Proposal for a MSc-Thesis Project and Plan of Work

Drug repurposing: Treatment of inflammatory diseases

Background: The ion channel ANO1 (TMEM16A) and the homologous protein ANO6 (TMEM16F) are members of a larger family of transmembraneous proteins (14). ANO1 and ANO6 are upregulated in tumors (9) and in inflamed tissues, like in inflammatory airway diseases such as chronic obstructive lung diseases, asthma, and Cystic fibrosis (1, 5, 7). It is also upregulated during bacterial infection (4). ANO1 may participate in the transition from inflammation to proliferation, which explains its strong impact in wound healing and tissue repair (10, 15, 18). ANO1 has a pronounced effect on intracellular Ca^{2+} signaling, similar to ANO6 (3). However, sustained large increases in intracellular Ca^{2+} can also lead to senescence or cell death (2, 6). Thus, it is not surprising that ANO1 and ANO6 can support both cell proliferation and cell death. ANO6 has been reported initially in the context of apoptosis, but is now also known to be activated during other forms of regulated cell death, such as necroptosis, pyroptosis and ferroptosis (8, 12, 13, 16, 17). Given the reported findings, it should be possible to interfere with inflammation, proliferation and cells death by inhibitors or activators of ANO1 and ANO6.

Therefore, the present MSc project will examine the role of ANO1 and ANO6 in pathological conditions. The goal is to identify compounds that act on ANO1 and ANO6, ideally in an ANO-subtype specific way. Chemicals or natural products that are already accepted for the treatment of disease will be preferred. This so-called repurposing approach (11) may lead much faster to an effective drug when compared to the classical drug development strategy.

Objective: To identify and examine the effect of chemical compounds that enhance or inhibit the activity of Ano1 or Ano6 in the context of inflammation, proliferation and cell death.

Methodology: This MSc project will make use of existing mouse models, which have been generated in our laboratory. These tissue specific mouse models can be further genetically modified to induce a knockout of ANO1 or ANO6 in specific tissues. Inflammation will be induced and the effect of ANO1 / ANO6 knockout and drug modifiers will be examined. Moreover, inflammatory *in vitro* models will be used to assess the effect of ANO1 / ANO6 – acting drugs on inflammation, proliferation or cell death.

A whole spectrum of methods and techniques is available and will be applied depending on their demand. Techniques range from genetic manipulation *in vitro* and in vivo, standard cell biological techniques, to a more specialized functional analysis.

SUPERVISORS

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WORK PLACE

- Dept. of Physiology, University of Regensburg, Germany. The University is located in Regensburg/Bavaria, which is a relatively small city and old medieval town about 1 hour car drive north of Munich.

  To cover costs for travel and housing in Regensburg, a fellowship will be provided.

Literature

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