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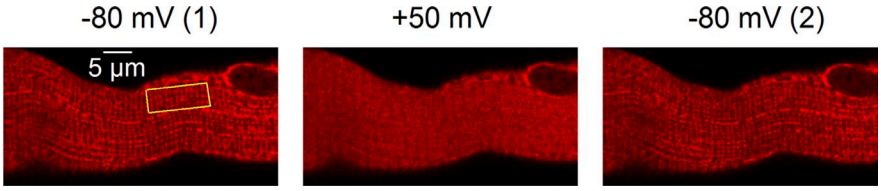
## Of muscle modulation and the CFTR gate

This month's installment of *Generally Physiological* considers regulation of excitation–contraction coupling by $PIP_2$ and the investigation of an appealing hypothesis for how a transporter might evolve into a channel.

### Modulating EC coupling

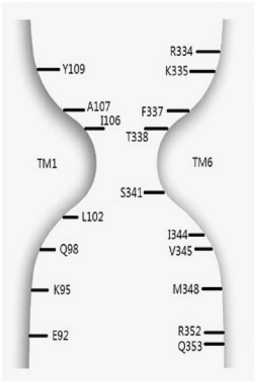
In this issue, Berthier et al. identified an intriguing role for phosphatidylinositol 4, 5-bisphosphate ($PIP_2$), a low abundance membrane phospholipid that modulates the activity of various membrane proteins, in regulating excitation–contraction coupling in skeletal muscle. Depolarization of the motor endplate initiates an action potential that propagates through the invaginations of the muscle plasma membrane that form the transverse tubule system. This triggers a conformational change in the dihydropyridine receptor, which acts as a voltage sensor to mechanically activate ryanodine receptors in the SR membrane, enabling $Ca^{2+}$ release from the SR to increase cytosolic $Ca^{2+}$ and thereby stimulate muscle contraction. Berthier et al. (2015) expressed voltage-sensing phosphoinositide phosphatases in mouse skeletal muscle and determined that their activation led to a reversible decrease in transverse tubule $PIP_2$ as well as a reversible decrease in $Ca^{2+}$ release from the SR. The authors thus conclude that $PIP_2$ depletion leads to a decrease in $Ca^{2+}$ release during excitation–contraction coupling, and make a compelling case that this depends on an interaction between $PIP_2$ and a protein partner of the excitation–contraction coupling machinery.




**Confocal images of a region of a muscle fiber expressing a voltage-sensing phosphoinositide phosphatase and a fluorescent probe for $PIP_2$, showing the loss of a pattern of fluorescence indicative of transverse tubule localization of $PIP_2$ with depolarization. See Berthier et al., 2015.**

### Identifying the CFTR gate

Although the CFTR is a member of the ATP-binding cassette (ABC) transporter superfamily, it acts as an ATP-gated chloride channel, leading to the appealing hypothesis that it evolved into a channel from a primordial ABC transporter through the loss of an intracellular gate. Gao and Hwang (2015) tested this hypothesis, using the channel-permeant probe $[Au(CN)_2]^-$ (dicyanoaurate, a thiol-reactive molecule with an estimated cross-sectional diameter [3.4 Å] slightly smaller than that of chloride) to target cysteines substituted for pore-lining residues and thereby define the location of the CFTR gate. The CFTR permeation pathway is thought to be shaped rather like an hourglass, with a narrow region that may act as the selectivity filter connecting two large vestibules. Gao and Hwang (2015) determined that cysteine residues on the cytoplasmic side of the constriction were accessible to intracellularly applied $[Au(CN)_2]^-$ regardless of channel state, whereas residues on the external side were only accessible in the open channel. In marked contrast, accessibility of the "external residues" to extracellularly applied $[Au(CN)_2]^-$ was actually enhanced in the closed channel.




**The CFTR conductance pathway consists of a narrow region flanked by large "internal" and "external" vestibules. Pore-lining residues from transmembrane segments 1 and 6 are indicated (Reprinted by permission from Localizing a gate in CFTR. Gao, X., and T.-C. Hwang, *Proc. Natl. Acad. Sci. USA.* 2015. http://dx.doi.org/10.1073/pnas.1420676112).**

The authors thus conclude that, in contrast to ABC transporters, the CFTR gate resides in the constricted region, rather than at the external end of the pore as would be predicted if it had been converted to a channel from a transporter simply through the loss of an internal gate.

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### REFERENCES

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