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Kinetic and molecular dissection of coupled ion-substrate membrane transport proteins

The Mhp1 Na^+, -hydantoin membrane symport protein from *Microbacterium liquefaciens* is a paradigm for the nucleobase-cation-symport, NCS-1, family of transport proteins found widely in archaebacteria, bacteria, yeasts and plants. Their metabolic roles include the capture by cells of nitrogen compounds and vitamins from the environment. Mhp1 is also a structural model for the huge range of '5-helix-inverted-repeat' superfamily of proteins, because, unusually, crystal structures are available for its open-outwards, occluded, and open-inward conformations. Here we accomplish a detailed dynamic model of the partial reactions in an alternating access cycle of membrane transport derived from substrate binding studies to the purified Mhp1 protein by combining novel mass spectrometry, stopped-flow and steady state kinetic analyses and mutagenesis. The mechanism of coupling substrate transport to the Na^+, -gradient is revealed during a sequence of mostly reversible kinetic steps that explain how transfer of substrate across the membrane is affected by changes in conformational states. The AceI H^+/substrate antiport protein from Acinetobacter baumannii is a paradigm for the proteobacterial antimicrobial compound efflux (PACE) family of drug efflux proteins found dispersed throughout the Proteobacteria. AceI contributes to the resistance of Acinetobacter baumannii towards the widely used antiseptic, chlorhexidine. Currently there is little structural information about the PACE family of transport proteins, but progress towards understanding the recognition of substrates and cations by AceI and its homologues will be discussed.

Figure 1: Scheme for the coupled transport of Na+ and hydantoins by Mhp1.

Recent Publications

1. Shimamura T, Weyand S, Beckstein O, Rutherford N G, Hadden J M et al. (2010) Molecular basis of alternating access membrane transport by the sodium-hydantoin transporter Mhp1. Science. 328(5977):470-473.
2. Simmons K J, Jackson S M, Brueckner F, Patching S G, Beckstein O et al. (2014) Molecular mechanism of ligand recognition by membrane transport protein. Mhp1. EMBO J. 33(16):1831-1944.
3. Calabrese A N, Jackson S M, Jones L N, Beckstein O, Gsponer J (2017) Topological dissection of the membrane

transport protein Mhp1 derived from cysteine accessibility and mass spectrometry. Anal. Chem. 89(17):8844-8852.

4. Hassan K A, Jackson S M, Penesyan A, Patching S G, Tetu S G et al. (2013) Transcriptomic and biochemical analyses identify a novel family of chlorhexidine efflux proteins. Proc Natl. Acad. Sci. USA. 110(50):20254-20259.
5. Hassan K A, Liu Q, Henderson P J F, Paulsen I T (2015) Homologs of the Acinetobacter baumannii AceI transporter represent a new family of bacterial multidrug efflux systems. mBio. 6(1):e01982-14. Pg.1-5.

Biography

Peter J F Henderson is a Professor of Biochemistry and Molecular Biology in the University of Leeds. He obtained his BSc in 1965 and PhD in 1968, both in Biochemistry, at the University of Bristol. After Postdoctoral training at the Enzyme Institute, Madison, University of Wisconsin and in the Department of Biochemistry at Leicester, he became a University Lecturer in 1973. In 1975 he moved to the Department of Biochemistry at Cambridge, where he became Reader in Molecular Biology of Membranes in 1990. He has held Visiting Professorships in Japan, Canada and Australia. He was Scientific Director of the European Membrane Protein (EMeP) consortium 2003-2008, Coordinator of the European Drug Initiative for Channels and Transporters (EDICT) 2008-2012 and held Leverhulme Trust Emeritus Research Fellowships in 2001-2002 and 2014-2017. He has published over 200 scientific papers in the fields of Membrane Transport, Enzyme Kinetics and Structural Biology.

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