Photopharmacological and optogenetic targeting of vascular endothelial function

Summary

Klaus Groschner, Gottfried Schatz Research Center for Cell Signaling, Metabolism and Aging, Biophysics, Medical University of Graz, Austria

Supervisor:	Prof. Dr. Klaus Groschner
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Hypothesis and objective:

Lipid-sensitive TRPC channels govern endothelial mediator production as well as phenotype switching and thereby angiogenesis. Recent insights into TRPC structure and gating (1) demonstrate a striking plasticity of channel function dependent on spatiotemporal features of input signals. We hypothesize that specific temporal patterns of channel modulation generate either productive, ineffective or inhibitory signaling pattern, resulting in divergent functional consequences. This project is designed to explore the concept of efficient and precise manipulation of vascular functions (barrier formation, phenotype switching and angiogenesis) by induction of distinct functional states in endothelial TRPC channels by light, using photopharmacology and optochemical genetics. These strategies shall be developed as a basis of novel therapeutic interventions.

Methodology:

We will use novel photopharmacological tools and technologies for light-mediated control of TRPC channels (TRPC3/6/7) in endothelial cells from human and murine blood vessels. Recently established knock-out mouse models expressing a single lipid-sensitive TRPC species will be used to identity isoform(s) linked to specific downstream signaling pathways and endothelial functions. Functional states of TRPC channels, generated by distinct optical activation protocols, will be characterized in endothelial cells by electrophysiological (patch-clamp) experiments, and state-dependent effects on dynamics of Ca^{2+} signaling, Ca^{2+}-dependent NO production and transcription coupling will be investigated using optical probes. Impact of defined activation/deactivation protocols on signaling dynamics and consequences for vascular endothelial functions will be investigated in cell-based assays combined with programmed light stimulation for photopharmacological or opto-chemogenetic manipulation.

Reference:

1. Lichtenegger, M., Tiapko, O., Svobodova, B., Stockner, T., Glasnov, T. N., Schreibmayer, W., Platzer, D., de la Cruz, G. G., Krenn, S., Schober, R., Shrestha, N., Schindl, R., Romanin, C., and Groschner, K. (2018) An optically controlled probe identifies lipid-gating fenestrations within the TRPC3 channel. *Nat Chem Biol 14*, 396-404

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