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# Protons at bio-interfaces

## Editorial

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Proton transporters transfer protons across cell membranes to generate and maintain proton gradients essential for bioenergetics. Among the best-studied proton transporters are the proton-transporting microbial rhodopsins –seven-helical membrane proteins that couple photo-isomerization of the covalently bound retinal chromophore with ion-transporting reaction cycles. The comprehensive *review article by Brown* [1] summarizes experimental data on proton transport by microbial rhodopsins with focus on more recently discovered rhodopsin variants. The discussion of the consensus picture of the reaction mechanism of bacteriorhodopsin, whose three-dimensional structure was solved with cryo-Electron Microscopy (cry-EM) back in 1975 [2], provides the foundation to present general models of outward and inward light-driven proton transport by microbial rhodopsins, passive transport (proton leakage), mechanisms for vectoriality of proton pumping, and challenges in identifying proton donor and acceptor groups in new rhodopsins such as Antarctic rhodopsin, AntR.

Synthetic peptides and other molecules that interact with membranes in a pH-dependent manner are of direct interest for bio-medical applications, particularly to modulate lipid bilayer properties and to deliver drugs to cells and cell compartments with acidic pH. Biochemical and biophysical characterization of the lipid interactions of such molecules is essential, as it may help guide the design and synthesis of compounds with activities suitable for specific bio-medical applications. Several contributions to this topical collection discuss synthetic membrane-binding peptides, pores and transporters with pH-dependent functionalities.

The pH low insertion peptide (pHLIPs) was designed back in 1997 using as a template helix C of bacteriorhodopsin [3]. The original 36-residues peptide contained the two Asp groups of bacteriorhodopsin helix C, and had a Glu-to-Gln substitution at its N-terminus [3]. The Asp groups make the peptide pH sensitive, such that at neutral pH the peptide is unstructured and located at the membrane periphery, whereas at pH <6 one of the Asp group protonates and the peptide is membrane-inserted as an  $\alpha$ -helix [3]. *Ataka and colleagues* [4] apply Surface Enhanced Infrared Absorption (SEIRA) spectroscopy [5] to characterize the insertion pathway of a pHLIP peptide into a lipid bilayer casted on a gold surface; this pathway is found to include a new intermediate state that is populated at pH values between 5.3 and 7. Moreover, the spectroscopy data identify two carboxylic groups implicated in the pH-dependent conformational dynamics of the peptide [4].

*Howe and colleagues* present experimental data on synthetic pH-switchable anion transporters based on phenylthiosemicarbazones, PTSC [6]. At pH 7.2 the PTSC molecule is neutral and has a *trans* conformation in which an intra-molecular H-bond makes the chloride-binding site inaccessible. At low pH, the PTSC binds a proton at its imine nitrogen, isomerizes to a *cis* conformation, and binds anions [6].

The paper reports on the synthesis and characterization, using X-ray diffraction and membrane transport assays, of nine PTSC-based transporters, and demonstrates that transporters have high selectivity for chloride over nitrate –such that nitrate transport is rate-limiting and inhibited at neutral pH [6].

*Salnikov and colleagues* [7] use solid-state Nuclear Magnetic Resonance (NMR) spectroscopy to characterize the pH-dependent topology change of the LAH4 peptide in lipid membranes distinguished by the headgroup and alkyl chains of the lipid molecules. LAH4 peptides, designed based cationic microbial peptides, are of interest as antimicrobial peptides and to deliver cargo to cells. The peptides are amphipatic, with a hydrophobic core, one Lys group at each terminus, and four His groups located on the same side of the helix. The four His groups make the membrane interactions of LAH4 pH sensitive, such that the peptides prefer the membrane interface at pH <5.5, and insert in POPC at pH > 7. Experimental data presented by Salnikov and colleagues demonstrate that the transition of LH4 from the in-plane (interfacial) to the transmembrane orientation depend on the lipid saturation.

#### **CRedit authorship contribution statement**

A-NB wrote the editorial with input from MB.

#### **Declaration of competing interest**

The Authors have no competing interests.

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