A minuscule change in the CLC “Chloride-Channel” may result in detrimental effect in health. How can a simple channel that regulates chloride and protons play such significant role in cardiovascular, neuronal, bone and epithelial function? The answer is: welcome to the fascinating world of science. Actually, many researchers do not have an answer and so now they are doing enormous amount of work on these channels, such as observing the change in conformation of the channel when a stress is imposed on it. Stress includes chemical modification, for example, varying the proton concentration of the channel environment.

Abraham et al have previously looked at the conformation of CIC-ec1 by crystallography. However, crystallographic techniques have severe limitations hence some particular structures of conformational states remain unknown. For example, CLC inner gate opening that was inferred by crosslinking studies has not been detected by crystallography. In this study, Abraham et al, used $^{19}$F solution-state NMR to detect conformational changes in CIC-ec1. In brief, they varied the concentration of chloride ions and protons in the chemical environment of the peptide in order to look at conformational changes. This work reflected the fact that two concentration changes in the chemical environment result in different conformational states. This is because active transporters tightly couple conformational changes to ion binding and ion release. With this strategy in mind Abraham et al reasoned solution-state NMR could detect CLC conformational changes that cannot be detected by crystallographic methods. They specifically targeted $^{13}$C methyl labeling of methionine and lysine residues. They identified one region as Helix R (a helix that extends from the center of the protein) as a part of the inner gate to the chloride permeation pathway that responds to proton concentration. Also, they found that proton concentration does not affect the channel beyond helix R, but has significant effects on the helices prior to helix R. They concluded that proton binding is mechanistically coupled to the closing of the intracellular access-pathway for chloride.