Linking arginine methylation, RG/RGG protein homeostasis, and disease

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:

We hypothesize that metabolism regulates ArgMet, and in turn, homeostasis of the large class of RG/RGG proteins. RG/RGG proteins can undergo ArgMet-dependent phase transition and by this build and tune dynamic membraneless organelles such as stress granules, RNA granules, P-bodies, and the nucleolus. The student will study the coupling of ArgMet-related metabolism and formation of phase transition of key proteins involved in metabolic and cardiovascular diseases.

Methodology:

The student will study the regulatory role of ArgMet-associated metabolism on key properties of RG/RGG proteins involved in metabolic and cardiovascular diseases *in vitro* and *in vivo*. To this end s/he will express and purify the recombinant proteins and study ArgMet-dependent phase separation, RNA-binding, and binding of ArgMet-related co-factors *in vitro*. Co-factors include, but are not limited to, the natural chaperone transportin-1 and the ArgMet reader protein survival motor neuron protein (SMN1). The tools developed in showcase 1 will be applied here to quantify and read-out ArgMet. Techniques and read-outs will be: recombinant protein production, read-outs of *in vitro*

and *in vivo* phase separation (spectroscopy, fluorescence microscopy, NMR, SAXS, EM), *in vitro* ArgMet assays, mutation/knock-down, quantitative analysis of protein-protein/RNA interaction, and functional read-outs for ArgMet (real-time PCR, transcriptomics, bioluminescence). Untargeted NMR-based metabolomics will be used to determine the metabolic impact of these modulations on a systemic level. Therewith, we aim to identify metabolic pathways that are related to ArgMet and reveal their disease-related properties.

References:

1. Kavscek M, Bhutada G, Madl T, Natter K (2015) Optimization of lipid production with a genome-scale model of Yarrowia lipolytica. BMC Syst Biol. 9:72. doi: 10.1186/s12918-015-0217-4
2. Dormann D, Madl T, Valori CF, Bentmann E, Tahirovic S, Abou-Ajram C, Kremmer E, Ansorge O, Mackenzie IR, Neumann M, Haass C (2012) Arginine methylation next to the PY-NLS modulates Transportin binding and nuclear import of FUS. EMBO J. 31(22):4258-75. doi: 10.1038/emboj.2012.261
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
4. Thandapani P, O'Connor TR, Bailey TL, Richard S (2013) Defining the RGG/RG motif. Mol Cell. 50(5):613-23. doi: 10.1016/j.molcel.2013.05.021

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