iNEXT workshop on Integrated methodologies and approaches for structural biology

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University / Research Institute / Department: **Regensburg University, Regensburg Center for Biochemistry, Biophysics I**

Title of Lecture: **The structure and activity of the mRNA decapping complex inside and outside of cytoplasmic processing bodies**

Abstract:

Liquid-liquid phase separations (LLPS) have emerged as an important process for cellular organization. In eukaryotic cells, the components of the mRNA degradation machinery can localize to cytoplasmic granules that are referred to as processing bodies (P-bodies).

In the recent years, we have shown that these P-bodies result from a large dynamic network of protein-protein and protein-RNA interactions. We found that the mRNA decapping enzyme Dcp2, its key activator Dcp1 and the scaffold proteins Edc3 or Pdc1 are sufficient to reconstitute an in vitro LLPS process, indicative for P-body formation. Based on high resolution structures, binding experiments and large scale in vitro phase separation screens, we identified a number of key interactions that can drive phase separation. In addition, we have been able to show that the activity of the mRNA decapping complex is reduced upon formation of in vitro P-bodies. Our results thus argue for a role of cellular P-bodies in temporary mRNA storage.

Based on high resolution NMR and crystallographic studies, we show that the mRNA decapping complex is highly mobile on the ms timescale. Interestingly, the conformations that the complex can sample correlate well with the catalytic activity. We show that this feature is exploited by activators of the enzyme that lock the complex in its functional and active state.

In summary, we show that cellular localization and conformational changes influence the activity of the mRNA degradation pathway. Our results thus show an example of how catalytic activity is regulated by different processes.

Research Profile:

The primary scientific goal of the research group is to understand the relationship between protein motions and protein function. This is especially relevant for most enzymes that have to undergo structural rearrangements to perform biological tasks. In the lab we focus on understanding the mechanism behind the bio-molecular complexes that play a role in the degradation of mRNA.

Three selected publications:

1. Changes in conformational equilibria regulate the activity of the Dcp2 decapping enzyme. Wurm JP, Holdermann I, Overbeck JH, Mayer PHO, Sprangers R. Proc Natl Acad Sci U S A. 2017 Jun 6;114(23):6034-6039.
2. A synergistic network of interactions promotes the formation of in vitro processing bodies and protects mRNA against decapping. Schütz S, Nöldeke ER, Sprangers R. Nucleic Acids Res. 2017 Jun 20;45(11):6911-6922.
3. The S. pombe mRNA decapping complex recruits cofactors and an Edc1-like activator through a single dynamic surface. Wurm JP, Overbeck J, Sprangers R. RNA. 2016 Sep;22(9):1360-72.

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