Deciphering the Molecular Mechanism of Queuosinylation of Human tRNA: Structural and Functional Analyses of the QTRT1/2 Complex

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All proteins in every organism on Earth are produced by the sophisticated cellular machinery called the ribosome. We have 20 various types of amino acids from which our proteins are composed. The ribosome, as a factory of proteins, requires small carriers to bring amino acids - the supply of which proteins are built from. These amino acid carriers are built of RNA and are called transfer RNAs (tRNAs). They not only bring building blocks to the factory but also can read the information (provided there by another type of RNA – mRNA) about the order in which amino acid chains should be composed to make functional proteins. To perform their function, carriers (tRNAs) have a specific 3D shape. This shape is achieved and maintained by various chemical modifications put on tRNAs by enzymes.

We are interested in one of them, called queuosine, which regulates for how long a particular carrier stays in the factory, thus providing the proper speed of the emerging polypeptide chain (the protein). Proteins need their time to properly fold in 3D when they leave the factory, so the regulation of speed of their synthesis is important to make them functional.

Queuosine is rare and affects only four tRNAs. Intriguingly, our organism cannot synthesize it from scratch – we rely on an external source which is the gut microbiome or simply food. While having the substrate received from the environment, our enzymatic complex called QTRT1/2 can recognize specific tRNAs and add queuosine in a very precise position. In this project, we are interested in how this enzymatic reaction works on the molecular level. To achieve this goal, we plan to use modern electron microscopy in cryogenic temperatures, enabling us to visualize protein-RNA complexes at work in 3D. We want to build a gallery of snapshots of QTRT1/2-tRNA complex at different stages of an enzymatic reaction. We will complement our 3D visualizations with various biochemical assays to fully understand what we see. Understanding the tRNA queuosinylation process is not only interesting per se but also, in the future, can lead to breaking the specificity of the enzyme to develop some biomedical and biotechnological applications, like e.g. RNA editing tools.