Elucidating the Zn2+ permeation pathway through the transient receptor potential 6 (TRPC6) ion channel: A molecular dynamic simulation

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1. Project Purpose

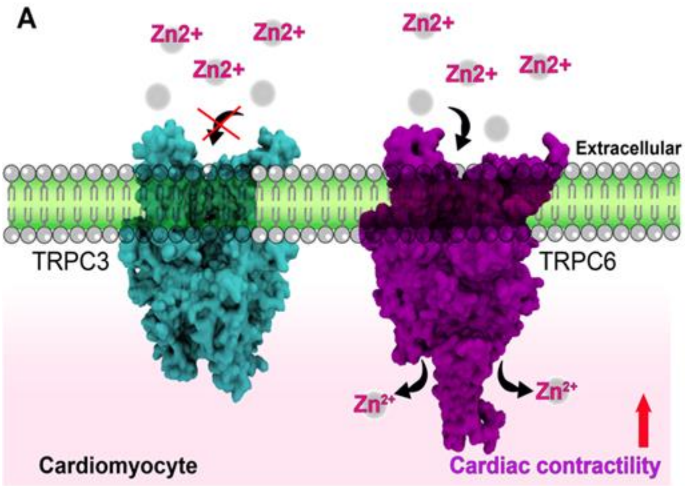

Figure 1 Cartoon representation of TRPC3 and TRPC6 channels illustrating Zn^{2+}-mediated modulation of ion entry.

We aim to elucidate the mechanism of Zn^{2+} permeation through the TRPC6 channel and to clarify the distinct cation selectivity of TRPC6 in comparison to TRPC3. This study will highlight the role of specific amino acid sequences, the pathway of Zn^{2+} entry through the TRPC6 channel, structural rearrangements associated with ion conduction, and the identification of favorable Zn^{2+} binding sites. Computational investigations provide key insights into TRPC6-mediated intracellular Zn^{2+} transport and provide strong support for experimental finding aimed at developing effective therapeutic strategies for patients with heart failure.

2. Results

We identified the NYN and KYD motifs as critical modulators of Zn^{2+} entry at the TRPC channel gate, each exhibiting distinct Zn^{2+} trapping behaviors. Zn^{2+} is weakly retained at the NYN motif, whereas the KYD motif displayed a higher Zn^{2+} density, indicating a stronger affinity for ion trapping. The structural and electrostatic features of these motifs are essential in defining the functional properties of TRPC channels. In particular, the spatial arrangement of negatively charged residues within the pore region—such as D696 and E672 in TRPC6, and D627 along with

E603/E604 in TRPC3—plays a significant role in regulating channel gating and ion selectivity. These findings support the hypothesis that the NYN motif in TRPC6 facilitates selective Zn^{2+} permeation, while the KYD motif may act as a regulatory barrier limiting Zn^{2+} influx.

3. Roles of the MCRP and its significance

Given the large size of the TRPC6 and TRPC3 crystal structures and their embedding within a POPC membrane, each simulation repeat—comprising over 800,000 atoms—demanded high computational capacity. The use of high-performance supercomputers, *Cygnus* and *Pegasus*, enabled efficient execution of these simulations and the generation of essential data for analysis. Accelerated computing capabilities were critical in minimizing processing time and advancing this research toward its objectives.

4. Future plan

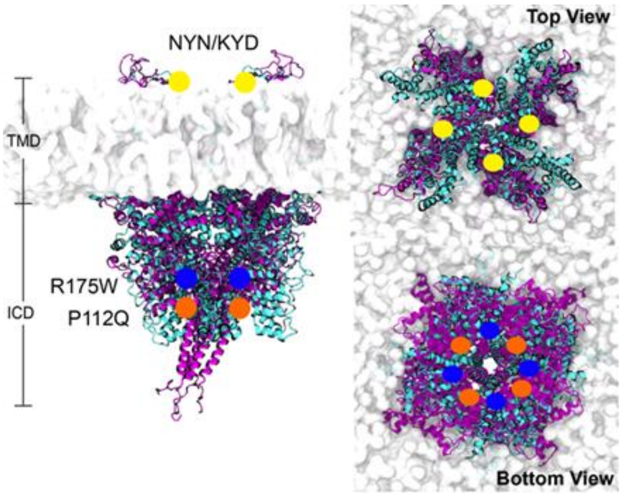

Figure 2 Overview of currently studied motifs (NYN and KYD) and proposed future targets for investigation (R175 and P112).

In addition to the NYN and KYD motifs located at the Zn^{2+} entry gate, other motifs such as R175 and P112—positioned near the Zn^{2+} exit pathway—will be investigated in future studies. Furthermore, additional motifs involved in the regulation of Na^{+} and Ca^{2+} permeation will also be explored. These regions are of particular interest as they may be susceptible to gain-of-function (GOF) mutations, which are associated with diseases such as familial focal segmental glomerulosclerosis (FSGS). Understanding how specific motifs contribute to TRPC6/TRPC3 over-activation is essential for linking the structural and functional consequences of GOF mutations with potential therapeutic strategies.

5. Publications and conference presentations

(1) Journal papers

(2) Presentations

Sittiwanichai S, Hengphasatporn K, Shigeta Y. "Zn2+ Ion Transportation Mechanisms of TRPC6 Channels: All-Atom Molecular Dynamics Simulation" IUPAB 2024, Kyoto, Japan, June 2024: Poster presentation.

(3) Others

Supercomputer	Use	Allocated resources*		
		Initial resources	Transferred resources**	Additional resources
Cygnus	Yes/No	10000 [6400]	-	-
Pegasus	Yes/No	10000 [8000]	-	-
Wisteria/BDEC-01	Yes/No			
	*in units of node-hour product ** If the budget transfer was performed, fill in here, such as "+2000" and "−1000".			