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RESEARCH NEWS

Predicting voltage sensing

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New method predicts the molecular basis of membrane proteins' voltage sensitivity.

Because the concentration of many ions is different inside of the cell compared with outside, cells experience an electrochemical potential difference across the cell membrane. This is harnessed by voltage-sensitive membrane proteins to govern complex cellular behaviors including action potential generation, muscle contraction, and even cell division. In this issue of the *Journal of General Physiology*, Kasimova et al. present a new computational method capable of identifying the features that drive voltage sensitivity in membrane proteins (1).

First author Marina Kasimova (left), senior author Lucie Delemotte (center), and colleague Erik Lindahl (not shown) present a new method for predicting structural elements involved in voltage sensing by membrane proteins. Red and blue colors highlight amino acid residues predicted to be involved in voltage sensing by Connexin 26. Photos courtesy of the authors.

Lucie Delemotte, assistant professor at KTH Royal Institute of Technology in Stockholm, Sweden, has been studying the basis of voltage sensitivity in voltage-gated ion channels for more than a decade. "But," she says, "we realized that voltage sensitivity is not restricted only to voltage-gated ion channels; it is also present in many other types of membrane proteins, such as G protein–coupled receptors, transporters, and others."

Marina Kasimova, a postdoc in Delemotte's laboratory, wondered whether it would be possible to predict how proteins sense and respond to membrane voltage. The researchers entertained two theories: first, that certain regions of a protein might be more sensitive to an external electric potential if they contain water-filled pockets or channels that focus the local electric field (2); second, that voltage sensitivity requires the presence of certain features that can sense and respond to an electric potential (3). For example, in voltage-gated potassium channels, membrane potential is sensed by charged amino acids, whereas in transporter proteins, it is thought to be sensed by transported ions (4). When a shifting electric potential pushes on these elements, it forces a conformational change in the protein, and the resulting movement of charged elements within the field generates a tiny but measurable current called a gating current, whose integral over time is called a gating charge (3, 5).

Starting from previously published high-resolution protein structures of voltage-sensitive and -insensitive proteins, Kasimova et al. conducted molecular dynamics simulations to examine how proteins sense and respond to electric potentials. The simulations showed that some voltage-sensitive proteins do not strongly reshape the local electric field, whereas some voltage-insensitive proteins do, suggesting this property by itself cannot predict voltage sensitivity. However, by estimating the fraction of a gating charge that is generated if a given element moves a small linear distance within the field, the researchers could pinpoint amino acids or bound ions that were likely to respond to an electric potential. For several proteins whose mechanism of voltage sensing was already known, the voltage-sensing elements identified by this approach were consistent with previous research.

Interestingly, the voltage-sensitive amino acids of voltage-gated ion channels clustered together in the same region of the protein within what had previously been identified as voltage-sensing domains. "But in most of the other proteins, we find that voltage-sensing elements are simply spread all over the protein. That was surprising and I think that may also be why it's been so difficult to pinpoint the molecular basis for voltage sensitivity in these proteins," says Delemotte. Although these voltage elements were widespread in many voltage-sensitive proteins, Kasimova et al. observed that they often occurred within regions that had some ability to reshape the local electric field. Voltage-insensitive proteins displayed no such overlap.

Having validated their approach, the authors next used it to predict voltage-sensitive elements for several proteins whose voltage-sensing mechanism is not yet known. If these predictions are experimentally verified, this technique could facilitate studies of voltage-sensitive proteins by identifying targets for site-directed mutagenesis.

"With our relatively cheap computational method, we can narrow down the number of residues that should be tested," says Delemotte.

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5. Stühmer, W., et al. 1991. *Pflugers Arch.* 418:423–429.

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