Novel concepts for therapeutic targeting of TRPC channels in tumors

Summary

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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:

Our recent findings suggest the existence of distinct TRPC signaling signatures based on structural (protein complex composition) but also temporal (channel kinetic, frequency dependence) aspects, which govern downstream TRPC signaling (1). We hypothesize that i) spatiotemporal TRPC signaling pattern rather than expression levels determine cell fate, and ii) selective targeting of TRPC in dysfunctional versus healthy cells may be achieved based on interference with cell type-specific TRPC signatures. Since there is growing consensus that TRPC molecules impact on nearly all “cancer hallmarks” and drive cancer progression, we aim to develop concepts for utilization of TRPC function as malignancy marker, and to use this information for the development of efficient all-optical screening systems for novel cancer therapeutics. Moreover, strategies for highly selective interference with tumor growth appear feasible. Development of therapeutic concepts aims at the specific targeting of tumor and immune cells in view of combining optical intervention with CAR T-cell therapy.

Methodology:

Investigations will focus on optical manipulation/interrogation of TRPC function in native tissues, using recent advances in TRPC photopharmacology. We will characterize subcellular localization and function of TRPC complexes in cancer models (cell lines; glioblastoma and melanoma) known to express lipid-gated TRPC species (TRPC3/6/7) by conventional immunohistochemical, biochemical and electrophysiological methods along with newly developed selective, TRPC photoswitches. TRPC complexes will be characterized in cancer cells and their signaling features will be explored utilizing novel optogenetic probes such as TRPC-Ca^{2+} sensor fusion constructs as well as activity reporters for down-stream transcriptional signaling. Cancer-specific TRPC signaling signatures will be identified and compared to those of native channels in healthy tissues including immune cells (T-cells and dendritic cells). By use of genetically encoded activity reporters and photopharmacological actuators, all-optical screening system will be established that enables efficient identification of drugs, which target cancer specific TRPC functions.

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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