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Review

Molecular mechanisms for generating transmembrane proton gradients ☆

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ABSTRACT

Membrane proteins use the energy of light or high energy substrates to build a transmembrane proton gradient through a series of reactions leading to proton release into the lower pH compartment (P-side) and proton uptake from the higher pH compartment (N-side). This review considers how the proton affinity of the substrates, cofactors and amino acids are modified in four proteins to drive proton transfers. Bacterial reaction centers (RCs) and photosystem II (PSII) carry out redox chemistry with the species to be oxidized on the P-side while reduction occurs on the N-side of the membrane. Terminal redox cofactors are used which have pK_as that are strongly dependent on their redox state, so that protons are lost on oxidation and gained on reduction. Bacteriorhodopsin is a true proton pump. Light activation triggers *trans* to *cis* isomerization of a bound retinal. Strong electrostatic interactions within clusters of amino acids are modified by the conformational changes initiated by retinal motion leading to changes in proton affinity, driving transmembrane proton transfer. Cytochrome c oxidase (CcO) catalyzes the reduction of O_2 to water. The protons needed for chemistry are bound from the N-side. The reduction chemistry also drives proton pumping from N- to P-side. Overall, in CcO the uptake of 4 electrons to reduce O_2 transports 8 charges across the membrane, with each reduction fully coupled to removal of two protons from the N-side, the delivery of one for chemistry and transport of the other to the P-side.

Contents

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1. Introduction

Organisms use a transmembrane electrochemical proton gradient as a key form of stored energy [1–4]. A group of transmembrane proteins generate this gradient using the energy stored in low potential reduced substrates [5–7] or light [8]. The protons then move downhill through other membrane embedded proteins, dissipating the proton gradient to do work. The gradient is primarily used to support ATP synthesis by the F_1/F_0 ATPase [9–12], but also fuels flagellar motors [13,14] and plays a role in supporting active transport of metabolites [15–17].

This review focuses on four proteins that add to the transmembrane proton gradient: bacterial reaction centers (RCs) [18–21], photosystem II (PSII) [22–26], bacteriorhodopsin [27–31] and cytochrome c oxidase (CcO) [7,32–41]. RCs, PSII and bacteriorhodopsin use light as the energy source, while CcO uses the energy liberated by the reduction of O_2 to water [42]. Proteins that generate the proton gradient can be classified into two fundamental molecular designs (Fig. 1) [7,43]. One uses redox reactions, arranging the sites that do chemistry vectorially with respect to the membrane (Fig. 2) [44]. The second is the transmembrane proton pump (Fig. 3). RCs and PSII carry out vectorial redox chemistry. Bacteriorhodopsin is a proton pump. CcO combines both mechanisms as vectorial redox chemistry leads to the reduction of O_2 and the liberated energy drives a proton pump.

1.1. Vectorial redox chemistry

In a vectorial, redox dependent system low potential substrates that are oxidized, releasing protons are placed in binding sites on the low pH (P, positive) side of the membrane while the groups that are reduced, binding protons, are near the high pH (N, negative) side (Figs. 1b,c, 2) [44–47]. There is no proton transfer through the protein from the N- to P-side of the membrane. Electrons tunnel, through a series of intermediate acceptors [48], across the protein from the electron donor on the P-side to the acceptor on the N-side. Bacterial photosynthetic reaction centers (RCs) and green plant photosystems PSI and PSII use light energy to build the proton gradient in this manner.

Building a proton gradient by vectorial electron transfer reactions requires that the reactants and products of the redox reactions have substantially different pK_as in their oxidized and reduced states (Fig. 2). In addition, their pK_as must shift across the value of the pH. Thus, the pK_a of each oxidized species must be below the pH, while the reduced species must be above the pH on the appropriate side of the membrane. If the pK_a remains above or below the pH in both oxidized and reduced states, there will be no proton binding or release even if there is a large change in the pK_a [49].

Vectorial redox chemistry relies on electron tunneling through the protein. Tunneling steps of 8–10 Å are optimal so the transmembrane region needs one or two intermediary cofactors to serve as stepping stones across the membrane [48,50]. The reduction chemistry of these bridging redox cofactors is usually not coupled to proton transfer. In principle, conformational changes are not required to carry out these long-range electron transfers and many of these reactions will occur in frozen samples [51–53]. While these proteins do not have transmembrane proton pathways, they will have short pathways providing access to transfer protons from the surface to the terminal electron donors and acceptors [20,54,55].

1.2. The proton pump

The other basic protein design that generates a transmembrane gradient is the proton pump. Here protons are moved through the

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