2023-12-19

International PhD Program IC-PhD

PhD thesis project

2024 Call for application

Characterization of alternative splicing programs associated with developmental origins of medulloblastoma

General information

Call	2024
Reference	2024-12-SAULNIER_AYRAULT
Keyword(s)	Cancer Genomics; Pediatric Oncology; Alternative Splicing; Transcriptomics; Cerebellar Development

Director(s) and team

Thesis director(s)	Olivier Saulnier & Olivier Ayrault
Research team	Genomics and Development of Childhood Cancers
Research department	U830 - Cancer, Heterogeneity, Instability and Plasticity - CHIP

Description of the PhD thesis project

Abstract

Medulloblastoma is a highly malignant tumor and the most common brain cancer in children. Current treatments for childhood cancers often lead to lifelong adverse effects, and understanding the distinct mechanisms underlying these cancers is crucial. Unlike adult cancers, pediatric cancers have a lower mutational burden and are thought to arise from disruptions in normal human development. This project aims to explore the role of alternative splicing in the developmental origins of medulloblastoma. In this study, we propose to comprehensively study the splicing landscape of medulloblastoma subgroups. We will also use RNAseq from normal human hindbrain, the tissue of origin of medulloblastoma, to determine the splicing dynamics in a physiological context in order to understand why cancer cells fail to differentiate at the post-transcriptional level. We are also interested to explore splicing defects caused by U1 mutations in adults SHH subgroup, specifically in generating neoantigens. Finally, we will examine the role of hijacked/amplified transcription factors on alternative splicing processes. This research program will propose a new model in which post-transcriptional programs regulate cell fate decision and their role in the developmental origins of medulloblastoma. It will help us to better understand splicing aberrations in medulloblastoma and potentially propose new therapeutic strategies to treat these deadly cancers.

Background

Medulloblastoma (MB) is a highly malignant embryonal brain tumor predominantly affecting children and adolescents. Over the years, genomics have transformed our understanding of this complex disease, leading to its subclassification into distinct molecular subgroups. This classification is not only crucial for prognostic and therapeutic purposes but also sheds light on the developmental origins of this deadly cancer. Medulloblastoma can be broadly categorized into four molecular subgroups: WNT, Sonic Hedgehog (SHH),

Group 3, and Group 4. These subgroups exhibit profound differences in their genetic alterations, gene expression profiles, clinical characteristics, and, most notably, their cell of origin. Each subgroup is thought to originate from distinct cells within the cerebellum and understanding these distinct diseases is crucial for tailoring precise treatment strategies. The WNT subgroup is believed to emanate from the lower rhombiclip (RL) in the developing cerebellum, a critical region for early cerebellar development. In contrast, the SHH subgroup is associated with cells derived from the external granule layer (EGL), a transient structure in the developing cerebellum responsible for the production of granule neuron precursors. The Group 3 and Group 4 MB subgroups appear to arise from the rhombic-lip (RL), which produces 80% of all the neurons in our entire brain. Recently it has been shown that the RL splits into two zones: a ventral stem cell zone (RL^{VZ}) and a dorsal progenitor cell zone (RL^{SVZ}) and that this split is specific to humans (and not observed in the RL of mice or macaques). We, and others, have identified that Group 3 MB have its roots in stem cell residing within the rhombic-lip ventricular zone (RL^{VZ}), while Group 4 MB is composed of undifferentiated cells from the rhombic lip subventricular zone (RL^{SVZ}). These distinct cellular origins provide important insights into the developmental processes that are dysregulated and providing potential therapeutic targets. However, these studies do not consider the role of post-transcriptional mechanisms, such as alternative splicing of mRNAs, as a determinant of cell fate decisions and MB oncogenesis.

Objectives

We hypothesize that the identification of splicing defects in Medulloblastoma will lead to uncover post-transcriptional processes altered in MB and will provide key insight into essential biological differences between the normal human hindbrain development and oncogenesis of this deadly cancer. To identify aberrant splicing in MB, we will investigate splicing dynamics occurring during cell differentiation of the tissue of origin and compare it with aberrant splicing events found in MB. This research proposal will address key questions that have not been answered so far: What are the splicing dynamics occurring in the normal murine and human cerebellum development? How aberrant splicing in MB recapitulates the developmental origins of these tumors? What are the consequences of the U1 mutations into the splicing landscape of SHH tumors? Do they produce neoantigens? How master transcription factors hijacked/amplified in MB contributes to alternative splicing landscape?

Recent publications

1. Hendrikse LD*, Haldipur P*, **Saulnier O***, …, Taylor MD*. Failure of human rhombic lip differentiation underlies medulloblastoma formation. Nature 2022

2. Vibert J*, **Saulnier O***, …, Waterfall JJ*, Delattre O*. Oncogenic chimeric transcription factors drive tumor-specific transcription, processing, and translation of silent genomic regions. Molecular Cell 2022

3. **Saulnier O***, Guerdi-Idjouadiene K*, …, Dutertre M*, Delattre O*, Dequiedt F*. ERG transcription factors have a splicing regulatory function involving RBFOX2 that is altered in the EWS-FLI1 oncogenic fusion. Nucleic Acids Research 2021

4. Jasmin Bartl, Marco Zanini, Flavia Bernardi, …, **Olivier Ayrault***, Marc Remke. The HHIP-AS1 lncRNA promotes tumorigenicity through stabilization of dynein complex 1 in human SHH-driven tumors. Nature Communications 2022

5. Daniel Rickert, Jasmin Bartl, … , **Olivier Ayrault***, Marc Remke. Circular RNA profiling distinguishes medulloblastoma groups and shows aberrant RMST overexpression in WNT medulloblastoma. Acta Neuropathologica 2021

Expected profile of the candidate

Scientific skills: should have **solid computational skills**, and a strong interest in cancer biology, genomics and/or developmental biology

Professional experience desirable: experience with NGS (RNAseq)

Language skills: very good English level and communication skills

Abilities: Ability to work independently, to communicate and to work in a team. The candidate should be highly motivated, curious, and enthusiastic to work in a collaborative team