EuReCa International PhD Program

PhD thesis project

2023 Call for application

Histone variant H3.3 and cellular programs during development and cancer

General information

Call	2023
Reference	2023-01-ALMOUZNI_SIMEONOVA
Keyword(s)	Epigenetics, Development and cancer; Histone variants; Animal models, Omics.

Director(s) and team

Thesis director(s)	Geneviève Almouzni & Iva Simeonova
Research team	Chromatin Dynamics
Research department	UMR3664 – Nuclear Dynamics

Description of the PhD thesis project

Background: The nucleosomes are the basic unit of chromatin - they are composed of DNA and histone proteins and are critical for genome organization. Distinct histone variants, which have different properties and are decorated with distinct post-translational modifications by chromatin modifiers, confer unique properties to the nucleosomes and define cell type-specific landscapes. In pathologies, such as cancers, the genomic context of histone variant incorporation by dedicated chaperone proteins is often altered (Yadav et al, Science 2018).

How does the network of histone variants, their chaperones and chromatin modifiers work together to dynamically regulate chromatin states, both in physiology and disease, remains one of the central questions of molecular biology and is the focus of our team research. Recently, we made major progress in understanding the role of histone variants in DNA replication regulation (Gatto et al. Mol Cell 2022), as well as their dynamic recycling during transcription (Torné et al, NSMB 2020), by exploring unique cellular system tools developed in the lab. We also demonstrated that the dynamics and subnuclear organization of the histone variant that epigenetically determines the centromere, can promote specific cell fate transition and the acquisition of chemoradiation resistance in patients and in human cell lines (Verrelle et al Cancers 2021, Jeffery et al, 2021 Commun Biol).

Strikingly, by using the amphibian *Xenopus laevis* as a developmental model, we also found that the presence of a specific histone variant, called H3.3, is essential at the time of gastrulation, when primitive germ layers form (Sitbon et al, Nature Communications 2020). Intriguingly, the same histone is mutated at high frequency both in some pediatric cancers, such as the deadly brain tumors called glioblastoma (Lowe et al, Cancers 2019), and in patients with neurodevelopmental disorders (Bryant et al 2020). Thus, proper chromatin organization through the use of specific histone variants appears essential for cell lineage choices and organism homeostasis.

The PhD project aims at further investigating histone variant H3.3 physiological importance. It builds on cellular and animal models established in the laboratory, to follow specific cell fates by using cutting-edge transcriptomic approaches, combined with *in silico* analysis of public datasets. We hypothesize that the regulation of H3.3 transcription by tissue-specific factors and the H3.3 unique properties could contribute to cell plasticity during normal physiology and would be high-jacked in pathological situation such as tumor programs in cancers, harboring H3.3 mutations.

International, interdisciplinary & intersectoral aspects of the project

The PhD student will acquire and develop a broad range of expertise in both bioinformatics and wet lab approaches ranging from basic biology to translational and medical implications. This will entail mastering the use of public datasets, use of cellular and in vivo models, and cutting-edge single cell transcriptomics (from sample preparation to analysis). The PhD student will benefit from mentoring and/or a secondment abroad via a collaborative network, to obtain additional training on early development embryos, single cell data and R&D applications.

Recent publications

1. HIRA-dependent boundaries between H3 variants shape early replication in mammals. Gatto A, Forest A, Quivy JP, **Almouzni G**, Mol Cell. 2022 May 19;82(10):1909-1923.e5, doi: 10.1016/j.molcel.2022.03.017, PMID 35381196

2. Two HIRA-dependent pathways mediate H3.3 de novo deposition and recycling during transcription. Torné J, Ray-Gallet D, Boyarchuk E, Garnier M, Le Baccon P, Coulon A, Orsi GA, **Almouzni G**. Nat Struct Mol Biol. 2020 Nov;27(11):1057-1068. doi: 10.1038/s41594-020-0492-7. PMID: 32895554

3. Histone variant H3.3 residue S31 is essential for Xenopus gastrulation regardless of the deposition pathway. Sitbon D, Boyarchuk E, Dingli F, Loew D, **Almouzni G**. Nat Commun. 2020 Mar 9;11(1):1256. doi: 10.1038/s41467-020-15084-4. PMID: 32152320

4. Dynamics of asymmetric and symmetric divisions of muscle stem cells in vivo and on artificial niches. Evano B, Khalilan S, Le Carrou G, **Almouzni G**, Tajbakhsh S. Cell Reports 2020 Mar 10;30(10):3195-3206.e7. doi: 10.1016/j.celrep.2020.01.097. PMID 32160529

5. Chromatin Plasticity: A versatile landscape that underlies cell fate and plasticity. Yadav T, Quivy JP, **Almouzni G**. Science 2018 Sep 28;361(6409):1332-1336. doi: 10.1126/science.aat8950. PMID: 30262494

Expected profile of the candidate

Applicants should have a strong desire to explore cell biological phenomena in an *in vivo* context and should show solid capacity for independent and creative thinking. Background in stem cell biology, mouse genetics, and/or molecular biology and biochemistry is strongly recommended. The project highly relies on transcriptomic approaches. The applicant should have either experience in bioinformatics or a strong motivation to learn.