ENS – IISER Network / BIOSANTEXC Project

Internship Proposal Form

(Discipline/Field name): Structural and computational Biochemistry_____

Internship title: Dynamical behavior of a nucleosome with H2A.Z variants and its impact on the circadian clock

Keywords related with the subject (minimum 3): Nucleosome, Circadian Clock, molecular dynamics simulations

Name of the laboratory at ENS: Laboratoire de Chimie (and IGFL)

Name of the internship supervisor(s): Natacha Gillet, orcid.org/0000-0002-7657-6861, Frédéric Brunet, orcid.org/0000-0001-5145-8925, Kiran Padmanabhan, orcid.org/0000-0001-7020-1682 ;

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Prerequisites for the internship: Molecular biology or biochemistry or computational chemistry
Requested level: Master

Foreseen internship dates: 1st April 2025-30th June 2025

Internship proposal (description and expected training outcomes / half page min, 1 page max):

Histones are the most conserved protein family in Eukaryotic cells. Their primary function is the packaging of the genetic material into a nucleosome, formed from an octamer of a central H3-H4 tetramer flanked by 2 H2A-H2B dimers, wrapped by 147 nucleotides of DNA. While canonical histones (CH) are involved in the replication process, there are other non-canonical ones, called histone variants (HV), that change the structural proprieties of the nucleosomes bearing them, influencing gene expression by facilitating or interfering with the recruitment of transcription factors for example. The unique temporal expression of each variant reflects more specific cellular functions especially in post-mitotic cells. For example, H2A.Z, which is incorporated at promoters, enhancers and transcription start sites will modify the stability of the nucleosome;[1] H2A.X is found at DNA damage sites. These HV can have indirect effects on chromatin organization and the maintenance of the genome organization. Their deposition or eviction is done by specialized chaperone and remodeling complexes, and any deregulation of one of the components (HV included) can promote senescence, contribute to, or drive tumor progression, for example by increasing epigenetic plasticity.

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Deregulation of histone variant expression and deposition is implicated in cancer and developmental syndromes.

Over two decades of genetic and proteomic screens have helped identify many components of the core clock and helped build a model of the regulatory network. Within mammalian cells, a BMAL1:CLOCK transcription factor heterodimer drives the rhythmic transcription of 15% of expressed genes in a tissue-specific manner. Besides its role in nucleosome stability, H2AZ.1 interact with BMAL1,[2] one of the protein of the core clock gene. H2A has a preferential binding site of CLOCK-BMAL1, an acidic patch (histone H2A (Glu61, Asp90 and Glu92) that is slightly longer in H2A.Z. In addition, some differences are observed in the sequence of the histone N-terminal tail which is intrinsically disordered.

In this project, we plan to perform molecular MD simulations to understand how this HV modifies the behavior of nucleosomal DNA and enhances the BMAL1 binding at a molecular level. Such approaches have been already used in our group to understand the DNA damages formations or structural behavior in the nucleosome.[3,4] Starting from available structural data (from Protein Data Bank), we aim to explore the conformational landscape of the nucleosome with H2AZ variants and decipher to key residues and molecular interactions that explains the difference with canonical H2A histone. Our simulations protocol allows to depict at an atomic level the dynamical behavior of a solvated nucleosome at a microsecond timescale. Then, the flexibility and the interaction landscapes of the biomolecules (DNA, histone core, histone tail, DNA binding domain of BMAL1) can be analyzed to understand the molecular mechanism at play in the different role of H2A.Z.

This project takes part of a collaborative work between the Chemistry Lab and IGFL from ENS de Lyon, involving computational chemistry, bioinformatics and *in vivo* experiments.

References

(1) Gaillard, H.; Ciudad, T.; Aguilera, A.; Wellinger, R. E. Histone Variant H2A.Z Is Needed for Efficient Transcription-Coupled NER and Genome Integrity in UV Challenged Yeast Cells. *PLOS Genet.* **2024**, *20* (9), e1011300. https://doi.org/10.1371/journal.pgen.1011300.
(2) Menet, J. S.; Pescatore, S.; Rosbash, M. CLOCK:BMAL1 Is a Pioneer-like Transcription Factor. *Genes Dev.* **2014**, *28* (1), 8–13. https://doi.org/10.1101/gad.228536.113.
(3) Bignon, E.; Gillet, N.; Jiang, T.; Morell, C.; Dumont, E. A Dynamic View of the Interaction of Histone Tails with Clustered Abasic Sites in a Nucleosome Core Particle. *J. Phys. Chem. Lett.* **2021**, *12* (25), 6014–6019. https://doi.org/10.1021/acs.jpclett.1c01058.
(4) Wen, T.; Kermarrec, M.; Dumont, E.; Gillet, N.; Greenberg, M. M. DNA–Histone Cross-Link Formation via Hole Trapping in Nucleosome Core Particles. *J. Am. Chem. Soc.* **2023**, *145* (43), 23702–23714. https://doi.org/10.1021/jacs.3c08135.

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