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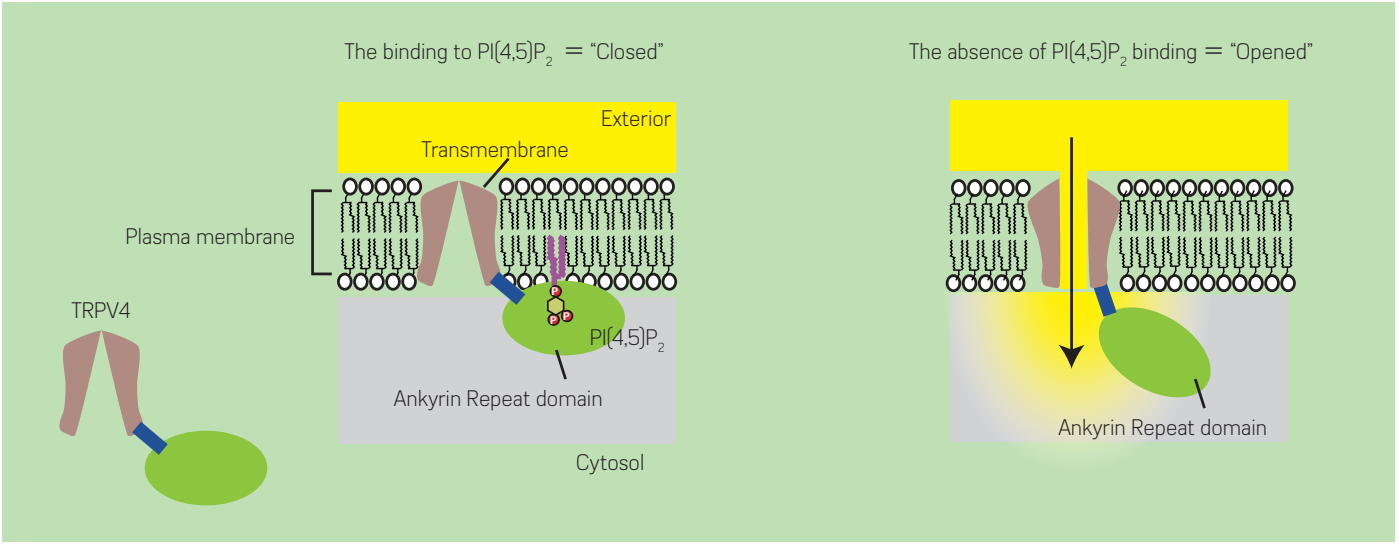

The protein structure of PIP2 in complex with TRPV4 ARD.

Cell biology

Ion channel mutations may cause disease

Mutations in the lipid-binding domain of one ion channel subfamily promotes function and cell death linked to a variety of inherited diseases

Transient receptor potential channels (TRPs) are a large group of ion channels found mostly in the plasma membranes of animal cells. One is TRPV4, a non-selective positive ion channel that allows the passage of several different cation species, such as sodium and calcium (Na+ and Ca2+). It has multiple regulatory sites and is activated by physical stimuli including heat, chemicals and shear stress.

Recent genetic studies on some families have linked mutations in TRPV4's ankyrin repeat domain (TRPV4 ARD) to inherited diseases, such as spinal muscular atrophy (SMA) and Charcot-Marie-Tooth disease. However, the molecular mechanisms underlying the pathogenesis of these diseases are unclear.

Shiro Suestsugu at NAIST and colleagues have now examined the binding affinity of TRPV4 ARD to various membrane lipids using functional assays[1]. They found that TRPV4 ARD binds most strongly to phosphatidylinositol-4,5-bisphosphate ($PI(4,5)P_2$), a membrane lipid known to regulate various intracellular signalling cascades and TRPV4 channel activity. Structural analyses revealed that TRPV4 ARD consists of six ankyrin repeats, which it uses to recognise $PI(4,5)P_2$.

"We decided to study TRPV4 because its mutations have implications for several hereditary diseases," says Suetsugu.

The researchers confirmed that disease-associated mutations cause protein unfolding and, they found, decrease the ability of TRPV4 ARD to bind $PI(4,5)P_2$. The lack of interactions between TRPV4 ARD and $PI(4,5)P_2$, in turn, increases TRPV4 channel activity, raises Ca^{2+} levels and promotes cell death due to increased cytotoxicity. The latter is probably an important factor contributing to the pathogenesis of SMA and Charcot-Marie-Tooth disease.

Suetsugu pointed out that the crystallization of TRPV4 ARD with $PI(4,5)P_2$ head group has been one of the greatest challenges in their study because the domain is relatively unstable.

In a sense, ARD is very much like the 'off-switch' for non-selective cation channels. It suppresses channel activity, prevents cations from permeating through the cell membrane and maintains the balance of Ca^{2+} level within the cell. Understandably, a broken off-switch could lead to all sorts of problems associated with malfunctioned cation channels.

Previous studies have identified ankyrin repeat domains (ARDs) in more than 400 human proteins with diverse binding specificities and affinities to proteins. The finding by Suetsugu and his team represents the first demonstration of the lipid-binding ability of ARD. Moreover, it may have important implications for the development of gene therapy for treating inherited diseases.

"We are very much interested in the functions of other ARDs," says Suetsugu. "Examining these widely expressed but poorly characterised ARDs will be the next step for our study."

Reference

1. Takahashi, N., Hamada-Nakahara, S., Itoh, Y., Takemura, K., Shimada, A. et al. TRPV4 channel activity is modulated by direct interaction of the ankyrin domain to $PI(4,5)P_2$. *Nature Communications* **5,** 4994 (2014).

More information about the group's research can be found at the Molecular Medicine and Cell Biology Laboratory webpage:
http://bsw3.naist.jp/suetsugu/?cate=278