The puzzling structure of Grainyhead-like human transcription factors involved in tumor growth regulation

This project aims to fully characterize the structure of transcription factors from the Grainyhead-like subfamily.

They are presumed to be pioneer factors. They bind the condensed DNA and shape it to allow more transcription factors to bind and subsequently the start of the translation. Thus, their proper functioning governs many processes in the organism, especially during embryonic development. Later in life, they affect the formation and development of multiple types of cancer. Usually, they act as tumor suppressors - preventing its growth. But cases in which their overexpression is connected with tumor development are known like development of breast and prostate cancers. Furthermore, their elevated level in colorectal and pancreatic cancers is associated with poor prognosis. This makes the studies of GRHL subfamily proteins of vital importance to understanding tumor growth and its curing.

It is well established that obtaining structural information greatly benefits understanding the molecular mechanism of protein action. However, only a structure of the sole DNA-binding domain of Grhl1 and Grhl2 is available so far. No full-length structure of any GRHL proteins is solved, and no structural information on Grhl3 is available whatsoever. Thus, our understanding of GRHL proteins' mode of action remains patchy.

Establishing the complete protein structure of GRHL proteins and elucidating their binding mechanisms will tremendously advance understanding molecular mechanisms governing embryonic development and cancerogenesis, potentially leading to the development of novel, targeted cancer treatments. It will be a milestone to answer how GRHL proteins shape the DNA and help in the recruitment of other transcription factors. The full-length structure solution will show us how the biologically active dimer is formed and how the pathogenic mutations outside its DNA-binding domain cripple its functioning. Furthermore, the analysis of the complex structures of GRHL protein with DNA will indicate how the specificity of this protein toward specific DNA sequences is achieved.

A new and highly successful technique, electron cryo-microscopy (CryoEM), will be used to determine the structure of the full-length GRHL protein complexes with ligands. However invaluable, these structures may lack the fine details necessary for comprehensive structural characterization. Therefore, X-ray crystallography will be employed to determine the structures of shortened proteins in complex with DNA.

Such a combination of two top structural biology techniques allows them to overcome their shortcomings and fully exploit the possibilities they bring.