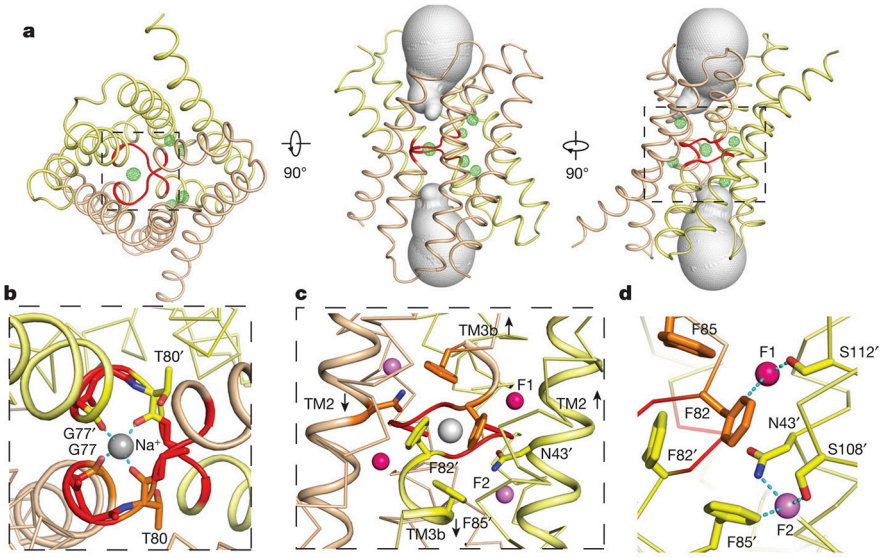
Generally Physiological

Of quirky channels and a fond farewell

This final installment of *Generally Physiological* concerns F^--selective channels, a surprising role for a tryptophan in determining channel identity, and a farewell note from the Executive Editor of *The Journal of General Physiology*.

A Fluc of nature?

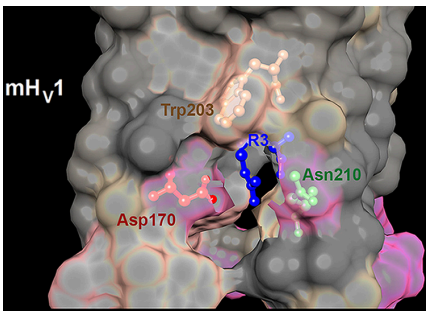
The recently identified Fluc channels mediate the export of fluoride (F^-) from microorganisms, helping them resist the toxic effects of this ubiquitous environmental anion. Fluc channels have various unusual features, including extreme selectivity for F^- and a dual-topology dimeric architecture unprecedented among ion channels (but reminiscent of that of some transporters), in which the two monomeric subunits assemble in an antiparallel orientation. Curious about the mechanistic basis of Fluc channel F^- selectivity, Stockbridge et al. (2015) solved the crystal structures of two different bacterial Fluc channels. These structures, obtained in complexes with monobody inhibitors, revealed that the two antiparallel subunits each consisted of four transmembrane helices (termed TM), with the third helix broken into two halves (TM3a and TM3b) by a six-residue nonhelical segment. The Fluc channel was shaped like an hourglass, with two wide vestibules separated by a protein plug and a centrally coordinated cation (likely Na^+) that the authors propose acts as a structural element to stabilize the dimer interface. Rather than mediating F^- permeation through a single central pore between the two vestibules, the channel was double-barreled, with two narrow F^- permeation pathways. Each of these narrow pores comprised amino acid side chains from TM2, TM3b, and TM4 of one subunit plus a TM3-break phenylalanine from the other. Mutational analysis confirmed the importance of a conserved TM2 asparagine (as well as that of conserved phenylalanines) in F^- permeation, leading the authors to the intriguing conjecture that F^- movement through the pore is facilitated by a rotameric switch of the asparagine side chain in a "channsporter" mechanism.



(a) *Bordetella pertussis* Fluc channel (Bpe) homodimer viewed from solution (left) and membrane (middle and right); aqueous volumes of vestibules are indicated in gray, and electron densities corresponding to Na^+ and F^- ions are indicated in green. (b) Na^+ coordination sphere. (c) Na^+ and F^- ions and crucial conserved asparagine and phenylalanines. (d) F^- coordination shells; a concerted movement of the N43 side chain is postulated to facilitate F^- movement through the channel (Reprinted by permission from Macmillan Publishers, Ltd. R.B. Stockbridge et al. *Nature*. http://dx.doi.org/10.1038/nature14981, copyright 2015.)

A crucial tryptophan

All known voltage-gated proton channels (H_V1) bear a conserved tryptophan as part of the H_V1 signature sequence motif (RxWRxxR) in the middle of the S4 transmembrane segment. Noting that tryptophan is the rarest amino acid in proteins, and often prefers the lipid–water interface, in this issue Cherny et al. used mutational analysis to investigate the contribution of this perfectly conserved S4 residue to H_V1 function. Surprisingly, they discovered that the conserved S4 tryptophan was crucial to four defining properties of H_V1 channels: the dependence of their gating on ΔpH (the transmembrane pH gradient [pH_o–pH_i]), their slow time constant of activation, the strong temperature dependence of their gating kinetics, and their selectivity for protons. Replacing human H_V1 Trp^{207} led to saturation of ΔpH-dependent gating at lower pH_o, but not lower pH_i (suggesting that there are distinct sensors for internal and external pH), facilitated channel opening, decreased the temperature dependence of gating, and compromised proton selectivity at high pH_o. Remarkably, the



"Pocket" enclosing electrostatic interactions involving R3 in an mH$_V$1 chimera in the closed state. Colors indicate local hydrophobicity: gray, hydrophobic; tan, intermediate; pink, hydrophilic. mH$_V$1 Trp203 corresponds to human Trp^{207}, and "R3" represents the third arginine in the H$_V$1 signature sequence. The authors propose that cation–π interaction between the conserved Trp and R3 may latch the channel closed. See Cherny et al. (2015).

effects of replacing Trp^{207} with alanine (hydrophobic), serine (hydrophilic), or phenylalanine (aromatic) were functionally indistinguishable, leading the authors to propose that tryptophan's heterocyclic aromatic side chain plays a crucial role in anchoring the S4 segment in the membrane to stabilize the closed state.

The general bids adieu

I am stepping down as Executive Editor of *The Journal of General Physiology*, and this is my final installment of *Generally Physiological*. It is the physiology community that makes *JGP* so special, and it has been my interactions with that community that have made the position of Executive Editor so rewarding. It has been a pleasure and a privilege to become acquainted with so many of you during my time at *JGP*—both through email and in vivo—and I hope that our paths continue to cross in the future. For now, my best wishes and a fond farewell to all *Generally Physiological* readers, and to all participants in the *JGP* community.

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REFERENCES

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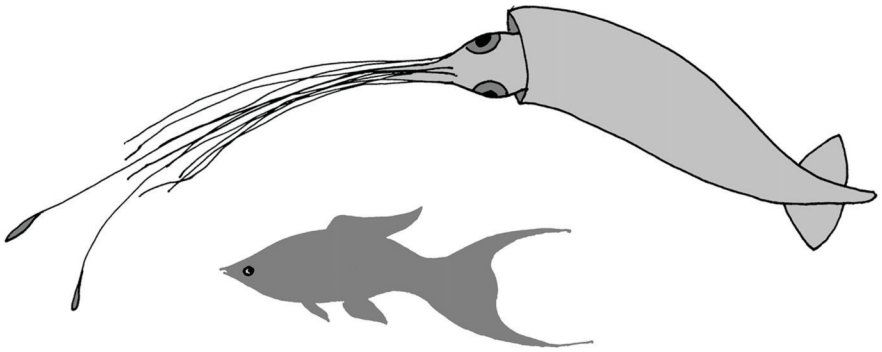

So long, and thanks for all the squid! (Illustration by Elizabeth M. Adler.)