**Duran C., Thompson C.H., Xiao Q., Hartzell C. Chloride channels: Often enigmatic, rarely predictable. Annu. Rev. Physiol. 2010;72:95–121. doi: 10.1146/annurev-physiol-021909-135811**

Although this review is a bit out dated now, it provides a good overview of the history of chloride channels and how they are organized. Chloride channels have been poorly characterized/organized into channel families, but they can be broadly grouped into five families: ClCs, ligand gated anion channels, CFTR, bestrophins, and anoctamins. In the ClC family, only a subset are channels while the rest are transporters. It describes some of the key structural properties of the ClCs, specifically that they form dimers and that each monomer is capable of ion conduction. The two lesser known families, anoctamins and bestrophins, were described and both are suggested to be Ca2+ activated chloride channels. However, the evidence for this in bestrophin channels is conflicting.

**Dutzler R, Campbell EB, Cadene M, Chait BT, MacKinnon R. X-ray structure of a ClC chloride channel at 3.0 Å reveals the molecular basis of anion selectivity. Nature. 2002;415:287–294. doi: 10.1038/415287a**

This is one of the earliest papers describing the structure of ClC channels from E. *coli* and *S. typhimurium*. Although the two-pore structure was already suggested, this demonstrated that the subunits have opposite orientations, or run antiparallel to one another. It also described the how the ion selectivity filter functions for anions and how the ion conduction pathway functions.

**Stölting G., Fischer M., Fahlke Ch. (2014b). ClC-1 and ClC-2 form hetero-dimeric channels with novel protopore functions. Pflugers Arch. 466, 2191–2204. 10.1007/s00424-014-1490-6**

This paper demonstrates that the gating properties of ClC-1 & ClC-2 monomers are partially dependent on their interaction when forming a homodimeric structure. Previously, it was believed that the dimeric structure only affected the slow gating of each of the protopores and not the fast gating of each protopore. However, the formation of the heterodimer refutes this evidence because both the fast and the slow gating of each protopore was altered when they only expected the slow gating to be.

**Robertson JL, Kolmakova-Partensky L, Miller C. Design, function and structure of a monomeric ClC transporter. Nature. 2010;468:844–847. doi: 10.1038/nature09556**

Before this paper was published, it was known that the channels and transporters of the ClC family typically formed homodimers. However, the idea that each monomer could function independently was only an inference. This article suggests that a single monomer (of a transporter) can conduct ions independently. They did this through mutations of the leucine and isoleucine side chains that normally link the subunits (or monomers) together. The monomers were able to conduct Cl- at half the rate as the dimers. Structurally, the monomer was very similar to the dimer when their crystallized structures were compared, although there were still a few differences.

**Chenal C, Gunner MR. Two Cl Ions and a Glu Compete for a Helix Cage in the CLC Proton/Cl(−) Antiporter. Biophys J. 2017;113:1025–1036. doi: 10.1016/j.bpj.2017.07.025**

The ClC family is split between channels and transporters, and this paper focused on the transporter. It has been shown previously that transporters will pump two Cl- ions in the opposite direction of one proton. The purpose of this paper was to see if and how this 2:1 ion exchange is thermodynamically favorable. There are three binding sites for Cl-: extracellular (SX), central (SC), and intracellular (SI) and one binding site for H+: the extracellular Glu (EX). Binding of one Cl- to SX is coupled to outward movement of EX, which increases its proton binding affinity. This isn’t observed when Cl- binds to SC. They also showed that having two Cl- ions bound at the same time is the most thermodynamically favored state, which agrees with experimental observations.

**Amjad A, Hernandez-Clavijo A, Pifferi S, Maurya DK, Boccaccio A, Franzot J, Rock JR, Menini A. 2015. Conditional knockout of TMEM16A/anoctamin1 abolishes the calcium-activated chloride current in mouse vomeronasal sensory neurons. J Gen Physiol. 145:285–301**

Vomeronasal sensory neurons possess calcium activated currents, which were shown to be calcium activated chloride currents (CaCC) through the ion substitution method. Because anoctamins are suggested to be CaCCs, they heterologously expressed TMEM16A & B (Ano1 & Ano2) channels and found that the currents from Ano1 were more similar to the native CaCCs than those from Ano2. Because of this, they knocked out Ano1 in the native vomeronasal sensory neurons and demonstrated that this eliminated the CaCCs. This suggested that Ano1 is necessary for CaCCs in these neurons, even though Ano2 is also expressed.

**Peters CJ, Gilchrist JM, Tien J, Bethel NP, Qi L, Chen T, Wang L, Jan YN, Grabe M, Jan LY. The sixth transmembrane segment is a Major gating component of the TMEM16A Calcium-Activated chloride channel. Neuron. 2018;97:1063–1077. doi: 10.1016/j.neuron.2018.01.048**

One class of calcium activated chloride channels (CaCCs) is made up by homodimers of TMEM16A (Ano1) or TMEM16B (Ano2). Internal Ca2+ and external anions modify voltage dependence of TMEM16A channel activation. This paper took advantage of previous studies detailing the structure of this channel (Ano 1) and identified several regions in the 6th TMD (which lines the pore) that would affect both calcium sensitivity and anion permeability. From this information, they did a series of point mutations in TM6 and noticed shifts in calcium dependent activation, voltage dependence, and anion permeability. Furthermore, the locations of these point mutations suggested binding locations for anions on the extracellular side of the channel.

**Vaisey G, Long SB. An allosteric mechanism of inactivation in the calcium-dependent chloride channel BEST1. J. Gen Physiol. 2018 Nov 5;150(11):1484-1497. doi: 10.1085/jgp.201812190**

Bestrophin channels (another calcium activated Cl- channel) exhibit current rundown and they wanted to determine what the cause of this was: an inherent property of the channel or a result of cellular processes. Using planar lipid bilayers, they showed that Best1 rundown is due to inactivation that is dependent on Ca2+ concentration. Using protein truncation, point mutations, and antibody fragments, they showed that there is a region on the C-terminus that is involved in inactivation. Unlike the ball and chain inactivation method (directly blocking the pore), this region of the C-terminus binds to a receptor site on Best1 that indirectly closes a gate near the neck of the pore.

**Messier, J. E., Chen, H., Cai, Z. L., & Xue, M. (2018). Targeting light-gated chloride channels to neuronal somatodendritic domain reduces their excitatory effect in the axon. *eLife*, *7*, e38506. doi:10.7554/eLife.38506**

This paper is a good example of how understanding chloride channel behavior could be applied to inhibiting or exciting neural networks. Various forms of light gated cation or anion channels & pumps have been commonly used in optogenetics, but the purpose of this paper was to identify an important drawback of this technique, which is localization. Having light gated Cl- channels expressed throughout the cell led to inhibitory effects in the soma and excitatory effects in the axon (because the chloride concentration was higher there), which defeated the purpose of using this channel as a dampener of excitability. They linked this channel with other proteins that are typically found in the soma and dendrites of the cell, so that it was trafficked there instead. This reduced the excitatory effect in the axon that was present with the wild type channel.

**Alexander, S. P., Mathie, A., & Peters, J. A. (2011). Guide to Receptors and Channels (GRAC), 5th edition. *British journal of pharmacology*, *164 Suppl 1*(Suppl 1), S1-324.**

This “review” is more so an encyclopedia or textbook than an article, but it provides an informative background on many types of channels and receptors, far more than can be covered in class. There are seven sub-categories that cover g-protein coupled receptors, ligand gated channels, ion channels, nuclear receptors, catalytic receptors, transporters, and enzymes. Although the entries on each are fairly short, they are densely packed with information on a protein’s structure, function, selectivity, activation, expression, blockers, other functional properties, and more. This is a good starting place for learning about the core properties of a protein. Additionally, it provides a selection of recommended articles should you wish to learn more about it.

Web resources

* <http://proteopedia.org/>
  + This website contains interactive 3-D structures of many proteins (not only ion channels).
* <https://www.hhmi.org/biointeractive/>
  + This is a broad biology website, but it contains plenty of information and has nice animations that can be helpful for presentations or teaching.
* <http://neuromorpho.org/>
  + Collection of digitally reconstructed neurons from a variety of species and regions.
* <http://crcns.org/>
  + Collaborative research in computational neuroscience (CRCNS) is a data sharing website that hosts data sets from a variety of electrophysiological studies that can be applied to computational modeling.
* <https://neuroelectro.org/>
  + This website collects information about the electrophysiological properties of a variety of neurons and places them into a centralized database.
* <https://www.nature.com/nmeth/>
  + Nature methods is a good way to stay up to date on new or adapted techniques that can be applied in many fields.
* <https://neurodata.io/>
  + This site contains volumetric datasets, atlases, and connectomes derived from research in several species and in a variety of regions
* <https://senselab.med.yale.edu/neurondb/>
  + This is another database for electrophysiological properties of neurons that allows for comparison with cells from other regions.
* <http://www.mbl.org/>
  + This is the mouse brain library and is useful for anyone that works with mice. It has stained and labelled sections from many mice strains.
* <https://www.wwpdb.org/>
  + Worldwide protein data bank is a repository of 3D structures of many proteins.