Dramatic Structural Change in CLIC1: Globular Protein that Forms an Ion Channel

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The CLIC proteins are an unusual family of mainly cytosolic proteins that can integrate into membranes to form ion channels. The family consists of six members that are highly conserved in vertebrates. The crystal structure of the soluble form of CLIC1 belongs to the GST fold family. On oxidation, CLIC1 undergoes a dramatic structural change, which is coincident with non-covalent dimerisation and the formation of an intramolecular disulphide bond.

In the oxidized form, the characteristic 4 stranded beta sheet of the GST fold has been transformed into helical and loop segments, resulting in the formation of a large hydrophobic surface which forms the dimer interface. We postulate that this altered structure represents the membrane docking form. Surface plasmon resonance, liposome chloride efflux experiments and tip dip electrophysiology show that CLIC1 binds to membranes to form a chloride ion channel under oxidizing conditions. Reducing agents inhibit or prevent channel activity. The electrophysiological characteristics of the channel form by CLIC1 alone in an artificial bilayer are identical to those observed in cells overexpressing CLIC1. Thus, we believe that oxidation triggers CLIC1 membrane insertion and that the dramatic structural rearrangement of the N-terminal domain is on pathway to channel formation.

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