

S021 Substrate recognition and transport mechanism of mitochondrial carriers

Edmund R.S. Kunji and Alan J. Robinson

*Medical Research Council, Dunn Human Nutrition Unit,
Hills road, CB2 0XY, Cambridge, United Kingdom*

Mitochondrial carriers transport nucleotides, co-factors and metabolic intermediates across the mitochondrial inner membrane. **The significant sequence conservation in the mitochondrial carrier family suggests that the specific recognition of substrates is coupled to a common mechanism of transport.** By using two different approaches a common substrate binding site was identified consisting of residues that are highly conserved and essential for function. The first approach used chemical and distance constraints from comparative structural models to identify a site capable of discriminating between different substrates. The second exploited the principle that mitochondrial carriers have a high degree of three-fold pseudo symmetry in contrast to the transported substrates that are asymmetric. Therefore, the substrate binding site must be asymmetric to accommodate the symmetry mismatch. A symmetry score based on sequence comparisons was devised to assess the degree of symmetry in the carriers. Conserved areas with a high degree of asymmetry contained residues that had been identified by the first approach, confirming the location of the substrate binding site. The site explains substrate selectivity, ion coupling and the effects of the membrane potential on transport. The substrate is bound at the midpoint of the membrane and may function as a pivot point for the movements of the transmembrane α -helices as the carrier changes conformation. In addition, the symmetry analysis has identified residues that are important for the transport mechanism of mitochondrial carriers.