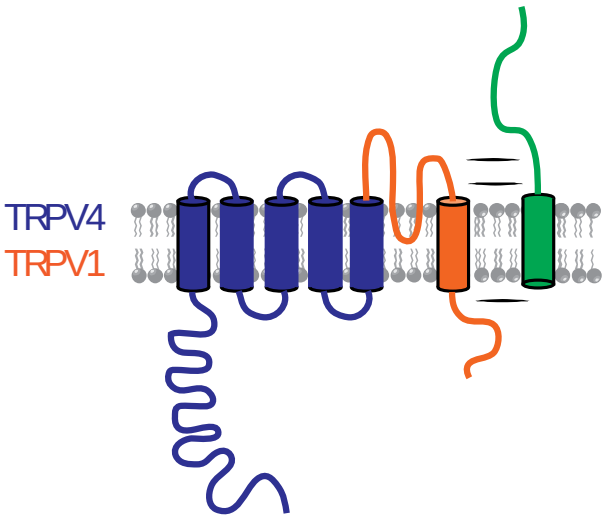
Identification of TRPV4 modules that enable channel gating via matrix

Supervisor/s:

Professor Gary R. Lewin Ph.D.
Max-Delbrück Center for Molecular medicine
Robert-Rössle str. 10
Berlin
Project A9



Collaboration Project/s (if applicable):

ZO2 Dr Jan Schmoranzer
Charité
Professor Dr Helge Ewers
FUB
ZO3 Professor Dr Christian Freund
FUB

Abstract:

It is now clear that extracellular interactions of channels can be very important for the gating of a variety of mechanosensitive channels (Poole et al., 2014a). We recently showed that the TRPV4 ion channel is necessary for fast mechanotransduction by chondrocytes that synthesize cartilage in the joint (Rocio Servin-Vences et al., 2017). The TRPV4 channel is specifically gated by movement of the membrane attached to extracellular matrix, and mechanosensitivity can be reproduced in heterologous cells (e.g. HEK293 cells)(Rocio Servin-Vences et al., 2017). The highly related capsaicin-gated TRPV1 channel is not mechanosensitive under the same conditions. We propose that there is a mechanical link between the TRPV4 ion channel and the extracellular matrix that acts as a scaffold to enable mechanosensitivity. In this project we wish to define the minimal sequences within the TRPV4 channel that confer mechanosensitivity, as we assume that these sequences mediate protein-protein interactions with molecular scaffolds necessary for gating. In order to define such modules we have generated a series of TRPV1/TRPV4 chimeric channels which we will further characterize using our pili assay to gate channels by moving the substrate underneath chimeric channels (Poole et al., 2014b). We assume that TRPV4 gating is enabled by fixing channels in a rigid environment and we wish to directly measure channel localization and mobility using single molecule and super-resolution techniques (collaboration with Helge Ewers and Jan Schmoranzer). Our preliminary results already suggest that we can generate functional chimeric channels that are either mechanosensitive or not. The Ph.D. student will characterize these chimeric channels in detail and determine with electrophysiological and molecular techniques what is the minimal module needed to confer mechanosensitivity on a TRP protein background. The student will then use super-resolution methods to ask whether the localization or mobility of chimeric proteins is correlated with their mechanosensitivity. Finally, molecular knowledge on the mechanosensitive module will allow us to use interaction proteomics to discover scaffold partners that are necessary for mechanosensitivity (with Z03 Christian Freund).

Publication/s:

Poole, K., Moroni, M., and Lewin, G.R. (2014a). Sensory mechanotransduction at membrane-matrix interfaces. Pflugers Arch. Eur. J. Physiol. *467*, 121–132.

Poole, K., Herget, R., Lapatsina, L., Ngo, H.-D.D., Lewin, G.R., Herget, R., Lapatsina, L., Ngo, H.-D.D., Lewin, G.R., Herget, R., et al. (2014b). Tuning Piezo ion channels to detect molecular-scale movements relevant for fine touch. Nat. Commun. *5*, 3520.

Rocio Servin-Vences, M., Moroni, M., Lewin, G.R., Poole, K., Servin-Vences, M.R., Moroni, M., Lewin, G.R., and Poole, K. (2017). Direct measurement of TRPV4 and PIEZO1 activity reveals multiple mechanotransduction pathways in chondrocytes. Elife *6*, e21074.