IMPRS on Multiscale Biosystems

Project description

Title: Control of translational efficiency by tRNA thiolation: biochemical and theoretical analysis
PI: Silke Leimkühler (UP) [biochemistry part]
In collaboration with: Angelo Valleriani (MPIKG) [computational & bioinformatics part]

Project description:
Thiomodifications of tRNAs were shown to be important for proper function of pro- and eukaryotic organisms. In particular, four different thionucleosides have been identified at different positions in several prokaryotic tRNAs to date. The role of the thio-modification at the wobble position U34 of nucleotides present in tRNAs for lysine, glutamine or glutamate was suggested to be responsible for improved translation efficiency by enhancing aminoacylation kinetics, assisting proper codon–anticodon pairing and preventing frameshifting during translation. For the formation of thionucleoside at the wobble position in *Escherichia coli*, a a sulfur-relay system has been identified that includes the initial sulfur mobilization by the L-cysteine desulfurase IscS and the proteins TusA, TusBCD, TusE and MnmA. TusA thereby directly interacts with IscS, stimulates its desulfurase activity and directs the sulfur flow to 2-thiouridine formation.
In close collaboration with the complex systems modeling group of Dr. Angelo Valleriani, we will make use of the available ribo-seq data in the literature and, additionally, we will acquire our own ribo-seq data from deletion strains in *tusA* and plan to compare the data. Using ribo-seq data, it is possible to quantify and determine the role played by translation in the control of gene expression. Additionally, we will measure changes in the translation efficiency of selected genes by constructing C-terminal fusions to the reporter gene eGFP. The production of eGFP consequently will be used as a readout for the translation of the gene of interest. Translation efficiencies in the *E. coli* wild-type strain will be compared to strains being impaired in tRNA thiolations. The characterization of the ultimate mechanisms causing differences in the translation behavior is a matter of intensive study.
In total, the role of U34 tRNA modifications on the translation efficiency of selected genes in addition to a global analysis of changes in the translation pattern by ribosomal profiling will be analyzed in detail.

Required background: The candidate should have a biological background and strong interest both in bioinformatics and in fundamentals of biochemistry and molecular biology. The peculiar professional profile achieved through this project will markedly foster possible future career steps. A potential collaboration with Dr Chiarugi (University of Cambridge) will be considered during the project.

Paper to read before the interview: P.B.F. O'Connor, D.E. Andreev, P.V. Baranov, *Nat. Comm.* **7**, 12915 (2016); Leimkühler, S., Bühning, M., Beilschmidt, L. (2017) *Biomolecules.*, 7(1).

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