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Chloride Ion Channels – Annotated Bibliography

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Literature

1. **Hwang, T. C., J. T. Yeh, et al. (2018). "Structural mechanisms of CFTR function and dysfunction." *Journal of General Physiology*. 150(4): 539-570.**

Cystic fibrosis (CF) transmembrane conductance regulator (CFTR) chloride channel plays a critical role in water and electrolyte regulation across the epithelilium. CF results from malfunction of the channel because of mutations in the cftr gene. Recently, the publication of atomic structures of CFTR in two distinct conformations has been provided. The goal of this review is to better understand the functional significance of the domains of CFTR.

1. **Anderson, M. P., R. J. Gregory, et al. (1991). "Demonstration That CFTR is a Chloride Channel by Alteration of its Anion Selectivity." *Science.* 253(5016): 202-205.**

It is shown that the cystic fibrosis transmembrane conductance regulator (CFTR) generates adenosine 3',5'-monophosphate (cAMP)-regulated chloride channels. CFTR is therefore one of two things, either a chloride channel or a chloride channel regulator. Basic amino acids lysine and arginine in the transmembrane domains of CFTR were mutated to test the two hypotheses. Anionic selectivity of these cAMP-regulated channels in HeLa cells containing either wild type or a recombinant CFTR was bromide > chloride > iodide > fluoride. Mutation of the lysines at positions 95 or 335 to acidic amino acids converted the selectivity preference to iodide > bromide > chloride > fluoride. The data indicates that CFTR is a cAMP-regulated chloride channel and that lysine 95 and lysine 335 determine anion selectivity. Furthermore, according to Eisenman's theory as possible explanation for the observed ionic selectivity differences, “anionic selectivity depends on the hydration energy of the anion and the energy of interaction between an anion and a positively charged site.”

1. **Puljak, L. and G. Kilic (2006). "Emerging roles of chloride channels in human diseases." Biochimica Et Biophysica Acta-Molecular Basis of Disease 1762(4): 404-413.**

This review discusses the roles chloride ion channels play in numerous diseases: myotonia congenita, dystrophia myotonica, cystic fibrosis, osteopetrosis and epilepsy. The paper discusses in depth the abnormal, damaging effects of chloride ion channels contribute to the development of these diseases.

1. **Duran, C., C. H. Thompson, et al. (2010). "Chloride Channels: Often Enigmatic, Rarely Predictable." Annual Review of Physiology 72: 95-121.**

Chloride channels have received less attention due to being originally perceived as being homeostatic regulators. For example, Cl- channels perform functions that might be considered regulatory, like fluid secretion and cell volume regulation. However, recent work has made their channel activity of paramount importance. This review outlines the different families of chloride ion channels: ClCs, ligand gated anion channels, CFTR, bestrophins, and anoctamins. The members of each family is also outlined. Of special note is that more than half of the ClC family members are antiporters, and not channels.

1. **Jentsch, T. J., V. Stein, et al. (2002). "Molecular structure and physiological function of chloride channels." Physiological Reviews 82(2): 503-568.**

Cl- channels are present in both the plasma membrane and organelles. Their functions range from ion homeostasis to cell volume regulation, transepithelial transport, and (of relatively recent discovery) regulation of electrical excitability. Their physiological roles are shown by various inherited diseases and by utilizing knock-out mice. The review outlines at length the (since updated – see reference 4) families of chloride ion channels and pays particular attention to X-ray crystallography data of CLC channels (see reference 6).

1. **Dutzler, R., E. B. Campbell, et al. (2002). "X-ray structure of a CIC chloride channel at 3.0 angstrom reveals the molecular basis of anion selectivity." Nature 415(6869): 287-294.**

The ClC chloride channels enable selective transportation of Cl- ions across cell membranes. This regulates electrical excitation in skeletal muscle and the flow of salt and water across epithelial barriers. Presented here is the X-ray crystallography structures of two prokaryotic ClC Cl- channels from *Salmonella enterica serovar typhimurium* and *Escherichia coli*. Both structures reveal two identical pores, each pore being shaped by a discrete subunit contained within a homodimeric membrane protein. Individual subunits are composed of two repeated halves that cross the membrane with opposite orientations (antiparallel). A selectivity filter results from this antiparallel construction in which Cl- ions are stabilized by electrostatic interactions with α-helix dipoles and also by chemical coordination. The paper has a nice figure detailing the differences in chloride ion channels (antiparallel structure) and cation channels (parallel/barrel stave structure) that account for the selectivity of each, respectively.

1. **Caputo, A., E. Caci, et al. (2008). "TMEM16A, a membrane protein associated with calcium-dependent chloride channel activity." Science 322(5901): 590-594.**

Calcium-dependent chloride channels are essential for normal electrolyte and fluid secretion, olfactory perception, and neuronal and smooth muscle excitability. This paper shows TMEM16A, a plasma membrane protein with unknown function, is connected with calcium-dependent chloride current, as measured in three ways: with halide-sensitive fluorescent proteins, short-circuit current, and patch-clamp techniques. The data indicates that TMEM16A is a component of the calcium-dependent chloride channel.

1. **Falzone, M. E., M. Malvezzi, et al. (2018). "Known structures and unknown mechanisms of TMEM16 scramblases and channels." Journal of General Physiology 150(7): 933-947.**

Review of the TMEM16 family of membrane proteins, which is composed of both Ca2+ -gated Cl- channels and Ca2+-dependent phospholipid scramblases. The review makes special note that ion transport and lipid scramblase enzyme activity may therefore be linked!

1. **Stolting, G., M. Fischer, et al. (2014). "ClC-1 and ClC-2 form hetero-dimeric channels with novel protopore functions." Pflugers Archiv-European Journal of Physiology 466(12): 2191-2204.**

This paper describes the gating processes and function of CLC-1 and CLC-2. The findings suggest that inter-subunit interactions do not only affect overall gating, but also ion permeation and gating of individual protopores in hetero-dimeric ClC channels.

1. **Ludewig, U., M. Pusch, et al. (1996). "Two physically distinct pores in the dimeric CIC-0 chloride channel." Nature 383(6598): 340-343.**

This paper is a great example of using patch-clamp to elucidate information about chloride channel proteins. ClC-0 opens in bursts with two identical conductance levels. They noted the following results: 1. Hyperpolarization slowly increases the burst probability (slow gating), and 2. Depolarization increases channel opening within bursts (fast gating). Site-directed mutagenesis of replacing serine 123 with threonine changes restructuring, ion selectivity and gating. Notable however is that characteristic bursting behavior is retained with two identical (and notably) independent, conductance states. This work strongly suggests that conductance, ion selectivity and 'fast' gating are determined only by the single subunit forming a single pore. This is independent from the attached pore; in contrast, slow gating is a function of both subunits. Thus, these results are interpreted to mean that ClC-0 is a homodimer with two largely independent pores. Note: this was proposed before reference 6 showed the homodimeric nature of the ClC family members definitively with x-ray crystallography six years later.

Web Resources

1. <https://www.europeanpharmaceuticalreview.com/article/20848/chloride-ion-channels-and-transporters/>

 - Web-available article that discusses chloride ion channels

2. <http://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=120>

 - Webpage dedicated to information about the various types of chloride ion channels

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3. <https://proteopedia.org/wiki/index.php/Chloride_Ion_Channel>

 -Resource for Chloride Channel Information

4. <https://www.ncbi.nlm.nih.gov/protein>

 -Database of protein structures

5. <https://www.youtube.com/watch?v=EhQ4q37AUgA>

 - Chloride ion channel structure from reference 6

6. <https://www.youtube.com/watch?v=6IbP1ASGv9w>

 - Video on the topic of CFTR and cystic fibrosis

7. <https://www.youtube.com/watch?v=wP9QD-5FL5U>

 - GABA receptors and the link to ligand-gated chloride ion channels

8. <https://www.khanacademy.org/test-prep/mcat/organ-systems/biosignaling/v/ligand-gated-ion-channels>

 - MCAT test prep video highlighting ligand-gated ion channels fundamentals

9. <https://www.youtube.com/watch?v=T_JN3qtfz1Y>

 - CLC structure video

10. <https://www.genenames.org/cgi-bin/genefamilies/set/278>

 - Chloride Channel Family Information