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Review

Mechanism divergence in microbial rhodopsins ☆

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ABSTRACT

A fundamental design principle of microbial rhodopsins is that they share the same basic light-induced conversion between two conformers. Alternate access of the Schiff base to the outside and to the cytoplasm in the outwardly open "E" conformer and cytoplasmically open "C" conformer, respectively, combined with appropriate timing of p*K*a changes controlling Schiff base proton release and uptake make the proton path through the pumps vectorial. Phototaxis receptors in prokaryotes, sensory rhodopsins I and II, have evolved new chemical processes not found in their proton pump ancestors, to alter the consequences of the conformational change or modify the change itself. Like proton pumps, sensory rhodopsin II undergoes a photoinduced E → C transition, with the C conformer a transient intermediate in the photocycle. In contrast, one light-sensor (sensory rhodopsin I bound to its transducer HtrI) exists in the dark as the C conformer and undergoes a light-induced C → E transition, with the E conformer a transient photocycle intermediate. Current results indicate that algal phototaxis receptors channelrhodopsins undergo redirected Schiff base proton transfers and a modified E → C transition which, contrary to the proton pumps and other sensory rhodopsins, is not accompanied by the closure of the external half-channel. The article will review our current understanding of how the shared basic structure and chemistry of microbial rhodopsins have been modified during evolution to create diverse molecular functions: light-driven ion transport and photosensory signaling by protein–protein interaction and light-gated ion channel activity.

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1. Introduction

The large family of microbial rhodopsins provides a vivid example of evolution modifying a single protein scaffold to produce diverse new functions (for reviews, see Refs. [1–6]). Family members share a membrane-embedded seven-helix architecture forming an internal pocket for the chromophore retinal bound in a protonated Schiff base linkage to a lysyl residue in the middle of the seventh helix. Similar photochemical reactions energized by photoisomerization of retinal have been engineered by nature to drive distinctly different processes in different microbial rhodopsins: light-driven outward proton transport, inward chloride transport, and as reported very recently outward sodium ion transport [7], photosensory signaling by protein–protein interaction, and light-gated ion channel conduction.

As microbial rhodopsins with new functions have been discovered it has been natural to analyze their physical and chemical properties in terms of their similarities and differences to those of the light-driven proton pump bacteriorhodopsin (BR), the first found and best characterized member of the family (for review, see Refs. [2,8]). For the prokaryotic sensory rhodopsins, SRI and SRII, subunits of phototaxis signaling complexes, such comparative analysis has been particularly informative. Their use of steps in the proton transport mechanism for signal relay and their latent proton transport activity when separated from other signaling complex subunits provide compelling evidence for their evolution from a light-driven proton pump [3,9]. The generalization of this evolutionary progression, i.e. proton pumps as the earliest microbial rhodopsins, is consistent with phylogenetic analysis [10], and a possible scenario is that proton-pumping rhodopsins appeared first in evolution, underwent extensive lateral gene transfer, and in multiple cells independently evolved interactions with their signal transduction machinery to acquire sensory functions. This notion may be reinforced or negated as our knowledge of rhodopsin photosensor mechanisms increases. In either case it is instructive to consider to what extent microbial rhodopsins with newfound functions share mechanistic processes with light-driven proton transporters, for which these processes have been worked out in considerable, in several aspects atomic, detail.

In this minireview we address aspects of the light-driven pumping mechanism of BR that are shared and new aspects that have emerged

Abbreviations: AFM, atomic force microscopy; BR, bacteriorhodopsin; BPR, blue-absorbing proteorhodopsin; EPR, electron paramagnetic resonance; FTIR, Fourier-transform infrared; HR, halorhodopsin; HtrI, haloarchaeal transducer for SRI; HtrII, haloarchaeal transducer for SRII; RNA*i*, RNA interference; SRI, sensory rhodopsin I; SRII, sensory rhodopsin II; *Ca*ChR1, *Chlamydomonas augustae* channelrhodopsin 1; *Cr*ChR2, *Chlamydomonas reinhardtii* channelrhodopsin 2; *Ds*ChR1, *Dunaliella salina* channelrhodopsin 1; *Mv*ChR1, *Mesostigma viride* channelrhodopsin 1; *Ps*ChR, *Platymonas subcordiformis* channelrhodopsin; *Vc*ChR1, *Volvox carteri* channelrhodopsin 1

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in the two types of light-sensors whose physiological functions have been identified: the prokaryotic phototaxis receptors sensory rhodopsins I and II (SRI and SRII) and the algal phototaxis receptors channelrhodopsins (ChRs). We consider the roles of key processes in the proton pump mechanism in these rhodopsins whose functions are other than proton pumping. The emerging information regarding conserved features and new molecular processes in these members of the microbial rhodopsin family provides intriguing insights into how the proteins work as well as how they have evolved.

2. The ion pumping mechanism

2.1. Proton transfers and the Schiff base connectivity switch

In proton pumps, as first shown for BR from *Halobacterium salinarum*, the dark conformation exhibits an outwardly-connected protonated Schiff base poised for proton release to an exterior half-channel. This conformation is denoted in this minireview as the E conformer (Fig. 1). Light induces release of the proton to a counterion of the Schiff base, an anionic aspartyl residue (Asp85) in the exterior channel, forming the blue-shifted photocycle intermediate M, named after the mammalian visual pigment's deprotonated Schiff base photoproduct "metarhodopsin." In *Hs*BR M formation is accompanied by an almost simultaneous release of the proton to the outside medium from a proton release group. The electrogenic Schiff base proton transfer to Asp85 is the first step in the pumping process. The protein then undergoes a conformational change during the lifetime of M (the M1 to M2 conversion) in which (i) a half-channel forms from the retinal chromophore's deprotonated Schiff base to the cytoplasm and (ii) the Schiff base switches its connection (i.e. accessibility) to the cytoplasmic side (the C conformer). A second aspartyl residue (Asp96) in the cytoplasmic channel serves as a proton donor to the Schiff base. The alternate access of the Schiff base in the E and C conformers combined with appropriate timing of p*K*a changes controlling Schiff base proton release and uptake make the proton path through the protein vectorial [2,8].

The inward pumping of chloride ions by halorhodopsin (HR) can be explained by the same Schiff base connectivity switch mechanism that results in outward proton pumping by BR [11]. HR contains a threonine residue at the corresponding position of Asp85 in BR. As in the D85T mutant of BR, the absence of an anionic proton acceptor at the 85 position inhibits deprotonation from the Schiff base. HR contains a chloride ion bound as a counterion to the protonated Schiff base near the threonine in the external half channel, and when the protonated Schiff base undergoes the photoinduced switch in connectivity from the external to the cytoplasmic half channel the chloride ion follows the positive charge, thereby being actively transported inward across the membrane. A striking confirmation that the same alternating access switch that accomplishes outward proton pumping in BR is capable of driving inward chloride pumping is that BR with the single mutation D85T exhibits light-driven inward chloride transport activity [11].

Schiff base connectivity can be defined empirically by electrophysiological measurement of the direction of current produced by the light-induced release of the proton from the Schiff base and its reprotonation. In BR and other light-driven proton pumps both currents are outwardly directed indicating that reprotonation occurs from the opposite side of the membrane than the side to which the proton was released (i.e. a Schiff base connectivity switch occurred). Equivalently, in HR the same direction of currents as in BR (positive outward movement) is observed due to the inward displacements of chloride ion. Such measurements performed in other rhodopsins have been informative as described below in elucidating the significance of connectivity switching in sensory signaling as well as transport mechanisms.

2.2. Helix movement in the conformational change

The largest structural change in the E → C conversion is a laterally outward movement of the cytoplasmic half of helix F [12,13]. Cryoelectron crystallography of natural functional 2-D crystals of BR

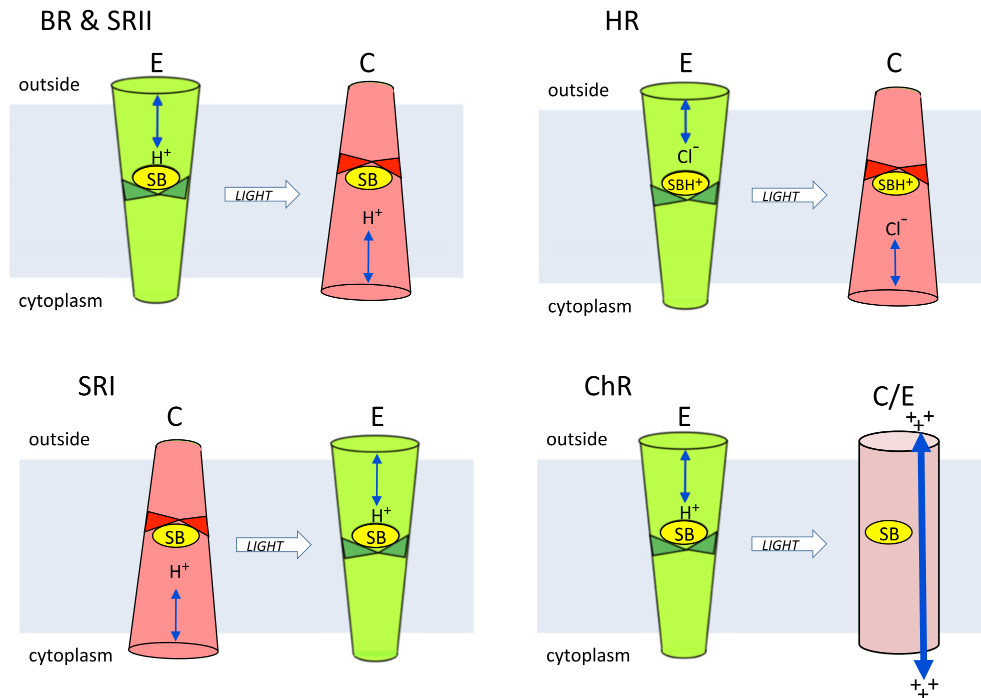

Fig. 1. Microbial rhodopsin conformers. The figure depicts light-induced conformer transitions in the indicated microbial rhodopsins in their native functional state. BR, bacteriorhodopsin; HR, halorhodopsin; SRI, sensory rhodopsin I; SRII, sensory rhodopsin II; ChR, channelrhodopsin. E (green), conformer with externally-connected Schiff base and exterior half-channel open; C (red), conformer with cytoplasmically-connected Schiff base and cytoplasmic half-channel open; C/E (purple), conformer with an open channel from the extracellular to cytoplasmic surfaces of the protein.

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