Cytoplasmic ATP-sensing CBS domains regulate gating of skeletal muscle ClC-1 chloride channels

B. Bennetts[1], G.Y. Rychkov[2], H-L. Ng[1], C.J. Morton[1], D. Stapleton[3], M.W. Paarker[1] and B.A. Cromer [1], [1]St. Vincent's Institute, Fitzroy, VIC 3065, Australia,[2] The University of Adelaide, Adelaide, SA 5005, Australia and [3]Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Parkville, VIC 3010, Australia.

ClC proteins are a family of chloride channels and transporters that are found in a wide variety of prokaryotic and eukaryotic cell-types. The mammalian voltage-gated chloride channel ClC-1 is important for controlling the electrical excitability of skeletal muscle. Reduced excitability of muscle cells during metabolic stress can protect cells from metabolic exhaustion and is thought to be a major factor in fatigue. Here we identify a novel mechanism linking excitability to metabolic state by showing that ClC-1 channels are modulated by ATP. The high concentration of ATP in resting muscle effectively inhibits ClC-1 activity by shifting the voltage-gating to more positive potentials. ADP and AMP had similar effects to ATP but IMP had no effect, indicating that the inhibition of ClC-1 would only be relieved under anaerobic conditions such as intense muscle activity or ischaemia, when depleted ATP accumulates as IMP. The resulting increase in ClC-1 activity under these conditions would reduce muscle excitability, thus contributing to fatigue. We show further that the modulation by ATP is mediated by cystathionine-β-synthase-related (CBS) domains in the cytoplasmic C-terminus of ClC-1. This defines a function for these domains as gating-modulatory domains sensitive to intracellular ligands, such as nucleotides, a function that is likely to be conserved in other ClC proteins.