Correspondence

Proton translocation by transhydrogenase

J. Baz Jackson*

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Transhydrogenase is a membrane protein that participates in the chemiosmotic proton circuit of mitochondria and bacteria. It has membrane-peripheral components that catalyse the redox reaction, and a membrane-spanning component that translocates hydrogen ions. At the 126th Nobel Symposium (Örsundsbro, 2003) recent X-ray structures of the peripheral components were described in the context of the likely mechanism by which the redox reaction is energetically coupled to proton translocation across the membrane. A review of the mechanism of proton translocation by transhydrogenase was recently published [1] and a summary of this article is featured below (Figs. 1 and 2).

Transhydrogenase, in animal mitochondria and bacteria, couples hydride transfer between NADH and $NADP^+$ to proton translocation across a membrane. Within the protein, the redox reaction occurs at some distance from the proton-translocation pathway and coupling is achieved through conformational changes. In an 'open' conformation of transhydrogenase, in which substrate nucleotides bind and product nucleotides dissociate, the dihydronicotinamide and nicotinamide rings are held apart to block hydride transfer; in an 'occluded' conformation, they are moved into apposition to permit the redox chemistry. In the two monomers of transhydrogenase, there is a reciprocating, out-of-phase alternation of these conformations during turnover.

References

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*Fax: (44)-121-414 5925.
E-mail address: j.b.jackson@bham.ac.uk

School of Biosciences, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

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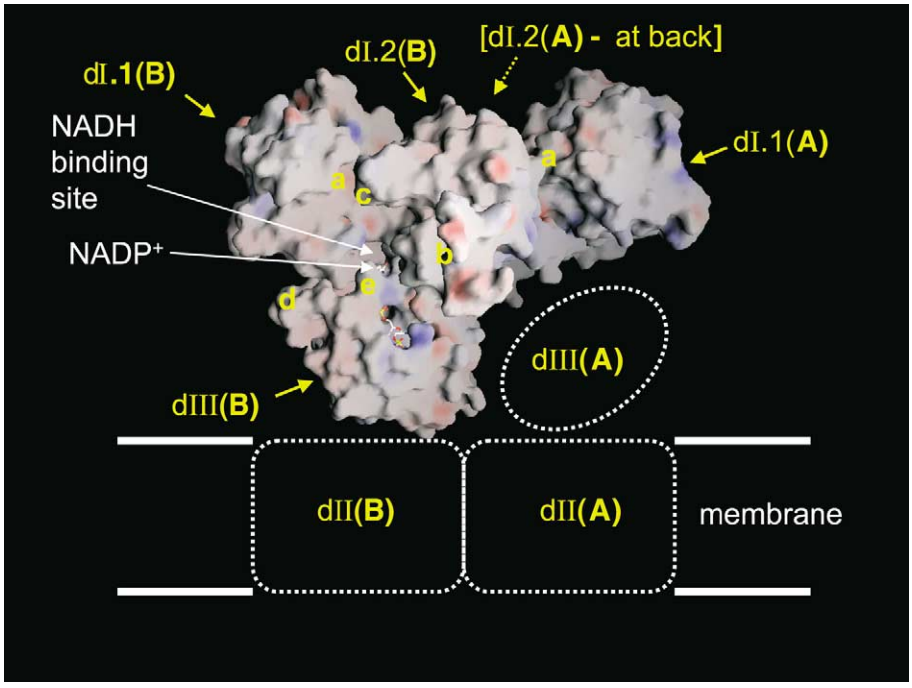

Fig. 1. The domain structure and some important secondary-structure features in transhydrogenase. The upper part of the figure is a surface representation of the crystal structure of the dI_2dIII_1 complex of *Rhodospirillum rubrum* transhydrogenase [2] showing positive and negative Coulombic fields in blue and red, calculated by the program GRASP [3]. Bound $NADP^+$, partly obscured by loop E, can be seen (in stick format) in the dIII component but dI(B) lacks NAD(H) in the crystal structure. Features referred to in the text are: *a*, the cleft between domains dI.1 and dI.2; *b*, the mobile loop of dI (truncated in this structure due to weak electron density); *c*, the TAGP loop of dI; *d*, helix D/loop D of dIII; *e*, the loop E 'lid' of dIII. The lower part of the figure shows the probable position of the second dIII component and expected topology of the intact enzyme in the membrane.

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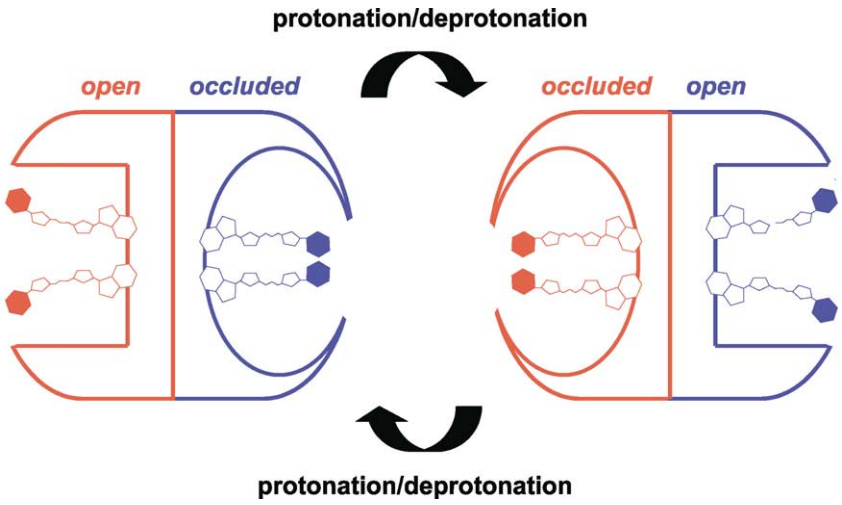

Fig. 2. The binding-change mechanism of transhydrogenase. In the 'open' state, bound nucleotides can exchange with those in the solvent, and hydride transfer between NADH and $NADP^+$ is blocked – the dihydronicotinamide and nicotinamide rings (shaded) are kept apart. In the 'occluded' state, bound nucleotides cannot exchange with those in the solvent and hydride transfer is allowed – the two rings are brought together. The conformational states of the two monomers of transhydrogenase (one monomer in red and the other in blue) alternate during turnover.