Regulation of nuclear import and phase separation

Summary

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Supervisor:	Prof. Dr. Tobias Madl
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Description

Background: Motifs rich in arginine and glycine residues were recognized several decades ago to play functional roles in RNA-binding and were termed RG/RGG motifs[1,2]. More than 1000 proteins harbor the intrinsically disordered RG/RGG motif, and these proteins play essential roles in a plethora of physiological processes such as transcription, pre-mRNA splicing, DNA damage signaling and mRNA translation[2], and very recently in neuroprotection[3]. We have shown that the RG/RGG-motif of FUS is involved in transportin-1 – mediated nuclear import, and that transportin-1 acts as a molecular chaperone regulating FUS phase separation[4-6]. Arginine methylation of the RG/RGG motif in combination with RNA-binding and mutations regulate phase separation of FUS and determine the formation of pathogenic inclusions in Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) patients. Very recently we have discovered a novel regulator of phase separation of not only FUS but many other proteins which will be the focus of this project (Madl lab, unpublished).

Hypothesis and Objectives: Based on our recent studies and supported by our preliminary data, we propose an alternative mechanism for chaperoning phase separation involving a novel regulator. We propose that this regulator acts in coordination with transportin-1 and that a code of post-translational modifications regulates import of the large class of RG/RGG proteins and a new class of proteins and that disease mutations found in cancer and neurodegeneration modulate these interactions. We propose to use newly discovered target proteins as model systems to reveal the structural and functional mechanisms of nuclear import and phase separation by:

1. 1) studying interaction, structure and function of the novel protein complexes
2. 2) studying regulation of the novel protein complexes by post-translational modifications, disease mutations, and co-factors

This might set the base for the discovery of new potential druggable targets in the future for the treatment of a plethora of diseases with different phenotypes, though caused by the same molecular disease mechanisms.

Methodology: The PhD candidate will make use of our recent methodological achievements for studying structure of large protein complexes by combining solution Nuclear Magnetic Resonance (NMR) spectroscopy, and molecular modeling[7-12], and extend it with complementary approaches such as Mass Spectrometry (MS) and cell biology.

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