Ph.D. projects in progress

1.

Mentor: Imre Boros, László Henn

Doctoral school: University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

Ph.D. student: Anikó Szabó

Title of the research topic: The role of Drosophila alternative linker histone BigH1 during early development

Description of the research topic: Linker histone H1 proteins are essential building blocks of chromatin and play role in stabilizing higher order structures. H1 histones have many tissue- and developmental stage-specific variants and frequently the initiation of embryogenesis requires a specific alternative linker histone. In Drosophila, BigH1 has been found to play role at the start of embryogenesis. Our work is aimed at understanding the specific function of BigH1. For this, we generated mutant fly lines in which the coding sequence of BigH1 is exchanged completely or partially with the coding sequence of somatic H1. Analysis of the fly lines revealed that BigH1 performs its specific function in early embryogenesis by being a more dynamic linker histone that facilitates fast nucleosome exchanges in S-phase during the rapid nuclear divisions in the early embryo, while providing greater stability to nucleosomes compared to somatic H1.

2.

Mentor: Imre Boros, László Henn

Doctoral school: University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

Ph.D. student: Andrea Ábrahám

Title of the research topic: The role of histone modifications and alternative histone usage in differentiated cells and tissues

Description of the research topic: Histones are highly conserved proteins of the chromatin that play critical role in the cellular homeostasis. Chromatin structure can be modulated through the post-translational modifications (PTMs) and replacements of histones. Numerous diseases have been connected to histones, therefore, it is important to understand the diverse roles histone modifications and replacement histones play. We use Drosophila melanogaster modell to investigate histone functions. It has been shown recently that ubiquitilation of H2A at Lys119 increases with age, and flies mutant to ubiquitin ligases that modify Lys119 show increased logevity. We generated UASt-GFPH2AK119R and an UASt-GFPH2Awt transgenic fly stocks and tested their longevity. The results revealed that flies overexpressing transgenic GFPH2A indeed show increased longevity, but there was no significant

difference between flies overexpressing point-mutant and non-mutant GFPH2A. Another direction of our research is to uncover the function of a unique alternative histone H4 of Drosophila. For this we created a transgenic line in which the His4r is in situ modified with a 3xFlag-tag. The tag allows us to distinguish the canonical and replacement H4 proteins. At present with the help of the constructed line we analyse the possible roles of His4r in stress responses and in transcriptional memory using chromatin immunoprecipitation and sequencing.

3.

Mentor: Zoltán Lipinszki

Doctoral school: University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

Ph.D. student: Zoltán Kármán

Title of the research topic: Investigation of the target-binding mechanisms of the evolutionarily conserves Protein Phosphatase 4

Description of the research topic: Reversible protein phosphorylation serves as a molecular switch to regulate the activity, localisation, half-life or interacting partners of proteins that govern complex cellular events, such as cell division in Eukaryotes. It is catalysed by the relatively well characterized protein kinases and reversed by protein phosphatases, whose function is poorly understood. Ser/Thr phosphoprotein phosphatases (PPP) play a crucial role in cell cycle regulation and often function as heteromeric holoenzyme complexes that recognize the target protein by binding to their special short linear motifs (SLiMs). The PPP family includes the evolutionarily conserved and essential heterotrimeric Protein Phosphatase 4 (PP4) holoenzyme, whose R3 subunit is responsible for substrate recognition. However, the mode of binding and the PP4-R3-specific SLiMs are not known. We found that at least two conserved domains, the N-terminal EVH1 and Smk-1 are responsible for substrate-recognition in fruit flies. We identified novel binding partners of these domains and defined the EVH1-specific consensus binding motifs using molecular biology, genetics and proteomics. Currently, we aim to understand how does EVH1 recognize its SLiMs, what the binding mechanism of the unknown function Smk-1 domain is and how does PP4 regulate the function of the newly identified cell cycle-related binding partners.

4.

Mentor: Zoltán Lipinszki

Doctoral school: University of Szeged, Faculty of Science and Informatics, Doctoral School of Biology

Ph.D. student: Zsuzsánna Réthi-Nagy

Title of the research topic: Identification and characterization of a cis-acting and universal protein stabilization motif

Description of the research topic: Intracellular controlled proteolysis by the ubiquitin-proteasome system (UPS) or the autophagy is essential for the maintenance of the healthy proteome (proteostasis) in Eukaryotes. UPS is responsible for the elimination of short-lived proteins, including transcription factors or cell cycle regulators, which are frequently involved in critical regulatory functions, therefore their selective and orchestrated destruction is essential for cellular integrity. Degradation signals, degrons, are present in short-lived proteins ensuring the selective recognition and elimination of these proteins by the UPS. While a large variety of degrons have been discovered, which are under the strict control of different regulatory influences, our knowledge on cis-acting protein motifs that can in vivo stabilize otherwise short-lived proteins is very limited. We have identified and characterized a short protein segment that fulfils all the characteristics of a protein stabilization motif. Attachment of this stabilon sequence to the C-terminal end of several short-lived proteins differing in structure, cellular localization, in vivo processing and C-terminal amino acid sequences, have significantly extended their half-life by preventing their proteasomal degradation. The consequence of its stabilization activity was most conspicuous on the production of a secreted protein. The quantity of the human erythropoietin fused to stabilon secreted into the tissue culture medium was orders of magnitude higher than that of the nascent erythropoietin. Finally, we found that this motif functions as a universal stabilon in higher Eukaryotes.