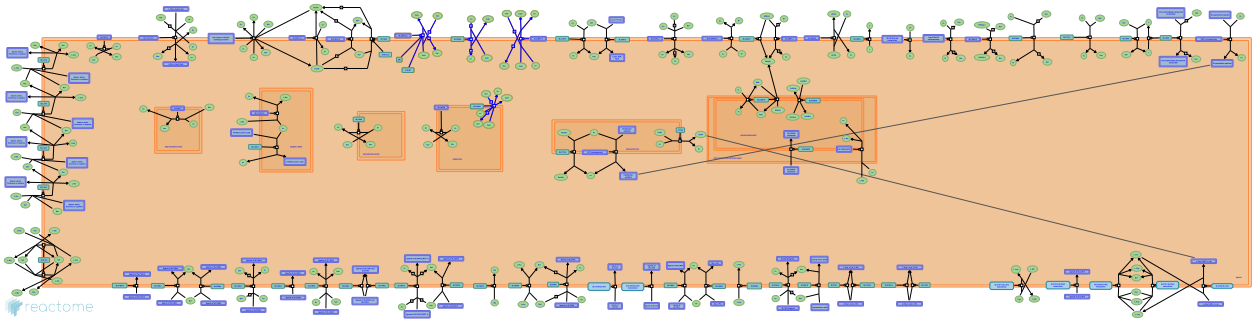
Sodium/Calcium exchangers



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

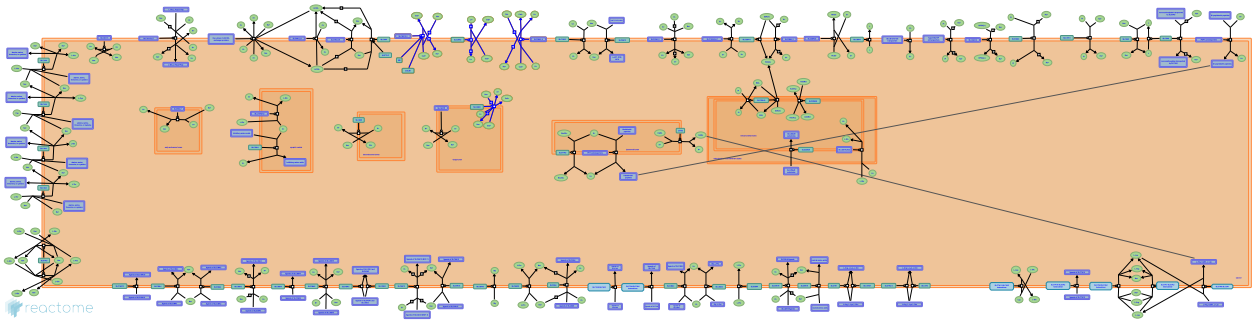
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Sodium/Calcium exchangers ↗

Stable identifier: R-HSA-425561



Calcium ions are used by cells as ubiquitous signalling molecules that control diverse physiological events. Three mammalian gene families control Ca2+ transport across plasma membranes and intracellular compartments (Lytton J, 2007). They are the Na+/Ca2+ exchanger family designated NCX (SLC8) (three members NCX1-3) (Quednau BD et al, 2004), the Na+/Ca2+-K+ exchanger family designated NCKX (SLC24) (five members NCKX1-5) (Schnetkamp PP, 2004) and a Ca2+/cation exchanger (NCKX6, NCLX) whose physiological function remains unclear.

Literature references

Schnetkamp, PP. (2004). The SLC24 Na+/Ca2+-K+ exchanger family: vision and beyond. *Pflugers Arch, 447*, 683-8. ↗

Quednau, BD., Nicoll, DA., Philipson, KD. (2004). The sodium/calcium exchanger family-SLC8. *Pflugers Arch, 447*, 543-8. ↗

Lytton, J. (2007). Na+/Ca2+ exchangers: three mammalian gene families control Ca2+ transport. *Biochem J, 406*, 365-82. ↗

Editions

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2009-08-24	Reviewed	He, L.

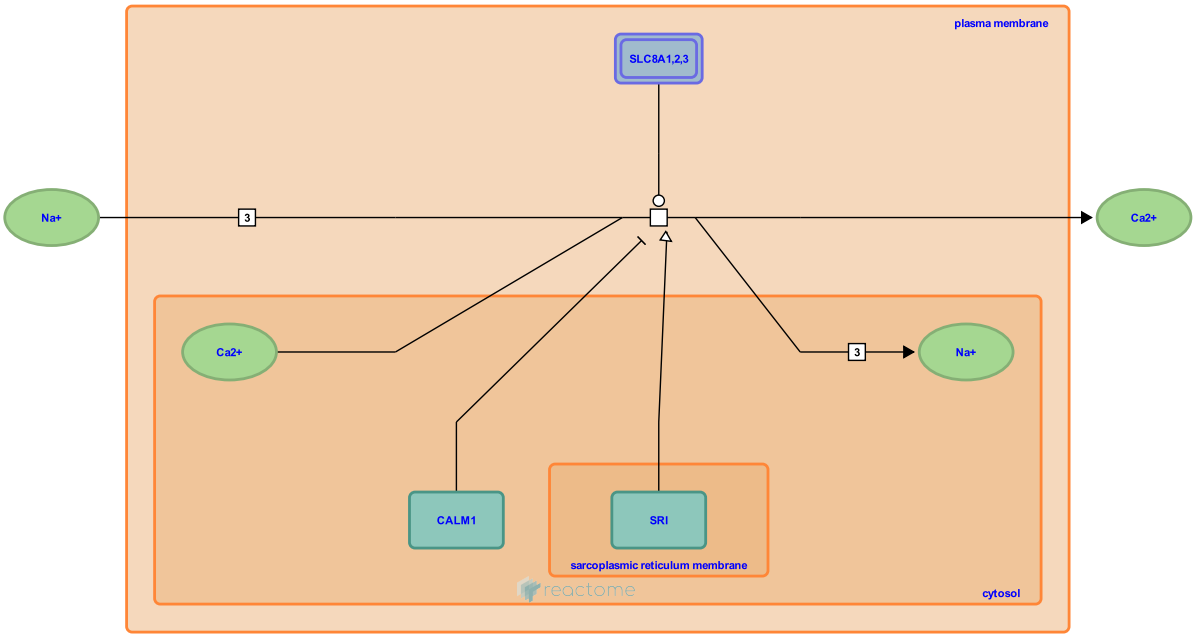
SLC8A1,2,3 exchange 3Na+ for Ca2+ ↗

Location: Sodium/Calcium exchangers

Stable identifier: R-HSA-425661

Type: transition

Compartments: plasma membrane, cytosol, extracellular region



The sodium/calcium exchangers 1, 2 and 3 (SCL8A1,2,3 aka NCX1,2,3) belong to one of three families that control Ca2+ flux across the plasma membrane or intracellular compartments. They extrude Ca2+ from the cell, using the electrochemical gradient of Na+ as it flows into the cell. One Ca2+ is exchanged for three Na+. During this electrogenic exchange, the membrane potential is altered. SLC8A1, 2, 3 play a minor role during phase 2, since they begin to restore ion concentrations. The high concentration of intracellular calcium starts contraction of those cells, which is sustained in the plateau phase. SLC8A1 has a ubiquitous expression profile (highest expression in heart, brain and kidney) and was originally cloned and characterized from human cardiac muscle (Komuro et al. 1992). Both SLC8A2) (Li et al. 1994) and SLC8A3 (Gabellini et al. 2002) are expressed in the brain.

In Rabbits, sorcin (SRI) activates SLC8A1, via the interaction of the respective Ca2+-binding domains (Zamparelli et al. 2010). Calmodulin (CALM1) binds to the cytoplasmic loop of NCX1 to negatively regulate exchange activity (Chou et al. 2015).

Literature references

Komuro, I., Wenninger, KE., Philipson, KD., Izumo, S. (1992). Molecular cloning and characterization of the human cardiac Na+/Ca2+ exchanger cDNA. *Proc Natl Acad Sci U S A, 89*, 4769-73. ↗

Li, Z., Matsuoka, S., Hryshko, LV., Nicoll, DA., Bersohn, MM., Burke, EP. et al. (1994). Cloning of the NCX2 isoform of the plasma membrane Na(+)-Ca2+ exchanger. *J Biol Chem, 269*, 17434-9. ↗

Gabellini, N., Bortoluzzi, S., Danieli, GA., Carafoli, E. (2002). The human SLC8A3 gene and the tissue-specific Na+/Ca2+ exchanger 3 isoforms. *Gene, 298*, 1-7. ↗

Zamparelli, C., Macquaide, N., Colotti, G., Verzili, D., Seidler, T., Smith, GL. et al. (2010). Activation of the cardiac Na(+)-Ca(2+) exchanger by sorcin via the interaction of the respective Ca(2+)-binding domains. *J. Mol. Cell. Cardiol., 49*, 132-41. ↗

Chou, AC., Ju, YT., Pan, CY. (2015). Calmodulin Interacts with the Sodium/Calcium Exchanger NCX1 to Regulate Activity. *PLoS ONE, 10*, e0138856. ↗

Editions

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2009-08-24	Reviewed	He, L.

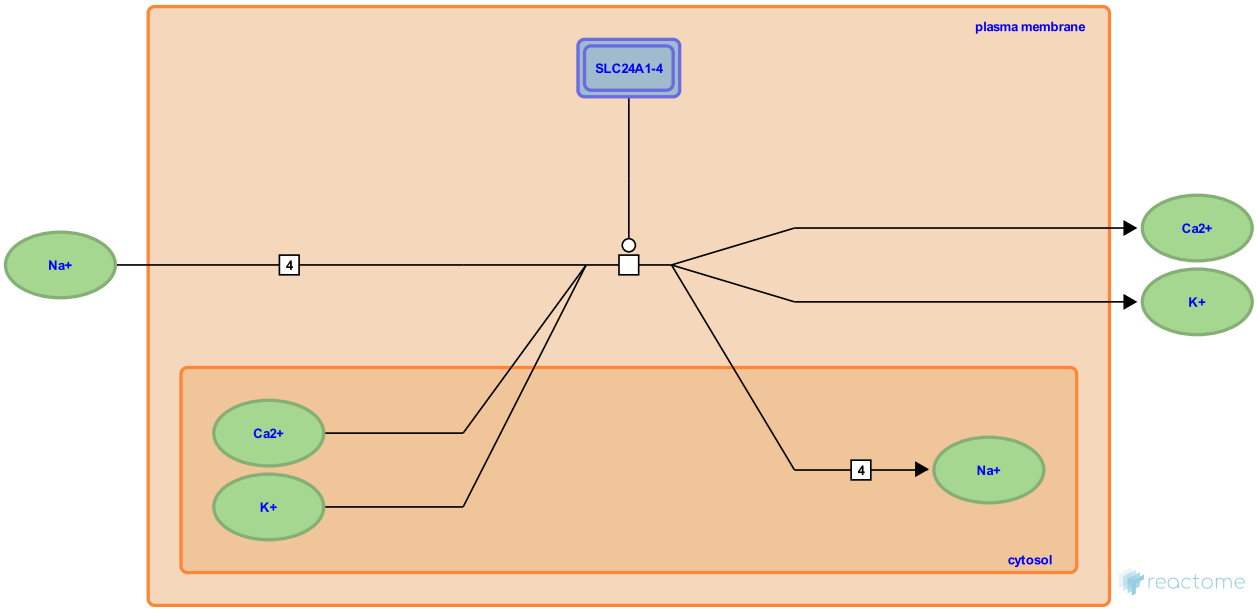
SLC24A1-4 exchange extracellular 4Na+ for cytosolic Ca2+, K+ ↗

Location: Sodium/Calcium exchangers

Stable identifier: R-HSA-425678

Type: transition

Compartments: plasma membrane



The five members of the NCKX (SLC24) family are all able to exchange one Ca2+ and one K+ for four Na+. NCKX1 (SLC24A1) encodes an exchanger protein which is the most extensively studied member (Tucker et al. 1998). It is highly expressed in the eye. Other members are expressed in the brain and skin as well as the eye (Prinsen et al. 2000, Kraev et al. 2001, Li et al. 2002, Lamason et al. 2005).

Literature references

Prinsen, CF., Szerencsei, RT., Schnetkamp, PP. (2000). Molecular cloning and functional expression of the potassium-dependent sodium-calcium exchanger from human and chicken retinal cone photoreceptors. *J Neurosci, 20*, 1424-34. ↗

Tucker, JE., Winkfein, RJ., Murthy, SK., Friedman, JS., Walter, MA., Demetrick, DJ. et al. (1998). Chromosomal localization and genomic organization of the human retinal rod Na-Ca+K exchanger. *Hum Genet, 103*, 411-4. ↗

Kraev, A., Quednau, BD., Leach, S., Li, XF., Dong, H., Winkfein, R. et al. (2001). Molecular cloning of a third member of the potassium-dependent sodium-calcium exchanger gene family, NCKX3. *J Biol Chem, 276*, 23161-72. ↗

Li, XF., Kraev, AS., Lytton, J. (2002). Molecular cloning of a fourth member of the potassium-dependent sodium-calcium exchanger gene family, NCKX4. *J Biol Chem, 277*, 48410-7. ↗

Lamason, RL., Mohideen, MA., Mest, JR., Wong, AC., Norton, HL., Aros, MC. et al. (2005). SLC24A5, a putative cation exchanger, affects pigmentation in zebrafish and humans. *Science, 310*, 1782-6. ↗

Editions

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2009-08-24	Reviewed	He, L.

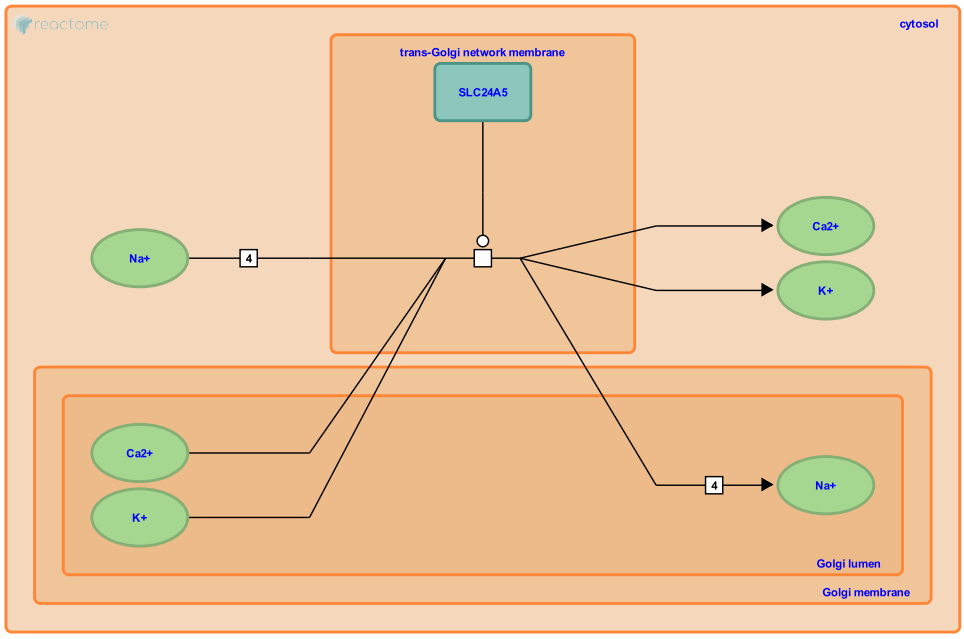
SLC24A5 exchanges cytosolic 4Na+ for Golgi luminal Ca2+, K+

Location: Sodium/Calcium exchangers

Stable identifier: R-HSA-5626316

Type: transition

Compartments: trans-Golgi network membrane, cytosol, Golgi lumen



The five members of the NCKX (SLC24) family are all able to exchange one Ca2+ and one K+ for four Na+. SLC24A5 encodes a trans-Golgi network exchanger protein NCKX5 which is expressed in melanocytes and regulates human epidermal melanogenesis (Ginger et al. 2008).

Literature references

Ginger, RS., Askew, SE., Ogborne, RM., Wilson, S., Ferdinando, D., Dadd, T. et al. (2008). SLC24A5 encodes a trans-Golgi network protein with potassium-dependent sodium-calcium exchange activity that regulates human epidermal melanogenesis. *J. Biol. Chem., 283*, 5486-95.

Editions

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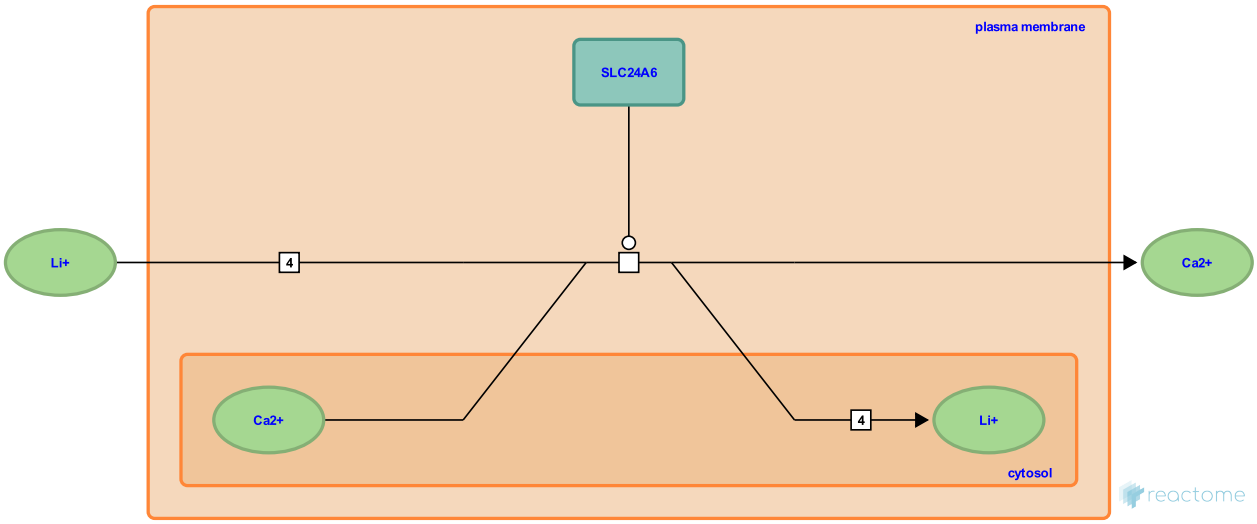
K+-independent Li+/Ca2+ exchanger transport ↗

Location: Sodium/Calcium exchangers

Stable identifier: R-HSA-425822

Type: transition

Compartments: plasma membrane



SLC24A6 (NCKX6, NCLX) (Palty R et al, 2004) encodes a protein which can transport Li+ or Na+ in exchange for Ca2+ in an K+-independent manner (Cai X and Lytton J, 2004). Lithium exchange with calcium is shown here.

Literature references

Palty, R., Ohana, E., Hershfinkel, M., Volokita, M., Elgazar, V., Beharier, O. et al. (2004). Lithium-calcium exchange is mediated by a distinct potassium-independent sodium-calcium exchanger. *J Biol Chem, 279*, 25234-40. ↗

Cai, X., Lytton, J. (2004). Molecular cloning of a sixth member of the K+-dependent Na+/Ca2+ exchanger gene family, NCKX6. *J Biol Chem, 279*, 5867-76. ↗

Editions

2009-06-08	Authored, Edited	Jassal, B.
2009-08-24	Reviewed	He, L.

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