

Abstract No. Dutz0326

X-ray Structures of Two CIC Chloride Channels

Raimund Dutzler, Ernest B. Campbell and Roderick MacKinnon (HHMI/Rockefeller University)

Beamline(s): X25

Introduction: The CIC chloride channels catalyze the selective flow of Cl⁻ ions across cell membranes [1]. Members of this large anion channel family are found throughout biology, from prokaryotic cells to plants and vertebrate animals. These channels control electrical excitation in skeletal muscle and in certain neurons and mediate the flow of salt and water across epithelial barriers. Genetic defects in CIC Cl⁻ ion channels underlie several familial muscle and kidney diseases.

Results: We have solved the X-ray structures of two prokaryotic CIC Cl⁻ channels from *S. typhimurium* and from *E. coli* at 3.0 Å and 3.5 Å resolution, respectively [2]. The majority of the data was collected at BNL X25. These structures are representative of the entire CIC chloride channel family. As anticipated from electrophysiological studies, the structures contain two identical pores, each pore being formed entirely by a separate subunit contained within a homodimeric membrane protein (Fig.1). Each subunit is comprised of two roughly repeated halves, inverted with respect to each other in the membrane. This anti-parallel architecture creates a pseudo 2-fold symmetry axis near the membrane center, surrounding a Cl⁻ selectivity filter. A Cl⁻ ion is stabilized through electrostatic interactions with oriented α helices and through chemical coordination by main chain amide nitrogen atoms and by the side chain hydroxyl groups of serine and tyrosine. These findings provide a structural basis for further understanding the function of CIC Cl⁻ channels, and establish the physical and chemical basis of their anion selectivity.

Acknowledgments: This work was supported by grants of the National Institutes of Health (NIH). R.M. is an investigator in the Howard Hughes Medical Institute.

References:

[1] Jentsch T.J., Stein V., Weinreich F. and Zdebik A.A. "Molecular structure and physiological function of chloride channels", *Physiol. Rev.*, **82**, 503-568 (2002)

[2] Dutzler R., Campbell E.B., Cadene M., Chait B.T. and MacKinnon R. "X-ray structure of a CIC chloride channel at 3.0Å reveals the molecular basis of anion selectivity", *Nature*, **415**, 287-294 (2002)

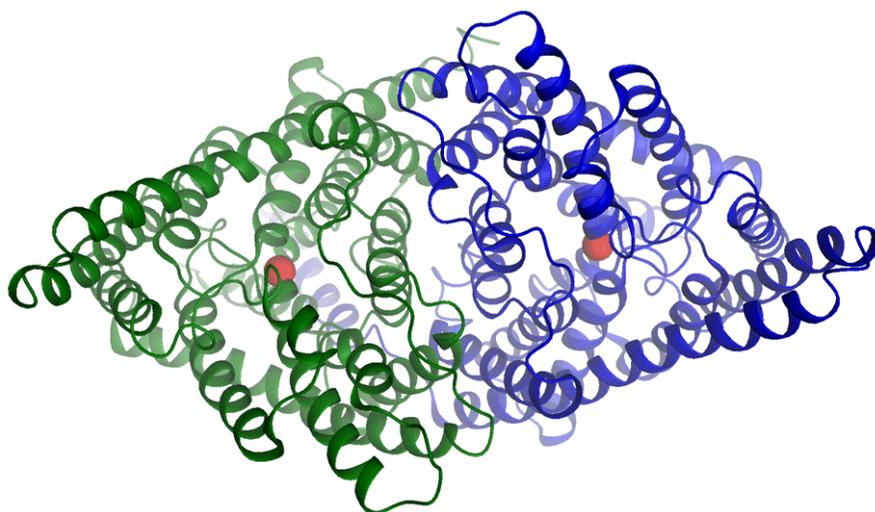


Figure 1.: Structure of the CIC chloride channel dimer from *S. typhimurium* viewed from the extracellular side. The two subunits are colored blue and green. Cl⁻ ions in the selectivity filters are represented as red spheres.