Project 9.6 Structural studies of herpesvirus proteins involved in DNA replication (NCN/OPUS)

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www: https://bit.ly/3ugJ7po

Background:

Herpesviruses are among the most widespread human pathogens. They establish lifelong infection with lytic and latent stages. Herpesviruses do not pose a major threat for healthy individuals, but they can cause severe diseases in immunocompromised patients. Most antiviral drugs that are used to treat symptoms of herpesvirus infections disrupt the process of viral DNA replication. The DNA replication mechanism in herpesviruses is largely conserved. It requires six conserved viral proteins: single-stranded DNA-binding protein, three proteins that form the helicase/primase complex, and polymerase and its associated processivity factor. Together, they constitute a macromolecular assembly called the replisome. The initiation of replication appears to be less conserved. In herpes simplex virus type 1 (HSV-1), the best studied herpesvirus, it requires an origin-binding protein.

Despite a wealth of biochemical data on herpesvirus replication proteins, our understanding of herpesvirus DNA replication is still incomplete. No structures have yet been determined for several of the replication proteins. Furthermore, unclear is how replication proteins are recruited to the replication fork and how the synthesis of both DNA strands is coupled. Finally, structural information about interactions of proteins that form HSV-1 replication machinery with each other and with their nucleic acid substrates is missing, so the architecture of the complete replisome or even its parts is unknown.

Aim:

In this project, we aim to improve our understanding of the process of DNA replication in herpesviruses. We plan to achieve this by determining atomic structures of herpesvirus proteins involved in DNA replication and their complexes with relevant nucleic acid substrates using cryo-electron microscopy (cryo-EM) and X-ray crystallography. These structural studies will be complemented by biochemical experiments. Based on the structures and the biochemical data we will reveal how the herpesvirus replisome works and how the activity of its components is regulated and coordinated. The results of this project will be a valuable resource for future efforts that seek to produce new anti-herpesvirus drugs.

Requirements:

- MSc degree in biology, biochemistry or related field,
- willingness to start education at the Doctoral School in the summer semester, February 2024,
- solid knowledge of the principles of molecular biology and biochemistry,
- hands-on experience in laboratory work and knowledge of basic molecular biology techniques,
- prior experience in recombinant protein expression, protein purification, X-ray crystallography or electron microscopy will be an advantage,
- proficiency in written and spoken English,
- excellent interpersonal skills, initiative, good work organization

Number of positions available: 1

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