

## RESEARCH NEWS

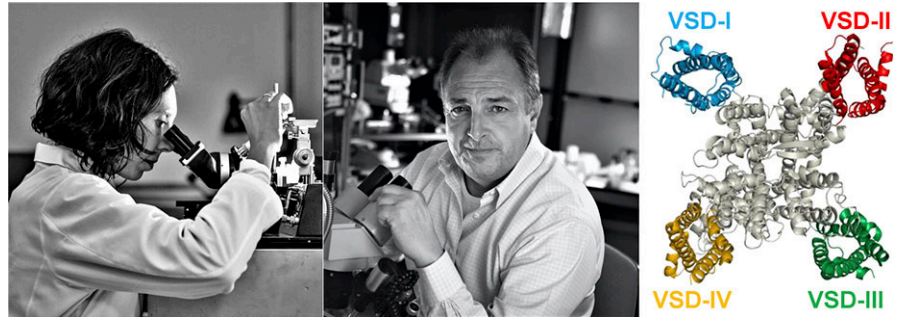
Distinct roles for  $\text{Ca}_v1.1$ 's voltage-sensing domainsBen Short **Study reveals how a slowly activating calcium channel is able to control rapid excitation–contraction coupling in skeletal muscle.**

Skeletal muscle contraction is initiated by action potentials that depolarize the muscle fiber and trigger the rapid release of  $\text{Ca}^{2+}$  from the SR via RYR1 channels. This process of excitation–contraction coupling depends on voltage-gated  $\text{Ca}_v1.1$  channels in the plasma membrane, or sarcolemma, of muscle fibers. But  $\text{Ca}_v1.1$  channels are only slowly activated by changes in the sarcolemma membrane potential, and it is therefore unclear how they are able to trigger the much faster activation of RYR1 channels. In this issue of *JGP*, Savalli et al. reveal that this paradox can be explained by the fact that each of  $\text{Ca}_v1.1$ 's four voltage-sensing domains (VSDs) have distinct biophysical properties (1).

RYR1 channels have no voltage-sensing machinery of their own and therefore rely on a physical connection to  $\text{Ca}_v1.1$  channels to release  $\text{Ca}^{2+}$  and initiate muscle contraction in response to muscle fiber depolarization. But RYR1 channels open  $\sim 25$  times faster than  $\text{Ca}_v1.1$  channels. “So, how can these slowly activating  $\text{Ca}_v1.1$  channels trigger the rapid release of  $\text{Ca}^{2+}$  from the SR?” asks Riccardo Olcese, a professor at the David Geffen School of Medicine, UCLA.

Olcese and colleagues, including Assistant Project Scientist Nicoletta Savalli, suspected that the answer might lie in the fact that, like many other voltage-gated ion channels,  $\text{Ca}_v1.1$  has four VSDs that alter their conformation in response to voltage changes. These domains are similar, but not identical, to each other, potentially enabling them to have distinct biophysical properties and perform distinct functions. Indeed, Olcese and colleagues previously demonstrated that, in the closely related channel  $\text{Ca}_v1.2$ , only VSDs II and III are involved in pore opening (2, 3).

Savalli et al. used voltage-clamp fluorometry to compare the properties of  $\text{Ca}_v1.1$ 's



Nicoletta Savalli (left), Riccardo Olcese (center), and colleagues reveal the distinct physical properties of the  $\text{Ca}_v1.1$  channel's four voltage-sensing domains (VSD I–IV, right). VSD-I shows slow activation kinetics and is the main contributor to the opening of  $\text{Ca}_v1.1$ . The other VSDs activate much faster and may therefore be coupled to RYR1 to mediate the rapid release of  $\text{Ca}^{2+}$  from the SR during skeletal muscle contraction.

VSDs, expressing the channel in *Xenopus* oocytes and labeling each of its VSDs in turn with an environmentally sensitive fluorophore to report voltage-dependent changes in their conformation (1). “We found that the four VSDs were very heterogeneous in both their kinetics and voltage dependencies,” says Olcese. “VSD-I had very slow kinetics, compatible with the slow activation of the  $\text{Ca}_v1.1$  pore. The other three VSDs had much faster kinetics and could, therefore, be good candidates to be the voltage sensors for RYR1 activation.”

Olcese and colleagues confirmed the importance of VSD-I for  $\text{Ca}_v1.1$  activation by analyzing a naturally occurring, charge-neutralizing mutation in this domain, R174W, that is linked to malignant hyperthermia (4). The team found that this mutation reduced the voltage-sensitivity of VSD-I and abolished the ability of  $\text{Ca}_v1.1$  to conduct  $\text{Ca}^{2+}$  at physiological membrane potentials, but had no effect on the behavior of the other three VSDs.

Finally, Savalli et al. applied their data on both the wild-type and mutant VSDs to an allosteric model of  $\text{Ca}_v$  activation (2, 3), which predicted that VSD-I contributes most of the energy required to stabilize the open state of  $\text{Ca}_v1.1$ , while the other VSDs contribute little to nothing.

Thus,  $\text{Ca}_v1.1$  activation is mainly driven by a single VSD—a mechanism that hasn't been seen in any other voltage-gated ion channel—leaving the other VSDs free to perform other functions, such as the rapid activation of RYR1. Olcese and colleagues now want to pinpoint exactly which VSD(s) are coupled to RYR1 and determine how they trigger rapid  $\text{Ca}^{2+}$  release from the SR.

## References

1. Savalli, N., et al. 2021. *J. Gen. Physiol.* <https://doi.org/10.1085/jgp.202112915>
2. Pantazis, A., et al. 2014. *Proc. Natl. Acad. Sci. USA* <https://doi.org/10.1073/pnas.1411127112>
3. Savalli, N., et al. 2016. *J. Gen. Physiol.* <https://doi.org/10.1085/jgp.201611586>
4. Eltit, J.M., et al. 2012. *Proc. Natl. Acad. Sci. USA* <https://doi.org/10.1073/pnas.1119207109>

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