Molecular Characterization of large tRNA modification Complexes

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Description for the General Public

All living organisms use information coded in their genomic deoxyribonucleic acid (DNA) to produce proteins, so called enzymes. These molecular working horses are responsible for carrying out fundamental cellular function to reproduce, stay alive and allow them to sense and react to changing environmental conditions. During a process called “transcription” regions that are the blueprints for specific proteins (genes) are activated and give rise to messenger ribonucleic acid (mRNA) molecules. These mRNA molecules contain copies of the respective DNA sequence and in higher organisms are transported out from the nucleus into the cytoplasm. During a process called “translation”, ribosomes and transfer RNA (tRNA) molecules translate sequence information encoded in mRNAs into correctly assembled chains of linked amino acids. These chains fold into specific three-dimensional structures and are then called proteins, which have a specific enzymatic activity depending on their intrinsic properties and structural architecture.

Both processes, transcription and translation, are tightly controlled to assure the correct production of the right enzymes at the right time in the right cellular context. In addition, the three dimensional folding of a poly-peptide chain is a very complicated multi-step process that needs tight regulation to produce correctly assembled and functionally active enzymes. Mutated or incorrectly folded proteins, inappropriate expression levels as well as the production of a protein in the wrong cellular context can lead to cellular dysfunction and in the worst case promote the development of severe diseases, like cancer.

In my research group, we aim to understand fundamental cellular mechanisms that are highly conserved from yeast to humans and affect protein synthesis at the level of translation. In detail, cells use a multi-protein machines to attach small chemical modifications to tRNAs, which guarantee that proteins are produced with highest precision and at the right speed. Our work from previous years has revealed that various modification pathways are directly interacting and communicating with each other. Furthermore, different additional regulatory proteins transiently dock onto these relatively large cellular machines and regulate the conducted enzymatic reactions in a very precisely timed fashion. In the proposed project, we would like to understand how do these transiently and dynamically formed intermediates look and understand them on the atomic level.

We will mainly employ cryo-electron microscopy, which has recently received major public attention, due to the fact, that the inventors of these method received the Nobel Prize for Chemistry in 2017. The project will be implemented together with the newly created “Krajowe Centrum Kriomikroskopii Elektronowej” at the neighboring Solaris Synchrotron in Krakow. Therefore, the project will strongly contribute to establish and develop a leading scientific technology in Poland.

Foremost, mutations in the proteins under investigation are associated with severe neurodegenerative diseases, intellectual disabilities and cancer. We first need to understand (i) how they carry out the modification reactions, (ii) how they are assembled, (iii) how they regulate each other and (iv) how they are influenced by additional factors. After characterizing the structures of the respective protein complexes, we will be able to understand the consequences of the patient derived mutations and the molecular reasons for the diseases. This knowledge will ultimately allow us to develop novel diagnostic methods and therapeutic treatment strategies for the benefit of the affected patients in the future.