CLIC proteins: chameleon proteins at the interface between membranes and the cytoskeleton

D.R. Littler,[1,2] S.J. Harrop,[1,2] L.J. Brown,[2,3] G,J, Pankhurst,[2] A.V. Mynott,[1,2] J. Phang,[1,2] P. Luciani,[4] R.A. Mandyam,[3] M. Mazzanti,[4] S. Tanda,[5] M.A. Berryman,[5] S.N. Breit[2] and P.M.G. Curmi ,[1,2] [1]School of Physics, University of New South Wales, NSW 2052, Australia, [2]Centre for Immunology, St Vincent's Hospital and University of New South Wales, Sydney, NSW 2010, Australia, [3]Department of Chemistry and Biomolecular Sciences, Macquarie University, NSW 2109, Australia, [4]Department of Cellular and Developmental Biology, University of Rome "La Sapienza", 00185 Rome, Italy and [5]Department of Biomedical Sciences, Molecular and Cellular Biology Program, Ohio University College of Osteopathic Medicine, Athens, OH 45701, USA.

Most proteins exist as either soluble or integral membrane proteins, however, there is a growing class of proteins that can adopt both of these states. Traditionally, these proteins have been mainly limited to bacterial toxins such as colicin and diphtheria toxin. More recently, eukaryotic cytoplasmic proteins have been shown to exhibit these properties. The CLIC family represents a class of proteins that are generally soluble, but can integrate into membranes to form chloride ion channels. CLICs are members of the GST fold family, but, in contrast to the GSTs, they have a reactive cysteine within their putative active site. The CLICs are highly conserved in all chordates and vertebrates, with related proteins in the invertebrates. We have used x-ray crystallography determine the structures of both human and invertebrate CLICs. In particular, human CLIC1 is shown to undergo a dramatic structural transition which is redox regulated. Under oxidising conditions, CLIC1 forms a non-covalent dimer with a radically altered monomer conformation. This novel conformation is stabilised by an intramolecular disulphide bond and the transition is reversed on reduction. Using biophysical and electrophysiological methods, we have shown that both the reduced CLIC1 monomer and the oxidised dimer can auto-insert into artificial lipid bilayers and form anion channels with properties that are indistinguishable from those observed in cells. Our best model for the CLIC1 transmembrane channel state indicates that residues 24 to 46 form a putative transmembrane domain with the first 23 residues on one side of the membrane and C-terminus on the opposite side of the membrane. If this model is correct, then the oxidised CLIC1 dimer must undergo an isomerization of its intramolecular disulphide bond prior to membrane insertion.