Molecular basis of hypusination

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Our project aims at understanding the molecular and functional basis of protein network that regulate the synthesis of hypusine. Hypusination is a modification described only for one protein: eukaryotic translational factor eIF5A and spermidine is used as a substrate in this process. In the first step of hypusination, the enzyme deoxyhypusine synthase (DHS), attaches 4-aminobutyl moiety of spermidine to the lysine residue present in eIF5A, resulting in the formation of a non-standard amino acid residue: deoxyhypusine. The deoxyhypusine is then modified to hypusine by deoxyhypsuine hydroxylase (DOHH). eIF5A is involved in the translation process of proteins, and hypusinated lysine is essential for its activity. eIF5A is also involved in the development of certain diseases such as diabetes, certain types of cancer and malaria. In addition, hypusinated eIF5A promotes cell proliferation.

In order to get molecular insights to the mechanism of hypusination we will solve the atomic structures of eIF5A in the complex with DHS and DOHH. Then, using various biochemical tests, we will validate the structural data at the place of protein interaction, which will additionally confirm which regions or amino acids of the proteins are necessary to form complexes. In addition, we intend to investigate the molecular basis of substrate binding by DHS, as well as the effect of DHS mutations described in neurological diseases on the structure and function of the protein. In the last research task, we will carry out extensive screening tests aimed at finding new potential inhibitors of DHS activity and formation of the DHS-eIF5A complex.

In our research, we will use the structural biology methodology, including such techniques as X-ray crystallography, small-angle X-ray scattering (SAXS), mass spectrometry (MS) and cryo-electron microscopy (cryoEM).

Because the process of hypunization is associated with excessive proliferation, growth and survival of cells, characteristic for tumour progression, the development of chemical molecules that regulate or block hypunization in the cell may also be important from a clinical point of view. We are convinced that the results of the project will contribute to a better understanding of the hypusination process and therefore enable the future design of molecules with therapeutic potential.