Structure, function and pharmacology of TRP channel TRPV3

Transient receptor potential (TRP) family of ion channels is comprised of 28 members, which based on sequence homology are segregated into 6 subfamilies. Previous studies carried out with the members of TRP channel family have greatly transformed our understanding of sensory modalities of our body, including temperature, pain, and touch. Our research is focused on building up a comprehensive understanding of structure and function of TRP channels family members in physiology and pathophysiology.

Currently we are focusing on the TRPV3 member of TRPV (vanilloid) subfamily of TRP channels, which is predominantly expressed in skin keratinocytes and is implicated in cutaneous sensation including thermo-sensation, nociception and itch, in addition to maintenance of the skin barrier, wound healing, and hair growth. Malfunctioning of TRPV3 is associated with a number of skin diseases, including a genodermatosis known as Olmsted syndrome, atopic dermatitis, psoriasis and rosacea. Furthermore, overexpression of TRPV3 is implicated in the development and progression of colorectal and lung cancer. Therefore, understanding the structure and function of TRPV3 would greatly accelerate the development of novel drugs to treat TRPV3-associated diseases.

TRPV3 is activated at innocuous temperatures (~33°C and higher) as well as by natural compounds such as camphor, carvacrol, eugenol and thymol, as well as by the small synthetic compound 2-aminoethoxydiphenyl borate (2-APB), which has recently been shown to suppress tumor growth and invasiveness. In our efforts towards TRPV3 structure determination, we screened a number of TRPV3 orthologues and discovered mouse TRPV3 as a promising target for our structural studies. Recently, we used cryo-EM to determine the first structures of mouse TRPV3 in the closed and agonist 2-APB bound open states (Singh et al, NSMB 2018). Comparing the structures of TRPV3 in the closed and open states, we deduced the dramatic conformational changes associated with TRPV3 gating. More specifically, our structures explain how 2-APB, a small molecule with anti-cancer properties, binds to and interacts with TRPV3.

Next we want to better understand pharmacology of this channel in order to design small molecules with enhanced efficacy and affinity to inhibit TRPV3. Currently, our structural efforts are focused on understanding of how the small, naturally occurring molecules, including camphor, carvacrol, eugenol and thymol, bind to and modulate gating of TRPV3 (Figures 1-3). Our studies will not only explain the molecular mechanism of action of natural compounds on TRP channels but provide a spring board to design novel antagonists of TRPV3 with higher efficacy and affinity that might eventually become therapeutically useful drugs.

Reference:

Singh A. K., McGoldrick L. L. and *Sobolevsky A. I.* (2018) Structure and Gating Mechanism of the Transient Receptor Potential Channel TRPV3. ***Nature Structural and Molecular Biology*** 25: 805-813 (cover image).

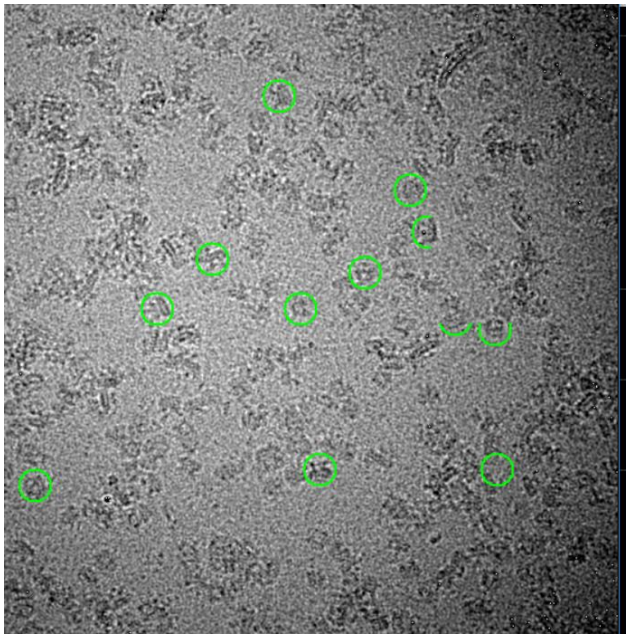

Figure 1: Exemplary cryo-EM micrograph of TRPV3 in presence of camphor.

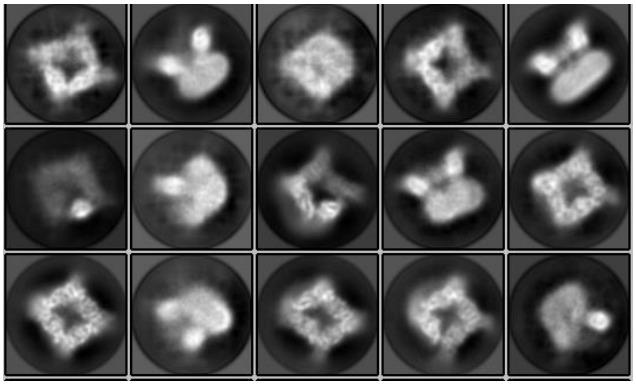

Figure 2: 2D class averages.

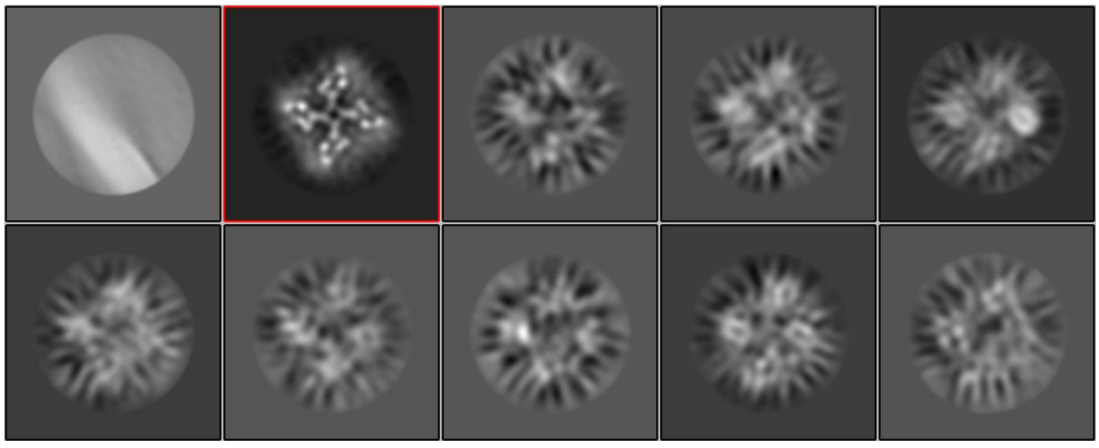

Figure 3: First round of 3D classification, the single class which was selected for next round of 3D classification is shown in red square.