DFG Transregio CRC/TR 296 "Local control of TH action" (LocoTact)

Summary

Circulating concentrations of thyroid hormones (TH) and thyroid stimulating hormone (TSH) are routinely used for diagnosis of thyroid disorders in patients. However, the recent discoveries of patients with mutations in TH transporters or TH receptors have demonstrated that circulating hormone levels can be insufficient to correctly assess thyroid state in the body. More importantly, further studies have shown that tissues or cells can be in a hyper- or hypothyroid state discordant to serum TH concentrations due to several cellular layers controlling TH action in tissues. These include i) TH transport across the cell membrane regulating hormone import and export, ii) intracellular TH metabolism through different deiodinases and iii) canonical signalling via nuclear receptors (TRs), and noncanonical signalling via cytosolic TRs. Taken together, these findings have challenged the importance of systemic TH and have shifted the focus to regulation of TH action at the organ or cell level. It is, however, still poorly understood, how these local control mechanisms are organized under physiological and pathophysiological conditions. Moreover, there is accumulating evidence, that a restoration or modulation of TH action in a specific tissue can be highly beneficial in certain pathologies such as non-alcoholic steatohepatitis, myocardial infarction, or stroke.

Positions available within this CRC (comprising 18 projects and 3 central research areas):

Project P16: Strategies to increase local T3 availability in liver

PIs: Prof. Dr. rer. nat. Josef Köhrle & Dr. rer. nat. Eva Katrin Wirth

T3 is a key regulator of hepatic lipid metabolism. Hypothyroidism has been linked to non-alcoholic (obesity-/ diabetes-associated) hepatosteatosis and its sequelae. We aim to elevate local T3 concentrations by steering activities of T3-degrading deiodinase isozymes in hepatocytes by using selective deiodinase (DIO) isozyme inhibitors. Local T3 effects will be monitored by T3-sensitive reporter constructs expressed in THAI mouse-derived primary hepatocyte cultures and hiPSC-derived hepatocyte cell lines.

Research Goals:

- Identification of isoenzyme-specific inhibitors of DIO1 by HTS
- in vitro testing of DIO1 inhibitors in primary THAI mouse hepatocytes
- Establishing T3-sensitive hiPSC-derived TH-reporter cells
- Evaluating DIO-steered T3-dependent modulation of lipid metabolism-related gene expression

Open Positions: 2 PhD students (65 % E13) *[or 1 Postdoc, E13]*

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