



Stimuli-sensing channels

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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. 7
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. A
- 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. *オ*

This document contains 2 pathways and 26 reactions (see Table of Contents)

Stimuli-sensing channels 7

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reactome

Ion channels that mediate sensations such as pain, warmth, cold, taste pressure and vision. Channels that mediate these sensations include acid-sensing ion channels (ASICs) (Wang & Xu 2011, Qadri et al. 2012, Deval et al. 2010) and the transient receptor potential channels (TRPCs) (Takahashi et al. 2012, Numata et al. 2011 in "TRP Channels" Zhu, MX editor, CRC Press, 2011, Ramsey et al. 2006, Montell 2005). Many channels are sensitive to changes in calcium (Ca2+) levels, both inside and outside the cell. Examples are protein tweety homologs 2 and 3 (TTYH2, 3) (Suzuki 2006), bestrophins 1-4 (BEST1-4) (Sun et al. 2002, Tsunenari et al. 2003, Kunzelmann et al. 2009, Hartzell et al. 2008) and ryanodine receptor tetramers (RYRs) (Beard et al. 2009).

Literature references

- Diochot, S., Salinas, M., Gasull, X., Noël, J., Deval, E., Baron, A. et al. (2010). Acid-sensing ion channels (ASICs): pharmacology and implication in pain. Pharmacol. Ther., 128, 549-58. 7
- Suzuki, M. (2006). The Drosophila tweety family: molecular candidates for large-conductance Ca2+-activated Clchannels. Exp. Physiol., 91, 141-7. 7
- Xu, TL., Wang, YZ. (2011). Acidosis, acid-sensing ion channels, and neuronal cell death. Mol. Neurobiol., 44, 350-8. 🛪
- Yau, KW., Williams, J., Sun, H., Smallwood, P., Nathans, J., Tsunenari, T. et al. (2003). Structure-function analysis of the bestrophin family of anion channels. J. Biol. Chem., 278, 41114-25.
- Xiao, Q., Hartzell, HC., Qu, Z., Chien, LT., Yu, K. (2008). Molecular physiology of bestrophins: multifunctional membrane proteins linked to best disease and other retinopathies. Physiol. Rev., 88, 639-72.

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ASICs bind STOML3, (STOM) 🛪

Location: Stimuli-sensing channels

Stable identifier: R-HSA-8863494

Type: binding

Compartments: plasma membrane



Stomatin (STOM) and Stomatin-like protein 3 (STOML3) are accessory proteins for the ASIC channels (Zeng et al. 2014). STOML3 and stomatin are expressed by primary sensory neurons of the dorsal root ganglia (DRG) (Mannsfeldt et al. 1999, Wetzel et al. 2007) and regulate mechanoreceptor sensitivity in mice (Wetzel et al. 2007, Martinez-Saldago et al. 2007). STOML3 and to a lesser extent STOM can modulate the gating of ASICs (Price et al. 2004, Wetzel et al. 2007). STOML3 can bind ASIC1a, 1b, 2a, 2b, 3 and 4 (Lapatsina et al. 2012). The function of STOML3 may be to prime the transduction complex for insertion into the plasma membrane (Lapatsina et al. 2012). Alternatively, STOML3 may control membrane mechanics by binding cholesterol to tune the sensitivity of mechanogated channels(Qi et al. 2015).

Literature references

Heppenstall, PA., Lewin, GR., Kozlenkov, A., Jira, JA., Lapatsina, L., Smith, ES. et al. (2012). Regulation of ASIC channels by a stomatin/STOML3 complex located in a mobile vesicle pool in sensory neurons. *Open Biol, 2*, 120096. 7

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ASIC trimers bind H+ ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-9650165

Type: transition

Compartments: plasma membrane, extracellular region



Acid-sensing ion channels 1, 2, 3 and 5 (ASIC1, 2, 3 and 5, aka amiloride-sensitive cation channels) are homotrimeric, multi-pass membrane proteins which can transport sodium (Na+) when activated by extracellular protons. Members of the ASIC family are sensitive to amiloride and function in neurotransmission. The encoded proteins function in learning, pain transduction, touch sensation, and development of memory and fear. Many neuronal diseases cause acidosis, accompanied by pain and neuronal damage; ASICs can mediate the pathophysiological effects seen in acidiosis (Wang & Xu 2011, Qadri et al. 2012). The diuretic drug amiloride inhibits these channels, resulting in analgesic effects. NSAIDs (nonsteroidal anti-inflammatory drugs) can also inhibit ASICs to produce analgesia (Voilley et al. 2001). ASICs are also partially permeable to Ca2+, Li+ and K+ (not shown here). ASIC1 and 2 are expressed mostly in brain (Garcia-Anoveros et al. 1997, Price et al. 1996), ASIC3 is strongly expressed in testis (de Weille et al. 1998, Ishibashi & Marumo 1998) and ASIC5 is found mainly in intestine (Schaefer et al. 2000). ASIC4 subunits do not form functional channels and it's activity is unknown. It could play a part in regulating other ASIC activity (Donier et al. 2008).

Followed by: ASIC trimers:H+ transport extracellular Na+ to cytosol

Literature references

- Lazdunski, M., Schaefer, L., Lingueglia, E., Sakai, H., Mattei, M. (2000). Molecular cloning, functional expression and chromosomal localization of an amiloride-sensitive Na(+) channel from human small intestine. *FEBS Lett.*, 471, 205-10. *¬*
- Marumo, F., Ishibashi, K. (1998). Molecular cloning of a DEG/ENaC sodium channel cDNA from human testis. *Biochem. Biophys. Res. Commun.*, 245, 589-93. *¬*
- Lazdunski, M., de Weille, JR., Bassilana, F., Waldmann, R. (1998). Identification, functional expression and chromosomal localisation of a sustained human proton-gated cation channel. *FEBS Lett.*, 433, 257-60. 7
- Lazdunski, M., Voilley, N., Mamet, J., de Weille, J. (2001). Nonsteroid anti-inflammatory drugs inhibit both the activity and the inflammation-induced expression of acid-sensing ion channels in nociceptors. J. Neurosci., 21, 8026-33
- Snyder, PM., Price, MP., Welsh, MJ. (1996). Cloning and expression of a novel human brain Na+ channel. J. Biol. Chem., 271, 7879-82.

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ASIC trimers:H+ transport extracellular Na+ to cytosol 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2671885

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Acid-sensing ion channels 1, 2, 3 and 5 (ASIC1, 2, 3 and 5, aka amiloride-sensitive cation channels) are homotrimeric, multi-pass membrane proteins which can transport sodium (Na+) when activated by extracellular protons. Members of the ASIC family are sensitive to amiloride and function in neurotransmission. The encoded proteins function in learning, pain transduction, touch sensation, and development of memory and fear. Many neuronal diseases cause acidosis, accompanied by pain and neuronal damage; ASICs can mediate the pathophysiological effects seen in acidiosis (Wang & Xu 2011, Qadri et al. 2012). The diuretic drug amiloride inhibits these channels, resulting in analgesic effects. NSAIDs (Nonsteroidal anti-inflammatory drugs) can also inhibit ASICs to produce analgesia (Voilley et al. 2001). ASICs are also partially permeable to Ca2+, Li+ and K+ (not shown here). ASIC1 and 2 are expressed mostly in brain (Garcia-Anoveros et al. 1997, Price et al. 1996), ASIC3 is strongly expressed in testis (de Weille et al. 1998, Ishibashi & Marumo 1998) and ASIC5 is found mainly in intestine (Schaefer et al. 2000). ASIC4 subunits do not form functional channels and it's activity is unknown. It could play a part in regulating other ASIC activity (Donier et al. 2008).

Preceded by: ASIC trimers bind H+

Literature references

- Lazdunski, M., Schaefer, L., Lingueglia, E., Sakai, H., Mattei, M. (2000). Molecular cloning, functional expression and chromosomal localization of an amiloride-sensitive Na(+) channel from human small intestine. *FEBS Lett.*, 471, 205-10. *¬*
- Marumo, F., Ishibashi, K. (1998). Molecular cloning of a DEG/ENaC sodium channel cDNA from human testis. *Bio-chem. Biophys. Res. Commun.*, 245, 589-93. ↗
- Lazdunski, M., de Weille, JR., Bassilana, F., Waldmann, R. (1998). Identification, functional expression and chromosomal localisation of a sustained human proton-gated cation channel. *FEBS Lett.*, 433, 257-60.
- Lazdunski, M., Voilley, N., Mamet, J., de Weille, J. (2001). Nonsteroid anti-inflammatory drugs inhibit both the activity and the inflammation-induced expression of acid-sensing ion channels in nociceptors. J. Neurosci., 21, 8026-33
- Snyder, PM., Price, MP., Welsh, MJ. (1996). Cloning and expression of a novel human brain Na+ channel. J. Biol. Chem., 271, 7879-82. ↗

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ASIC3 channel blockers bind ASIC3 trimer 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-9649963

Type: binding

Compartments: plasma membrane, extracellular region



Acid-sensing ion channels 1, 2, 3 and 5 (ASIC1, 2, 3 and 5, aka amiloride-sensitive cation channels) are a subfamily of the ENaC/Deg superfamily of ion channels. ASICs are low pH-activated Na+-permeable ion channels that are widely expressed in the central and peripheral nervous systems. ASICs act as pH sensors, leading to neuronal excitation when the pH drops. ASICs play important roles in mediating pain sensation in conditions such as stroke, inflammation, arthritis, cancer and migraine. They may additionally control the adverse behavioral and emotional symptoms of chronic pain such as anxiety and depression. ASIC3 channels are mainly expressed in the peripheral nervous system and inhibition of activity of these channels by ASIC3 channel blockers could be a promising tool for pain relief.

The diuretic amiloride, a nonspecific blocker of sodium channels, is a well-known drug that possesses a nonspecific inhibitory effect on ASICs (Ugawa et al. 2002).

Literature references

- Ugawa, S., Ishida, Y., Nishigaki, M., Shibata, Y., Ueda, T., Shimada, S. (2002). Amiloride-blockable acid-sensing ion channels are leading acid sensors expressed in human nociceptors. J. Clin. Invest., 110, 1185-90. 7
- Lazdunski, M., Voilley, N., Mamet, J., de Weille, J. (2001). Nonsteroid anti-inflammatory drugs inhibit both the activity and the inflammation-induced expression of acid-sensing ion channels in nociceptors. J. Neurosci., 21, 8026-33

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SCNN channels transport extracellular Na+ to cytosol 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2672334

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Amiloride-sensitive sodium channels (SCNNs, aka ENaCs, epithelial Na+ channels, non voltage-gated sodium channels) belong to the epithelial Na+ channel/degenerin (ENaC/DEG) protein family and mediate the transport of Na+ (and associated water) through the apical membrane of epithelial cells in kidney, colon and lungs. This makes SCNNs important determinants of systemic blood pressure. The physiological activator for SCNNs is unknown but as they belong in the same family as acid-sensitive ion channels (ASICs, which are mediated by protons), these may also be the activating ligands for SCNNs. SCNNs are probable heterotrimers comprising an alpha (or interchangeable delta subunit), beta and gamma subunit (Horisberger 1998).

Literature references

Horisberger, JD. (1998). Amiloride-sensitive Na channels. Curr. Opin. Cell Biol., 10, 443-9. ↗

Xu, JJ., Spielman, AI., Ozdener, MH., Garcia-Blanco, A., Chung, HY., Bachmanov, AA. et al. (2017). Arginyl dipeptides increase the frequency of NaCl-elicited responses via epithelial sodium channel alpha and delta subunits in cultured human fungiform taste papillae cells. *Sci Rep*, *7*, 7483. *¬*

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RAF1:SGK:TSC22D3:WPP ubiquitinates SCNN channels ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2682349

Type: transition

Compartments: plasma membrane, cytosol



Amiloride-sensitive sodium channels (SCNNs, aka ENaCs, epithelial Na+ channels, non voltage-gated sodium channels) comprises three subunits (alpha, beta and gamma) and plays an essential role in Na+ and fluid absorption in the kidney, colon and lung. The number of channels at the cell's surface (consequently its function) can be regulated. This is achieved by ubiquitination of SCNN via E3 ubiquitin-protein ligases (NED4L and WPP1) (Staub et al. 2000, Farr et al. 2000). NED4L/WPP1 is found in a signaling complex including Raf1 (RAF proto-oncogene serine/threonine-protein kinase), SGK (serum/glucocorticoid-regulated kinase) and GILZ (glucocorticoid-induced leucine zipper protein, TSC22D3) (Soundararajan et al. 2009). Ubiquitinated SCNN (Ub-SCNN) is targeted for degradation so a lesser number of channels are present at the cell surface, reducing the amount of Na+ absorption. Proline-rich sequences at the C-terminus of SCNNs include the PY motif containing a PPxY sequence. PY motifs bind WW domains of NED4L/WPP1. Protein kinases with no lysine K (WNKs) can activate SCNN activity by interacting non-enzymatically with the signaling complex, specifically SGK although the mechanism is unknown (Heise et al. 2010).

Literature references

- Earnest, S., Cobb, MH., Deaton, SL., Cha, SK., Heise, CJ., Sengupta, S. et al. (2010). Serum and glucocorticoid-induced kinase (SGK) 1 and the epithelial sodium channel are regulated by multiple with no lysine (WNK) family members. J. Biol. Chem., 285, 25161-7. ↗
- Rohlfs, M., Wiemuth, D., Ke, Y., McDonald, FJ. (2007). Epithelial sodium channel (ENaC) is multi-ubiquitinated at the cell surface. *Biochem J*, 405, 147-55. ↗
- Melters, D., Wang, J., Soundararajan, R., Pearce, D., Shih, IC. (2009). Epithelial sodium channel regulated by differential composition of a signaling complex. *Proc. Natl. Acad. Sci. U.S.A.*, 106, 7804-9. 7
- Horisberger, JD., Ishikawa, T., Rotin, D., Kanelis, V., Plant, P., Schild, L. et al. (2000). Regulation of the epithelial Na+ channel by Nedd4 and ubiquitination. *Kidney Int.*, *57*, 809-15. **7**
- Snyder, PM., Farr, TJ., Coddington-Lawson, SJ., McDonald, FJ. (2000). Human Nedd4 interacts with the human epithelial Na+ channel: WW3 but not WW1 binds to Na+-channel subunits. *Biochem. J.*, 345, 503-9. 7

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ANOs transport cytosolic Cl- to extracellular region *オ*

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2684901

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Calcium-activated chloride channels (CaCCs) are ubiquitously expressed and implicated in physiological processes such as sensory transduction, fertilization, epithelial secretion, and smooth muscle contraction. The anoctamin family of transmembrane proteins (ANO, TMEM16) belong to CaCCs and have been shown to transport Cl- ions when activated by intracellular Ca2+ (Galietta 2009, Huang et al. 2012). There are currently 10 members, ANO1-10, all having a similar structure, with eight putative transmembrane domains and cytosolic amino- and carboxy-termini. ANO1 and 2 possess Ca2+ activated Cl- transport activity (Yang et al. 2008, Scudieri et al. 2012) while the remaining members also show some demonstrable activity (Tian et al. 2012). All CLCAs contain a consensus cleavage motif which is recognised by an internal zincin metalloprotease domain within the N terminus. Self-proteolysis within the secretory pathway yields N- and C-terminal fragments, a step critical for CLCA activation of calcium-activated chloride channels (CaCCs) mediated through the N-terminal fragment (Yurtsever et al. 2012).

Literature references

Kunzelmann, K., Schreiber, R., Tian, Y. (2012). Anoctamins are a family of Ca2+ activated Cl- channels. J. Cell. Sci.. 7

- Oh, U., Shim, WS., Shin, YK., Lee, B., Cho, Y., Raouf, R. et al. (2008). TMEM16A confers receptor-activated calciumdependent chloride conductance. *Nature*, 455, 1210-5. ↗
- Galietta, LJ., Ferrera, L., Scudieri, P., Sondo, E. (2012). The anoctamin family: TMEM16A and TMEM16B as calciumactivated chloride channels. *Exp. Physiol.*, *97*, 177-83. *7*

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ANO1 transports cytosolic Cl- to extracellular region 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-9659568

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Calcium-activated chloride channels (CaCCs) are ubiquitously expressed and implicated in physiological processes such as sensory transduction, fertilization, epithelial secretion, and smooth muscle contraction. The anoctamin family of transmembrane proteins (ANO, TMEM16) belong to CaCCs and have been shown to transport Cl- ions when activated by intracellular Ca2+ (Galietta 2009, Huang et al. 2012). ANO1 and 2 possess Ca2+ activated Cl- transport activity (Yang et al. 2008, Scudieri et al. 2012) while the remaining members also show some demonstrable activity (Tian et al. 2012). All CLCAs contain a consensus cleavage motif which is recognised by an internal zincin metalloprotease domain within the N terminus. Self-proteolysis within the secretory pathway yields N- and C-terminal fragments, a step critical for CLCA activation of calcium-activated chloride channels (CaCCs) mediated through the N-terminal fragment (Yurtsever et al. 2012).

Literature references

Kunzelmann, K., Schreiber, R., Tian, Y. (2012). Anoctamins are a family of Ca2+ activated Cl- channels. J. Cell. Sci.. 🛪

Oh, U., Shim, WS., Shin, YK., Lee, B., Cho, Y., Raouf, R. et al. (2008). TMEM16A confers receptor-activated calciumdependent chloride conductance. *Nature*, 455, 1210-5. ↗

Galietta, LJ., Ferrera, L., Scudieri, P., Sondo, E. (2012). The anoctamin family: TMEM16A and TMEM16B as calciumactivated chloride channels. *Exp. Physiol.*, *97*, 177-83. *¬*

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ANO1 inhibitors bind ANO1 🛪

Location: Stimuli-sensing channels

Stable identifier: R-HSA-9659611

Type: binding

Compartments: plasma membrane, extracellular region



Calcium-activated chloride channels (CaCCs) are ubiquitously expressed and implicated in physiological processes such as sensory transduction, fertilization, epithelial secretion, and smooth muscle contraction. Anoctamin 1 (ANO1, TMEM16A) is a Ca(2+)-activated Cl(-) channel (CACC) expressed in smooth muscle and epithelial cells and highly expressed in interstitial cells of Cajal throughout the GI tract (Sanders et al. 2012). ANO1, amongst other ion channels, generates electrical activity that drives contractility in the GI tract (Yang et al. 2008, Scudieri et al. 2012). Crofelemer (trade name Mytesi) is a purified proanthocyanidin oligomer extracted from the bark latex of Croton lechlerifor used for the treatment of diarrhoea associated with anti-HIV drugs (Yeo et al. 2013). Crofelemer was found to strongly inhibit the intestinal ANO1 by a voltage-independent inhibition mechanism (Tradtrantip et al. 2010). ANO1 blockers like niflumic acid have been shown to block slow waves, which produce motility, in the human intestine (Strege et al. 2015). Anthracene-9-carboxylic acid (A9C) is an open ANO1 channel blocker and gating modifier (Ta et al. 2016).

Literature references

- Verkman, AS., Tradtrantip, L., Namkung, W. (2010). Crofelemer, an antisecretory antidiarrheal proanthocyanidin oligomer extracted from Croton lechleri, targets two distinct intestinal chloride channels. *Mol. Pharmacol.*, 77, 69-78.
- Farrugia, G., Bernard, CE., Linden, DR., Strege, PR., Mazzone, A., Gibbons, SJ. et al. (2015). A novel exon in the human Ca2+-activated Cl- channel Ano1 imparts greater sensitivity to intracellular Ca2. Am. J. Physiol. Gastrointest. Liver Physiol., 309, G743-9. ↗
- Garnett, H., Rorsman, NJ., Tammaro, P., Ta, CM., Adomaviciene, A. (2016). Mechanism of allosteric activation of TMEM16A/ANO1 channels by a commonly used chloride channel blocker. *Br. J. Pharmacol., 173*, 511-28.
- Yeo, QM., Tucker, A., Crutchley, R., Garey, KW., Cottreau, J. (2013). Crofelemer, a novel antisecretory agent approved for the treatment of HIV-associated diarrhea. *Drugs Today*, 49, 239-52.

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TPCN1/2 transport lysosomal Ca2+ to cytosol 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2685505

Type: transition

Compartments: lysosomal lumen, cytosol, lysosomal membrane



Calcium (Ca2+) can be mobilised from intracellular stores by the presence of nicotinic acid adenine dinucleotide phosphate (NAADP). Two pore calcium channel proteins 1 and 2 (TPCN1 and 2) are expressed on endosomal (not shown here) and lysosomal membranes and mediate the mobilization of Ca2+ from these organelles when activated by NAADP (Brailoiu et al. 2009, Calcraft et al. 2009).

Literature references

- Lin, P., Galione, A., Wang, C., Arredouani, A., Hao, X., Rietdorf, K. et al. (2009). NAADP mobilizes calcium from acidic organelles through two-pore channels. *Nature*, 459, 596-600.
- Patel, S., Boulware, MJ., Brailoiu, E., Dun, NJ., Brailoiu, GC., Cai, X. et al. (2009). Essential requirement for two-pore channel 1 in NAADP-mediated calcium signaling. J. Cell Biol., 186, 201-9.

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UNC79:UNC80:NALCN transports Na+ extracellular region to cytosol 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2730664

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The sodium leak channel non-selective protein NALCN, a nonselective cation channel, forms the background Na+ leak conductance and controls neuronal excitability (Lu et al. 2007, Ren 2011). Mice with mutant NALCN have a severely disrupted respiratory rhythm and die within 24 hours of birth. Calcium (Ca2+) influences neuronal excitability via the NALCN:UNC79:UNC80 complex, with high Ca2+ concentrations inhibiting transport of Na+ (Lu et al. 2010). Mutations in human NALCN lead to complex neurodevelopmental syndromes, including infantile hypotonia with psychomotor retardation and characteristic facies (IHPRF) and congenital contractures of limbs and face, hypotonia and developmental delay (CLIFAHDD) (Bouasse et al. 2019).

Literature references

- Ren, D., Su, Y., Lu, B., Xia, J., Das, S., Liu, J. (2007). The neuronal channel NALCN contributes resting sodium permeability and is required for normal respiratory rhythm. *Cell*, 129, 371-83. 7
- Ren, D., Lu, B., Wang, H., Zhang, Q., Nakayama, M., Wang, Y. (2010). Extracellular calcium controls background current and neuronal excitability via an UNC79-UNC80-NALCN cation channel complex. *Neuron, 68,* 488-99. 7

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CLCN1/2/KA/KB transport cytosolic Cl- to extracellular region 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2744228

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Chloride channel proteins 1, 2, Ka and Kb (CLCN1, 2, KA, KB) can mediate Cl- influx across the plasma membrane of almost all cells. CLCN1 is expressed mainly on skeletal muscle where it is involved in the electrical stability of the muscle. CLCN1 is thought to function in a homotetrameric form (Steimeyer et al. 1994). CLCN2 is ubiquitously expressed, playing a role in the regulation of cell volume (Cid et al. 1995, Niemeyer et al. 2009). Defects in CLCN1 cause myotonia congenita, an autosomal dominant disease (MCD aka Thomsen disease, MIM:160800). It is characterized by muscle stiffness due to delayed relaxation, resulting from membrane hyperexcitability (Meyer-Kleine et al. 1995, Steimeyer et al. 1994). Defects in CLCN1 also cause autosomal recessive myotonia congenita (MCR aka Becker disease, MIM:255700) (Koch et al. 1992, Meyer-Kleine et al. 1995), a nondystrophic skeletal muscle disorder characterized by muscle stiffness and an inability of the muscle to relax after voluntary contraction. Becker disease is more common and more severe than Thomsen disease.

CLCNKA and B (Kieferle et al. 1994) are predominantly expressed in distal nephron segments of the kidney (Takeuchi et al. 1995) and the inner ear (Estevez et al. 2001, Schlingmann et al. 2004). They are tightly associated with their essential beta subunit barttin (BSND), requiring it to be fully functional channels (Fischer et al. 2010, Scholl et al. 2006). These channels bound to BSND are essential for renal Cl- reabsorption (Waldegger & Jentsch 2000) and K+ recycling in the inner ear (Estevez et al. 2001). Defects in CLCNKA and B cause Bartter syndrome type 4B (BS4B; MIM:613090) characterized by impaired salt reabsorption and sensorineural deafness (Schlingmann et al. 2004, Nozu et al. 2008). Defects in BSND cause Bartter syndrome type 4A (BS4A aka infantile Bartter syndrome with sensorineural deafness; MIM:602522) characterized by impaired salt reabsorption in the thick ascending loop of Henle and sensorineural deafness (Birkenhager et al. 2001, Nozu et al. 2008).

Literature references

- Janssen, AG., Fischer, M., Fahlke, C. (2010). Barttin activates ClC-K channel function by modulating gating. J. Am. Soc. Nephrol., 21, 1281-9. 7
- Bens, M., Fong, P., Jentsch, TJ., Kieferle, S., Vandewalle, A. (1994). Two highly homologous members of the ClC chloride channel family in both rat and human kidney. *Proc. Natl. Acad. Sci. U.S.A.*, *91*, 6943-7. *¬*
- Marumo, F., Takeuchi, Y., Uchida, S., Sasaki, S. (1995). Cloning, tissue distribution, and intrarenal localization of ClC chloride channels in human kidney. *Kidney Int., 48*, 1497-503.
- Kaito, H., Nakanishi, K., Igarashi, T., Fu, XJ., Iijima, K., Kanda, K. et al. (2008). Molecular analysis of digenic inheritance in Bartter syndrome with sensorineural deafness. J. Med. Genet., 45, 182-6. 7
- Stein, V., Hildebrandt, F., Boettger, T., Jentsch, TJ., Otto, E., Estévez, R. et al. (2001). Barttin is a Cl- channel beta-subunit crucial for renal Cl- reabsorption and inner ear K+ secretion. *Nature*, 414, 558-61. 7

2012-12-06	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.

CLCN3 exchanges Cl- for H+ ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2731002

Type: transition

Compartments: late endosome membrane, late endosome lumen, cytosol

Inferred from: Clcn3 exchanges Cl- for H+ (Mus musculus)



The H+/Cl- exchange transporter CLCN3 (Borsani et al. 1995) mediates the exchange of endosomal Cl- for cytosolic H+ across late endosomal membranes, contributing to the acidification of endosomes. The activity of CLCN3 is inferred from experiments in mice (Stobrawa et al. 2001, Hara-Chikuma et al. 2005).

Literature references

- Ruether, K., Zdebik, AA., Bösl, MR., Jentsch, TJ., Jahn, H., Jahn, R. et al. (2001). Disruption of ClC-3, a chloride channel expressed on synaptic vesicles, leads to a loss of the hippocampus. *Neuron, 29*, 185-96.
- Uchida, S., Hara-Chikuma, M., Yang, B., Sasaki, S., Sonawane, ND., Verkman, AS. (2005). ClC-3 chloride channels facilitate endosomal acidification and chloride accumulation. J. Biol. Chem., 280, 1241-7. ↗
- Taglialatela, M., Ballabio, A., Rugarli, EI., Wong, C., Borsani, G. (1995). Characterization of a human and murine gene (CLCN3) sharing similarities to voltage-gated chloride channels and to a yeast integral membrane protein. *Genomics, 27*, 131-41. *¬*

2012-12-05	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.

CLCN4/5/6 exchange Cl- for H+ ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2730692

Type: transition

Compartments: endosome membrane, cytosol, endosome lumen



The H+/Cl- exchange transporters CLCN4 (Kawasaki et al. 1999, Zdebik et al. 2008), CLCN5 (Zdebik et al. 2008) and CLCN6 (Neagoe et al. 2010) mediate the exchange of endosomal Cl- for cytosolic H+ across endosomal membranes, contributing to the acidification of endosomes.

Literature references

- Neagoe, I., Fidzinski, P., Stauber, T., Bergsdorf, EY., Jentsch, TJ. (2010). The late endosomal ClC-6 mediates proton/chloride countertransport in heterologous plasma membrane expression. J. Biol. Chem., 285, 21689-97. 7
- Marumo, F., Sakamoto, H., Yamauchi, K., Fukuma, T., Sasaki, S., Kawasaki, M. (1999). Identification of an acid-activated Cl(-) channel from human skeletal muscles. *Am. J. Physiol., 277*, C948-54.
- Scheel, O., Pusch, M., Soliani, P., Zifarelli, G., Bergsdorf, EY., Jentsch, TJ. et al. (2008). Determinants of anion-proton coupling in mammalian endosomal CLC proteins. J. Biol. Chem., 283, 4219-27. 🛪

2012-12-04	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.

CLCN7:OSTM1 exchanges Cl- for H+ ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2730959

Type: transition

Compartments: lysosomal lumen, cytosol, lysosomal membrane



Chloride channel 7 comprises H+/Cl- exchange transporter 7 (CLCN7) and osteopetrosis-associated transmembrane protein 1 (OSTM1) (Leisle et al. 2011). This complex localises to the lysosomal membrane where it mediates the exchange of Cl- and H+ ions, perhaps playing a role in the acidification of the lysosome (Graves et al. 2008).

Defects in CLCN7 cause osteopetrosis autosomal recessive types 2 and 4 (OPTB2, MIM:166600 and OPTB4, MIM:611490) (Frattini et al. 2003, Pangrazio et al. 2010). Defects in OSTM1 cause osteopetrosis autosomal recessive type 5 (OPTB5, MIM:259720) (Pangrazio et al. 2006).

Literature references

- Albertini, A., Flanagan, A., Orchard, PJ., Van Hove, J., Sobacchi, C., Horwitz, EM. et al. (2003). Chloride channel ClCN7 mutations are responsible for severe recessive, dominant, and intermediate osteopetrosis. J. Bone Miner. Res., 18, 1740-7.
- Di Rocco, M., Facchetti, F., Poliani, PL., Pangrazio, A., Megarbane, A., Lucchini, F. et al. (2006). Mutations in OSTM1 (grey lethal) define a particularly severe form of autosomal recessive osteopetrosis with neural involvement. J. Bone Miner. Res., 21, 1098-105.
- Curran, PK., Smith, CL., Graves, AR., Mindell, JA. (2008). The Cl-/H+ antiporter ClC-7 is the primary chloride permeation pathway in lysosomes. *Nature*, 453, 788-92. ↗
- Ludwig, CF., Wagner, FA., Stauber, T., Leisle, L., Jentsch, TJ. (2011). ClC-7 is a slowly voltage-gated 2Cl(-)/1H(+)-exchanger and requires Ostm1 for transport activity. *EMBO J.*, 30, 2140-52.
- Zecca, M., Melis, D., Wright, M., Tamhankar, PM., Abinun, M., Pusch, M. et al. (2010). Molecular and clinical heterogeneity in CLCN7-dependent osteopetrosis: report of 20 novel mutations. *Hum. Mutat.*, 31, E1071-80.

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CLCAs self cleave ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-5333671

Type: transition

Compartments: plasma membrane, extracellular region



Calcium-activated chloride channel regulators 1,2,3P and 4 (CLCA1,2,3P and 4), originally named as CLCAs based on the observation that overexpression of them all induced chloride current in response to cytosolic calcium flux. More recent evidence points to them being secreted proteins (Gibson et al. 2005) and being responsible for chloride channel modulation rather that forming chloride channels per se (Hamann et al. 2009). CLCA1 has been found to be overexpressed in aiways of patients suffering from asthma and chronic obstructive pulmonary disease (Hoshino et al. 2002, Toda et al. 2002, Kamada et al. 2004). All CLCAs contain a consensus cleavage motif which is recognised by an internal zincin metalloprotease domain within the N terminus. Self-proteolysis within the secretory pathway yields N- and C-terminal fragments, a step critical for CLCA activation of calcium-activated chloride channels (CaCCs) mediated through the N-terminal fragment (Yurtsever et al. 2012).

Literature references

- Hamid, Q., Toda, M., Tulic, MK., Levitt, RC. (2002). A calcium-activated chloride channel (HCLCA1) is strongly related to IL-9 expression and mucus production in bronchial epithelium of patients with asthma. J. Allergy Clin. Immunol., 109, 246-50.
- Affleck, K., Main, M., Davies, N., Jowett, A., Hamann, M., Partington, L. et al. (2009). Human ClCa1 modulates anionic conduction of calcium-dependent chloride currents. J. Physiol. (Lond.), 587, 2255-74.
- Aitken, AJ., Affleck, K., Thompson, N., Lewis, AP., Meldrum, E., Gibson, A. (2005). hCLCA1 and mCLCA3 are secreted non-integral membrane proteins and therefore are not ion channels. J. Biol. Chem., 280, 27205-12.
- Tamari, M., Suzuki, Y., Hasegawa, K., Kure, S., Fujita, K., Mao, XQ. et al. (2004). Association of the hCLCA1 gene with childhood and adult asthma. *Genes Immun.*, *5*, 540-7.
- Heier, RF., Patel, AC., Scheaffer, SM., Sala-Rabanal, M., Roswit, WT., Romero, AG. et al. (2012). Self-cleavage of human CLCA1 protein by a novel internal metalloprotease domain controls calcium-activated chloride channel activation. J. Biol. Chem., 287, 42138-49.

2014-02-20	Authored, Edited	Jassal, B.
2014-10-03	Reviewed	Hamann, M.

TTYH1 transports cytosolic Cl- to extracellular region 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2744349

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Protein tweety homolog 1 (TTYH1) has 5 isoforms. Isoform 3 (Campbell et al. 2000) mediates the Ca+-independent efflux of Cl- across plasma membranes (Suzuki & Mizuno 2004, Suzuki 2006).

Literature references

- Suzuki, Y., Young, IG., Hida, M., Kamei, M., Campbell, HD., Sugano, S. et al. (2000). Human and mouse homologues of the Drosophila melanogaster tweety (tty) gene: a novel gene family encoding predicted transmembrane proteins. *Genomics*, 68, 89-92. *¬*
- Mizuno, A., Suzuki, M. (2004). A novel human Cl(-) channel family related to Drosophila flightless locus. J. Biol. Chem., 279, 22461-8.
- Suzuki, M. (2006). The Drosophila tweety family: molecular candidates for large-conductance Ca2+-activated Clchannels. *Exp. Physiol.*, *91*, 141-7. 7

2012-12-06	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.

TTYH2/3 transport cytosolic Cl- to extracellular region 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2744242

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Human homologues 2 and 3 (TTYH2 and 3) mediate the efflux of Cl- from cells in response to the increase in intracellular Ca2+ levels (Suzuki & Mizuno 2004, Suzuki 2006). All CLCAs contain a consensus cleavage motif which is recognised by an internal zincin metalloprotease domain within the N terminus. Self-proteolysis within the secretory pathway yields N- and C-terminal fragments, a step critical for CLCA activation of calcium-activated chloride channels (CaCCs) mediated through the N-terminal fragment (Yurtsever et al. 2012).

Literature references

- Mizuno, A., Suzuki, M. (2004). A novel human Cl(-) channel family related to Drosophila flightless locus. J. Biol. Chem., 279, 22461-8. 7
- Suzuki, M. (2006). The Drosophila tweety family: molecular candidates for large-conductance Ca2+-activated Clchannels. *Exp. Physiol.*, *91*, 141-7. 7

2012-12-06	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.
2015-02-11	Revised	Jassal, B.

BESTs transport cytosolic Cl- to extracellular region 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2744361

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Bestrophins 1-4 (BEST1-4, aka vitelliform macular dystrophy proteins) mediate cytosolic Cl- efflux across plasma membranes. This transport is sensitive to intracellular Ca2+ concentrations (Sun et al. 2002, Tsunenari et al. 2003). Mutations in bestrophins that impair their function are implicated in macular degeneration in the eye. Defects in BEST1 cause vitelliform macular dystrophy (BVMD, Best's disease, MIM:153700), an autosomal dominant form of macular degeneration that usually begins in childhood and is characterized lesions due to abnormal accumulation of lipofuscin within and beneath retinal pigment epithelium (RPE) cells (Marquardt et al. 1998, Petrukhin et al. 1998). All CLCAs contain a consensus cleavage motif which is recognised by an internal zincin metalloprotease domain within the N terminus. Self-proteolysis within the secretory pathway yields N- and C-terminal fragments, a step critical for CLCA activation of calcium-activated chloride channels (CaCCs) mediated through the N-terminal fragment (Yurtsever et al. 2012).

Literature references

- Yau, KW., Sun, H., Nathans, J., Tsunenari, T. (2002). The vitelliform macular dystrophy protein defines a new family of chloride channels. *Proc. Natl. Acad. Sci. U.S.A.*, 99, 4008-13. 7
- Li, W., Bergen, AA., Petrukhin, K., Austin, CP., Caskey, CT., Forsman, K. et al. (1998). Identification of the gene responsible for Best macular dystrophy. *Nat. Genet.*, 19, 241-7.
- Yau, KW., Williams, J., Sun, H., Smallwood, P., Nathans, J., Tsunenari, T. et al. (2003). Structure-function analysis of the bestrophin family of anion channels. J. Biol. Chem., 278, 41114-25. ↗
- Stöhr, H., Weber, BH., Rivera, A., Passmore, LA., Krämer, F., Marquardt, A. (1998). Mutations in a novel gene, VMD2, encoding a protein of unknown properties cause juvenile-onset vitelliform macular dystrophy (Best's disease). *Hum. Mol. Genet.*, 7, 1517-25. ↗

2012-12-06	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.
2015-02-11	Revised	Jassal, B.

BESTs transport cytosolic HCO3- to extracellular region 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2752067

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Many Cl- channels such as CFTR, ClC, CaCC, and ligand-gated anion channels are permeable to bicarbonate (HCO3-) which is an important anion in the regulation of pH. Many tissues, including retinal pigment epithelium (RPE), utilize HCO3- transporters to mediate transport of HCO3-. Bestrophns 1-4 (BEST1-4, aka vitelliform macular dystrophy proteins) have high permeability to HCO3- (Hu & Hartzell 2008). Defective BEST1 may play a role in macular degeneration in the eye due to impaired HCO3- and Cl- conductance (Hu & Hartzell 2008).

Literature references

Hartzell, HC., Qu, Z. (2008). Bestrophin Cl- channels are highly permeable to HCO3-. Am. J. Physiol., Cell Physiol., 294, C1371-7. 🔻

2012-12-07	Authored, Edited	Jassal, B.
2013-01-28	Reviewed	He, L.

RYR tetramers transport Ca2+ from sarcoplasmic reticulum lumen to cytosol 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2855020

Type: transition

Compartments: sarcoplasmic reticulum membrane, cytosol, sarcoplasmic reticulum lumen



Ryanodine receptors (RYRs) are located in the sarcoplasmic reticulum (SR) membrane and mediate the release of Ca2+ from intracellular stores during excitation-contraction (EC) coupling in both cardiac and skeletal muscle. RYRs are the largest known ion channels (>2MDa) and are functional in their homotetrameric forms. There are three mammalian isoforms (RYR1-3); RYR1 is prominent in skeletal muscle (Zorzato et al. 1990), RYR2 in cardiac muscle (Tunwell et al. 1996) and RYR3 is found in the brain (Nakashima et al. 1997, Lanner et al. 2010). The function of RYRs are controlled by peptidyl-prolyl cis-trans isomerase (FKBP1B), intracellular Ca2+-binding proteins calsequestrin 1 and 2 (CASQ1 and 2) and the anchoring proteins triadin (TRDN) and junctin. Together, they make up the Ca2+-release complex. CASQ1 and 2 buffer intra-SR Ca2+ stores in skeletal muscle and cardiac muscle respectively (Fujii et al. 1990, Kim et al. 2007). When Ca2+ concentrations reach 1mM, CASQs polymerise (Kim et al. 2007) and can attach to one end of RYRs, mediated by anchoring proteins TRDN and junctin (Taske et al. 1995). By sequestering Ca2+ ions, CASQs can inhibit RYRs function (Beard et al. 2004, Beard et al. 2009a, Beard et al. 2009b).

A member of the intracellular Cl- channel protein family, CLIC2, has also been determined to inhibit RYR-mediated Ca2+ transport (Board et al. 2004), potentially playing a role in the homeostasis of Ca2+ release from intracellular stores. Inhibition is thought to be via reducing activation of the channels by their primary endogenous cytoplasmic ligands, ATP and Ca2+ (Dulhunty et al. 2005). Protein kinase A (PKA) phosphorylation of RYR2 dissociates FKBP1B and results in defective channel function (Marx et al. 2000). The penta-EF hand protein sorcin (SRI) can modulate Ca2+-induced calcium-release in the heart via the interaction with several Ca2+ channels such as RYRs. A natural ligand, F112L, impairs this modulating activity (Franceschini et al. 2008). Calmodulin (CALM1) is considered a gatekeeper of RYR2. CALM1 acts directly by binding to RYR2 at residues 3583–3603, inhibiting RYR2 both at physiological and higher, pathological Ca2+ concentrations (Smith et al. 1989, Ono et al. 2010).

Literature references

- Fujii, J., MacLennan, DH., Willard, HF. (1990). Characterization and localization to human chromosome 1 of human fast-twitch skeletal muscle calsequestrin gene. *Somat. Cell Mol. Genet.*, *16*, 185-9. *¬*
- Nishimura, S., Kita, T., Nakashima, Y., Imoto, K., Allen, PD., Nakai, J. et al. (1997). Molecular cloning and characterization of a human brain ryanodine receptor. *FEBS Lett.*, 417, 157-62. A
- Antaramian, A., Verzili, D., Rueda, A., Valdivia, HH., Zamparelli, C., Franceschini, S. et al. (2008). Molecular basis for the impaired function of the natural F112L sorcin mutant: X-ray crystal structure, calcium affinity, and interaction with annexin VII and the ryanodine receptor. *FASEB J., 22*, 295-306. 7

- Dulhunty, AF., Pouliquin, P., Coggan, M., Board, PG., Gage, PW. (2005). A recently identified member of the glutathione transferase structural family modifies cardiac RyR2 substate activity, coupled gating and activation by Ca2+ and ATP. *Biochem. J.*, 390, 333-43. *¬*
- Dulhunty, AF., Watson, S., Coggan, M., Gage, PW., Board, PG. (2004). CLIC-2 modulates cardiac ryanodine receptor Ca2+ release channels. *Int. J. Biochem. Cell Biol.*, *36*, 1599-612. 7

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2013-01-28	Reviewed	He, L.

SLC17A3-1 cotransports extracellular Na+ and Pi to cytosol 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2872498

Type: transition

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen, cytosol



The microsomal Na+/(PO4)3- transporter isoform 1 (SLC17A3, NPT4 isoform 1) is a member of the anion-cation symporter family. It is expressed in liver, kidney and intestine and may function as a cotransporter of sodium (Na+) and phosphate ((PO4)3- or Pi) across the ER membrane (Melis et al. 2004).

Literature references

Mancini, GM., Verbeek, E., Benedetti, A., Smit, GP., Verheijen, F., Melis, D. et al. (2004). NPT4, a new microsomal phosphate transporter: mutation analysis in glycogen storage disease type Ic. J. Inherit. Metab. Dis., 27, 725-33.

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SLC17A3-2 transports cytosolic urate to extracellular region 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2872497

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



Human serum urate levels are largely maintained by its reabsorption and secretion in the kidney. Loss of this maintenance can elevate urate levels leading to gout, hypertension, and various cardiovascular diseases. Renal urate reabsorption is controlled via two proximal tubular urate transporters; apical SLC22A12 (URAT1) and basolateral SLC2A9 (URATv1, GLUT9). On the other hand, urate secretion is mediated by the orphan sodium phosphate transporter 4 isoform 2 (SLC17A3, NPT4 isoform 2). It is mainly expressed at the apical side of renal tubules and functions as a voltage-driven urate transporter (Jutabha et al. 2010).

Genetic variations in SLC17A3 influence the variance in serum uric acid concentrations and define the serum uric acid concentration quantitative trait locus 4 (UAQTL4; MIM:612671). Excess serum urate (hyperuricemia) can lead to the development of gout, characterized by tissue deposition of monosodium urate crystals.

Literature references

Wempe, MF., Katada, T., Kimura, T., Fujita, T., Sakurai, H., Yamada, A. et al. (2010). Human sodium phosphate transporter 4 (hNPT4/SLC17A3) as a common renal secretory pathway for drugs and urate. J. Biol. Chem., 285, 35123-32. ↗

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SLC9B1/C2 exchange Na+ for H+ ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2872444

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The sodium/hydrogen exchanger 9B1 (SLC9B1 aka Na+/H+ exchanger like domain containing 1, NHEDC1) is specifically expressed on the plasma membrane of the testis and may be implicated in infertility (Ye et al. 2006). Sodium/hydrogen exchanger 9C2 (SLC9C2), also localized to the plasma membrane, may be involved in pH regulation although this protein has not been fully characterized.

Literature references

Yu, L., Chen, C., Han, D., Ye, G., Xiong, X., Wan, B. et al. (2006). Cloning of a novel human NHEDC1 (Na+/H+ exchanger like domain containing 1) gene expressed specifically in testis. *Mol. Biol. Rep.*, 33, 175-80. *¬*

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SLC9B2 exchanges Na+ for H+ ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2889070

Type: transition

Compartments: mitochondrial inner membrane, mitochondrial intermembrane space, mitochondrial matrix



The widely expressed mitochondrial sodium/hydrogen exchanger 9B2 (SLC9B2, aka NHA2) mediates the exchange of Na+ for H+ across the inner mitochondrial membrane. (SLC9B2 also mediates Li+/H+ exchange, annotated as a separate reaction.) This transport is thought to play a role in salt homeostasis and pH regulation in humans (Fuster et al. 2008; Xiang et al. 2007).

The close similarity between SLC9B2 protein and NhaA, its E. coli ortholog, which mediates electrogenic transport of these ions (Taglicht et al. 1993), suggested that SLC9B2 transport might likewise be electrogenic (Xiang et al. 2007). Later work, however, indicates that SLC9B2 mediates the exchange of a single metal ion for a single proton (Uzdavinys et al. 2017).

Mass spectroscopic studies suggest that SLC9B2 exists as a homodimer (Landreh et al. 2017).

Literature references

- Winkelmann, I., Ndi, M., Nji, E., von Ballmoos, C., Drew, D., Coinçon, M. et al. (2017). Dissecting the proton transport pathway in electrogenic Na⁺/H⁺ antiporters. *Proc Natl Acad Sci U S A*, 114, E1101-E1110. ↗
- Landreh, M., Gupta, K., Benesch, JL., Degiacomi, MT., Liko, I., Robinson, CV. et al. (2017). Integrating mass spectrometry with MD simulations reveals the role of lipids in Na⁺/H⁺ antiporters. *Nat Commun*, *8*, 13993. *¬*
- Padan, E., Taglicht, D., Schuldiner, S. (1993). Proton-sodium stoichiometry of NhaA, an electrogenic antiporter from Escherichia coli. J. Biol. Chem., 268, 5382-7. 🛪
- Muend, S., Xiang, M., Rao, R., Feng, M. (2007). A human Na+/H+ antiporter sharing evolutionary origins with bacterial NhaA may be a candidate gene for essential hypertension. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 18677-81. A
- Andersson, S., Bobulescu, IA., Fuster, DG., Shi, M., Zhang, J., Moe, OW. (2008). Characterization of the sodium/hydrogen exchanger NHA2. J Am Soc Nephrol, 19, 1547-56.

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2022-05-25	Revised	D'Eustachio, P.

SLC9C1 exchanges Na+ for H+ ↗

Location: Stimuli-sensing channels

Stable identifier: R-HSA-2872463

Type: transition

Compartments: extracellular region, sperm flagellum

Inferred from: Slc9c1 exchanges Na+ for H+ (Mus musculus)



The sperm-specific Na+/H+ exchanger SLC9C1 (aka sodium/hydrogen exchanger 10, NHE10) is localized to the flagellar membrane and is involved in pH regulation of spermatozoa required for sperm motility and fertility. The activity of human SLC9C1 is inferred from experiments using mouse Slc9c1 (Wang et al. 2003).

Literature references

Wang, D., Doolittle, LK., Garbers, DL., Quill, TA., King, SM. (2003). A new sperm-specific Na+/H+ exchanger required for sperm motility and fertility. *Nat. Cell Biol.*, *5*, 1117-22.

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2013-01-28	Reviewed	He, L.

TRP channels 7

Location: Stimuli-sensing channels

Stable identifier: R-HSA-3295583



Transient receptor potential (TRP) channel proteins were first discovered in Drosophila melanogaster and have many homologues in other species including humans. TRPs form cationic channels that can detect sensory stimuli such as temperature, pH or oxidative stress and transduce that into either electrical (change in membrane potential) or chemical signals (change in intracellular Ca2+ concentration). In humans, there are 28 TRP genes arranged into 6 subfamilies; TRPA, TRPC, TRPM, TRPML, TRPP, and TRPV (Wu et al. 2010). Each TRP channel subunit consists of six putative transmembrane-spanning segments (S1-S6) with a pore-forming loop between S5 and S6. These subunits assemble into tetramers to form functional channels. All functionally characterized TRP channels are permeable to Ca2+ except TRMP4 and 5 which are only permeable to monovalent cations such as Na+ (Latorre et al. 2009). Most TRPs can cause channelopathies which are risk factors for many disease states (Nilius & Owsianik 2010).

Literature references

- Zaelzer, C., Brauchi, S., Latorre, R. (2009). Structure-functional intimacies of transient receptor potential channels. Q. Rev. Biophys., 42, 201-46. 7
- Beck, A., Cheng, H., Nelson, PL. (2011). Transient receptor proteins illuminated: current views on TRPs and disease. Vet. J., 187, 153-64. ↗
- Clapham, DE., Wu, LJ., Sweet, TB. (2010). International Union of Basic and Clinical Pharmacology. LXXVI. Current progress in the mammalian TRP ion channel family. *Pharmacol. Rev.,* 62, 381-404.

Owsianik, G., Nilius, B. (2010). Transient receptor potential channelopathies. Pflugers Arch., 460, 437-50. 🛪

2013-04-17	Authored, Edited	Jassal, B.
2013-07-16	Reviewed	He, L.

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