Unité Biosciences et BioinGénierie pour la santE (BGE), UA13 Inserm-CEA-UGA

PhD project offer at CEA Grenoble: *Study of the links between the dysregulations of metabolism and epigenetics marks in Huntington's disease*

Project summary

Huntington's disease (HD) is a genetic neurodegenerative disease characterized by a triad of motor, cognitive and psychiatric symptoms usually starting during adulthood, and resulting from primary degeneration of the striatal neurons. Increasing evidence indicates that striatal neurons undergo molecular and cellular changes decades before the onset of symptoms. Altered energy metabolism and epigenetic regulation count among mechanisms early impaired in HD striatal neurons, which might be causally linked to the pathogenesis.

We want to focus on epigenetic dysregulation in HD, to better understand the pathogenic mechanism implicated in accelerated aging of striatal neurons. Specifically, we will investigate the interplay between altered energy metabolism and epigenetic impairment in HD striatal neurons to identify new targets/pathways for disease-modifying intervention. We aim to obtain detailed maps of histone post-translational modifications (PTMs), especially of methylations, acetylation and the recently described lactylation, which might be critical in the HD brain. Indeed, these PTMs are tightly regulated by the metabolic status of the cells. We will use proteomics which is the best suited approach to identify and quantify multiple protein PTMs. We consider working on the striatum of WT, R6/1 transgenic mice and the more progressive Q140 knock in model at various stages of disease, to assess evolution of histone PTMs and metabolism with aging. Additionally, to get a dynamic view of the links between metabolic and epigenetic imbalance in HD, we will inject intraperitoneally HD mice and controls with ^{13}C-glucose and analyze over a time course the incorporation of ^{13}C into histone PTMs. Finally, acetyl-CoA, the precursor for histone lysine acetylation, has been shown to be locally produced in the nucleus, by either acetyl-CoA synthetase 2 (ACSS2), ATP-citrate lyase (ACLY) or the pyruvate dehydrogenase complex. Regarding lactylation, it is currently unknown where, and by which enzymes, the pool of lactate used for modifying histone lysines by lactylation is produced. ACSS2 is a very good candidate, as it can catalyze the production of acyl-CoA molecules from the corresponding short chain fatty acids (SCFA). To address the question of the production of metabolites in the vicinity of chromatin in striatal cells, we will use epigenomics (ChIPseq or CUT&tag) to get the genomic distribution of ACSS2 and ACLY and compare it to distributions of acetyl and lactyl histone marks.

Direction of the PhD : Delphine Pflieger (team EDyP - Studying the Dynamics of Proteomes, Lab Biosciences and Bioengineering for Health, BGE UA13, CEA Grenoble) and Karine Merienne (*Laboratoire Neurosciences Cognitives et Adaptatives, UMR7364 CNRS/Strasbourg University, Strasbourg)*
Location: primarily team EDyP, Grenoble
PhD Funding: Association Huntington France, for 3 years
Contract start date: November 2024
Websites: https://www.edyp.fr/web/2019/10/22/integrative-omics/ ;
https://www.lnca.cnrs.fr/epigenetic-modulation-of-neurodegenerative-process/

To apply: please send to Delphine Pflieger (delphine.pflieger@cea.fr) a CV, a motivation letter and a letter of recommendation from one or two internship supervisors.

Relevant references

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