Structural insight into the CLIC1 integral membrane structure by fluorescence resonance energy transfer and electron microscopy

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Chloride Intracellular Ion Channels (CLICs) are a family of highly conserved proteins found to exist as both a soluble, globular form as well as an oligomeric membrane-inserted form. Electrophysiological studies have shown that the membrane-inserted form of the CLIC proteins can function as an ion channel. That the CLICs can exist as two considerably different folds makes this protein family highly controversial. The traditional protein structure paradigm is that the amino acid sequence of a protein provides the protein with a single, well-defined three-dimensional structure. However, it is becoming increasingly apparent, that some proteins defy this traditional view.

The structures of several CLIC family members in the soluble form have successfully been determined using X-ray crystallography. However, as CLICs can reversibly transit between the soluble and membrane-inserted forms, attempts to solve the membrane-inserted form have so far been unsuccessful. To gain a structural insight of the membrane-inserted form of human CLIC1, Fluorescence Resonance Energy Transfer (FRET) spectroscopy and Transmission Electron Microscopy (TEM) are being utlized. FRET measurements between the CLIC1 and the membrane have shown a clear interaction with the bilayer allowing for a membrane inserted model defining the position of the CLIC1 transmembrane region to be constructed. TEM is also being used to further examine the nature of the inserted CLIC1 oligomeric membrane form in lipid vesicles.