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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 O₂ 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 O₂ 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.

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100 1. Introduction

101 Organisms use a transmembrane electrochemical proton gradient
 102 as a key form of stored energy [1–4]. A group of transmembrane proteins
 103 generate this gradient using the energy stored in low potential
 104 reduced substrates [5–7] or light [8]. The protons then move downhill
 105 through other membrane embedded proteins, dissipating the proton
 106 gradient to do work. The gradient is primarily used to support ATP
 107 synthesis by the F₁/F₀ ATPase [9–12], but also fuels flagellar motors
 108 [13,14] and plays a role in supporting active transport of metabolites
 109 [15–17].

110 This review focuses on four proteins that add to the transmembrane
 111 proton gradient: bacterial reaction centers (RCs) [18–21], photosystem
 112 II (PSII) [22–26], bacteriorhodopsin [27–31] and cytochrome c oxidase
 113 (CcO) [7,32–41]. RCs, PSII and bacteriorhodopsin use light as the energy
 114 source, while CcO uses the energy liberated by the reduction of O₂ to
 115 water [42]. Proteins that generate the proton gradient can be classified
 116 into two fundamental molecular designs (Fig. 1) [7,43]. One uses redox
 117 reactions, arranging the sites that do chemistry vectorially with respect
 118 to the membrane (Fig. 2) [44]. The second is the transmembrane proton
 119 pump (Fig. 3). RCs and PSII carry out vectorial redox chemistry. Bacteri-
 120 orhodopsin is a proton pump. CcO combines both mechanisms as vector-
 121 ial redox chemistry leads to the reduction of O₂ and the liberated
 122 energy drives a proton pump.

123 1.1. Vectorial redox chemistry

124 In a vectorial, redox dependent system low potential substrates that
 125 are oxidized, releasing protons are placed in binding sites on the low pH
 126 (P, positive) side of the membrane while the groups that are reduced,
 127 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-
 128 to P-side of the membrane. Electrons tunnel, through a series of inter-
 129 mediate acceptors [48], across the protein from the electron donor on
 130 the P-side to the acceptor on the N-side. Bacterial photosynthetic reac-
 131 tion centers (RCs) and green plant photosystems PSI and PSII use light
 132 energy to build the proton gradient in this manner. 133

134 Building a proton gradient by vectorial electron transfer reactions
 135 requires that the reactants and products of the redox reactions have
 136 substantially different pK_as in their oxidized and reduced states
 137 (Fig. 2). In addition, their pK_as must shift across the value of the pH.
 138 Thus, the pK_a of each oxidized species must be below the pH, while
 139 the reduced species must be above the pH on the appropriate side
 140 of the membrane. If the pK_a remains above or below the pH in both
 141 oxidized and reduced states, there will be no proton binding or re-
 142 lease even if there is a large change in the pK_a [49]. 142

143 Vectorial redox chemistry relies on electron tunneling through the
 144 protein. Tunneling steps of 8–10 Å are optimal so the transmembrane
 145 region needs one or two intermediary cofactors to serve as stepping
 146 stones across the membrane [48,50]. The reduction chemistry of
 147 these bridging redox cofactors is usually not coupled to proton trans-
 148 fer. In principle, conformational changes are not required to carry out
 149 these long-range electron transfers and many of these reactions will
 150 occur in frozen samples [51–53]. While these proteins do not have
 151 transmembrane proton pathways, they will have short pathways pro-
 152 viding access to transfer protons from the surface to the terminal
 153 electron donors and acceptors [20,54,55]. 153

154 1.2. The proton pump

The other basic protein design that generates a transmembrane
 155 gradient is the proton pump. Here protons are moved through the 156

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