Title of the PhD project:
HuntAcyl: Altered dynamics of acylations of histone H3 Lysine 27 (H3K27): a mechanism contributing to transcriptional dysregulation in Huntington's disease?

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Project summary:
Dynamic post-translational modifications (PTMs) of histones are essential to regulate gene expression. Acetylation of histone lysines has been discovered more than 50 years ago and is now well known to be associated with increased DNA accessibility and active gene transcription. Over the past decade, however, a wealth of other lysine acylations resembling acetylation but varying in length and hydrophobicity have been described, whose functions largely await characterization. One particular residue, lysine 27 of histone H3 (H3K27) has a central role in the control of gene expression: it either activates or represses transcription when modified by acetylation or trimethylation. In the context of Huntington Disease (HD), a rare genetic neurodegenerative disorder, we observed a decrease of H3K27ac in genomic regions regulating the expression of neuronal identity genes, correlating with their transcriptional down-regulation. Interestingly, H3K27 was recently described to be also modifiable by crotonylation in the brain. Besides, lactate is a key metabolite in this organ and was described last year to induce histone lysine lactylation. We have detected crotonylation and lactylation on H3K27 in histones extracted from mice striatum, the brain region that is primarily affected in HD. Using proteomics, we wish to quantify the relative stoichiometry of variably acylated H3K27 forms compared to H3K27ac in the striatum of WT and HD mouse models. The genomic distribution of H3K27acyl forms will be obtained and compared to the distribution of H3K27ac. Integration of these datasets with RNA-seq data will allow assessing the relative contributions of these marks on the regulation of gene expression. Finally, we will identify the selective protein binders of the various H3K27acyl forms that mediate the specific roles of these marks. Overall, this project will integrate omics data to study the interplay between PTM dynamics at H3K27 and the recruitment of specific protein binders and protein machineries on histones, to better decipher transcription deregulations in HD. We expect that the data generated in the project will provide important mechanistic insights with respect to the role of epigenetic and transcriptional deregulations in HD, which might foster the development of innovative therapeutic strategies for neurodegenerative diseases.

Required/Preferred/Desired skills:
This PhD project lies at the interface between analytical chemistry, biology and bioinformatics to handle large-scale omics datasets. The candidate should have at least a theoretical training in some analytical techniques to characterize biomolecules, and a strong interest to learn proteomics. He/she should ideally have had classes and/or practical experience in biochemistry. The candidate should also be interested in learning how to make biological sense from large-scale omics datasets (e.g. RNA-seq data) using scripts written in R language.

Student role:
The PhD student will perform the preparation of histone samples for their proteomic analysis, interpret these data to highlight variably modified lysine residues between WT mice and mice models of HD. He/she will also perform different experiments of biochemistry: confirm proteomics results by Western Blots; affinity-purify crosslinked protein/DNA complexes using antibodies raised against selected histone modifications, to identify both the genomic regions bound by these histone molecules (by ChIP-seq) and the proteins preferentially binding onto them (by proteomics). The student will also be involved in the integration of the ChIP-seq data with available RNA-seq data to assess the impact on gene expression of histone lysine modifications perturbed in HD. In conclusion, the PhD student will have the opportunity to gain a very solid experience in proteomic and genomic data acquisition and integrative (bioinformatics) analysis, as well as in biochemistry to affinity-purify protein/DNA samples. This training is compatible with a future career in either the academic or the private sector.

Keywords:
Histone lysine acylations, selective protein assemblies, Huntington disease, quantitative proteomics, functional genomics

Relevant publications of the team (5 max.):

Achour M., […], Merienne K.
Neuronal identity genes regulated by super-enhancers are preferentially down-regulated in the striatum of Huntington's disease mice.
Hum. Mol. Genet. 2015; 24, 3481-96. doi: 10.1093/hmg/ddv099

El Kennani S*, Crespo M, Govin J, Pflieger D*.
Proteomic analysis of histone variants and their PTMs: strategies and pitfalls.
Proteomes. **2018** Jun 21;6(3). pii: E29. doi: 10.3390/proteomes6030029

Crespo M. […], Battail C.*, Cocquet J.*, Pflieger D.* .
Multi-omic analysis of gametogenesis reveals a novel signature at the promoters and distal enhancers of active genes.
Nucleic Acids Res*.,* 2020. doi:10.1093/nar/gkaa163

Alcala Vida R., Seguin J., Lotz C., […], Awada A., […], Merienne K.
Age-related and disease locus-specific mechanisms contribute to early remodelling of chromatin structure in Huntington's disease mice.
Nat. Commun**.** 2021 Jan 13;12(1):364. doi: 10.1038/s41467-020-20605-2.