Epithelial Ion Channels in Health and Disease

Modelling and Molecular Dynamics Simulations of Typical and Atypical Ion Channels

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In Short

- Structure and Stability of non-canonical ENaC sodium channels
- Enhanced sampling techniques to compute the conformational space
- Simulating electrophysiology of the membrane-bound ion channels

Epithelial barrier and membrane transport in organisms is critically dependent on the function of ion channels and transporters. Diseases associated with an impaired substance transport include nephrological, immunological, metabolic, gastrointestinal diseases and various forms of cancer. Hence, understanding and modulating substance transport is crucial for developing novel therapeutic approaches. Mechanisms of cellular transport processes involve wide resolution scales from atomistic and molecular scales to single cells and epithelial barriers.

at the same time allow for a specific exchange of electrolytes between cellular compartments. Particularly electrolyte homeostasis is controlled by epithelial ion transport. The epithelial sodium channel ENaC (encoded by the *SCNN1* genes) plays a key role in epithelial ion transport in vertebrates. ENaCs are localized in the apical cell membrane of the aldosterone-sensitive distal nephron and colon, and are sodium-selective ion channels. They mediate the rate-limiting step of transepithelial sodium ion absorption. Dysfunction or dysregulation of ENaCs are associated with severe human diseases, including Liddle syndrome, nephrotic syndrome, and cystic fibrosis.

In contrast to related members of the degenerin/ENaC protein family, such as acid sensing ion channels (ASICs), ENaCs are consecutive-active ion channels. Thus, they do not require any stimulus or ligand to open. Structurally, canonical ENaCs are trimers, build by three different subunits α, β, and γ. However, in tetrapods a fourth δ subunit exists, which can form both homomeric, and heteromeric assemblies with the other types of subunits. In addition, experimental data indicates that mixed assemblies of ENaC and ASIC1 subunits

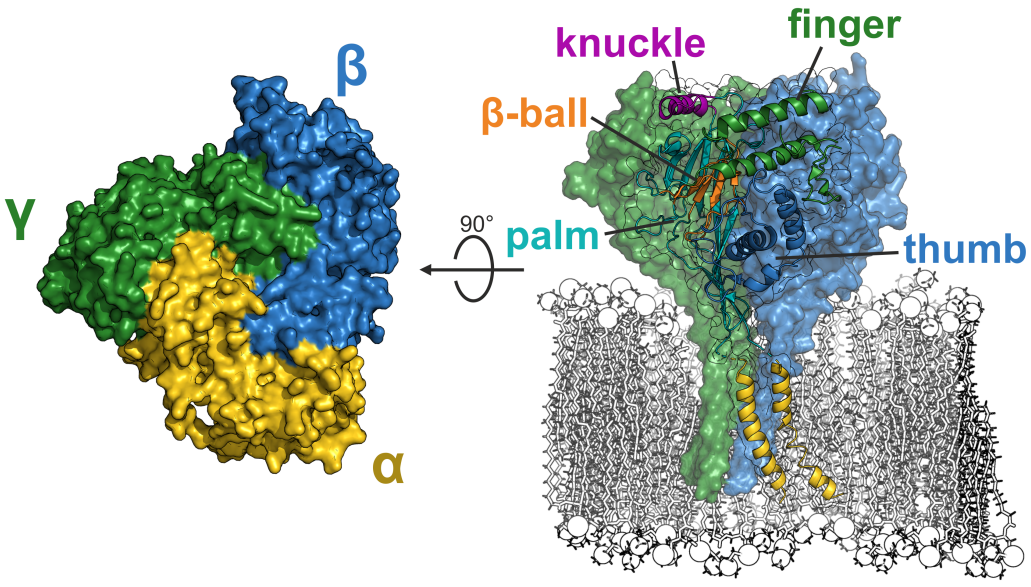

***Figure 1:** Structure of the heterotrimeric human $\alpha\beta\gamma$-ENaC. The different domains of one subunit are indicated by individual coloring.*

Epithelial barriers provide compartmentalization, physically shielding the inner milieu from the outer environment, as e.g. in the gastrointestinal tract, and

exist and form active ion channels. The physiological and pathophysiological roles of these non-canonical ion channel assemblies remain mostly elusive. However, experimental data suggest that important transport processes in health and disease are linked to these atypical channel assemblies.

The recently solved cryo-electron microscopy structure of the canonical, human $\alpha\beta\gamma$-ENaC revealed that, similar to related ASICs, the overall structure of each ENaC subunit resembles a hand, which holds a ball, formed by β-sheets. The domains of the extracellular structure are therefore called thumb, finger, knuckle, palm, wrist, and β-ball. There is a gap in the mechanistic und structural understanding of non-canonical ENaC sodium channels. We aim to use classical molecular dynamics simulations in combination with enhanced sampling simulations to model and establish structure-activity relationships of different atypical subunit assemblies. Enhanced sampling techniques allow to overcome limitations in the accessible time scales and conformational space of classical molecular dynamics simulations. Thereby, we plan to comprehensively compute the energy landscapes of the atypical ion channels, and investigate differences in the underlying structural dynamics. Systematic and targeted changes in the simulation conditions, such as alterations in the ion concentrations at the extracellular and intracellular side of the double-layered lipid membrane, or in the applied voltage will allow to analyze the function of the different ion channels. Changes in the open-to-closed transition, inactivation (gating), or ion transport across the membrane through the ion channels can directly be compared to electrophyiological measurements by our collaboration partners.

WWW

https://www.h-brs.de/de/anna/prof-dr-matthias-preller

More Information

[1] J. Lin, S.M. Gettings, K. Talbi, R. Schreiber, M.J. Taggart, M. Preller, K. Kunzelmann, M. Althaus, M.A. Gray *Pflugers Arch.* **475**, 167-179 (2023). doi:10.1007/s000424-022-02758-9

[2] R.Y. Lawong, F. May, E.C. Etang, P. Vorrat, J. George, J. Weder, D. Kockler, M. Preller, M. Althaus *Membranes* **13**, 529 (2023) doi: 10.3390/membranes13050529

Funding

DFG FIP 26/1 Forschungsimpuls “CytoTransport – Mechanisms and Modulation of Cellular Transport Processes”

DFG Subject Area

201-04