Novel tools for monitoring arginine methylation

Summary

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Supervisor:	Prof. Dr. Tobias Madl
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

Background:

Both projects aim at revealing the molecular details of the role of arginine methylation (ArgMet) as metabolic master switch. Metabolic systems reflect changes downstream of genomic, transcriptomic, and proteomic fluctuations, and are often the first networks to respond to changes. Deregulation of cellular metabolism is a hallmark of several human diseases, including metabolic and cardiovascular diseases, cancers, and neurological disorders. To meet the special demands, metabolism of diseased cells differs from normal cells and is rewired to support their special needs. The metabolic state of the cell or the organism could be an important messenger and itself act as a key regulator of signaling pathways. Thus, metabolites can not only depict the metabolic status of a cell or organism but act as master switches that act as a feedback regulatory system on signaling pathways.

Both projects aim at elucidating the molecular mechanisms of biologically important, but poorly understood links between metabolism, signaling and disease that converge on ArgMet as metabolic master switch.

In recent studies focusing on the RNA-binding protein Fused-in-Sarcoma (FUS), the Madl group found that protein arginine methyltransferase 1 (PRMT1)-mediated ArgMet within a disordered arginine-glycine(-glycine) (RG/RGG) repeat region regulates FUS localization, liquid-liquid phase separation, and disease development (1-3). RG/RGG motifs are highly abundant in RNA-binding proteins, including more than 500 proteins involved in metabolism and cardiac function (4). These proteins play key roles in numerous physiological processes including DNA damage signaling, transcription, splicing, translation, and the regulation of apoptosis. Strikingly, many human diseases show alterations in PRMT1 expression levels and/or ArgMet, which would in turn effect the intra-cellular localization and phase separation of the RG/RGG proteome. For example, PRMT1 is highly expressed in human cancers, including colorectal, breast, liver, and lung cancer, but low in several neurological disorders such as frontotemporal lobar degeneration (FTLD) and homocystinuria (4). Given that ArgMet is strongly dependent on the essential amino acid methionine, which is the precursor for the PRMT1 co-factor and methyl donor S-adenosyl-L-methionine, we hypothesize that ArgMet is strongly coupled to metabolism. Here we aim to study the link between metabolism, post-translational modification, signaling and disease by focusing on ArgMet as key metabolic switch.

Hypothesis and objective:

Based on our previous work we hypothesize that ArgMet is strongly coupled to metabolism. By developing novel tools for monitoring ArgMet *in vitro* and *in vivo* we aim to reveal the metabolic pathways regulated by substrate and PRMT1.

Methodology:

The DK-MCD student will develop novel fluorescence-, NMR spectroscopy-, and mass spectrometry (MS)-based tools to be able to monitor ArgMet in cells and *in vivo*. These tools aim at overcoming the current limitations in studying ArgMet, such as monitoring ArgMet in living cells and organoids (fluorescent probe, high-resolution (confocal) fluorescence microscopy; in collaboration with W. Graier), to quantify the overall level of arginine methylation (NMR), and to identify sites of protein arginine methylation (MS, in collaboration with R. Birner-Gruenberger). The student will then apply these novel tools together with the student working on showcase 2 to answer key questions in (mis)regulation of metabolic pathways and protein ArgMet in cell lines, stem cells, and organoids under conditions modulating ArgMet

and ArgMet-sensitive disease-related proteins. Techniques and read-outs will be: transcriptomics, proteomics, and quantitative analysis of protein-protein interaction, subcellular analyses of signaling pathways, protein expression, mutation/knock-down, real-time PCR, and bioluminescence. Untargeted NMR-based metabolomics will be used to determine the metabolic impact of these modulations on a systemic level.

References:

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3. Hofweber M, Hutten S, Bourgeois B, Spreitzer E, Niedner-Boblenz A, Schifferer M, Ruepp MD, Simons M, Niessing D, Madl T, Dormann D (2018) Phase Separation of FUS Is Suppressed by Its Nuclear Import Receptor and Arginine Methylation. Cell. 173(3):706-19 e713. doi: 10.1016/j.cell.2018.03.004
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