PASTEUR PARIS UNIVERSITE (PPU) INTERNATIONAL DOCTORAL PROGRAM 2020

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PROJECT

- **FILE #10**
- **ACRONYM:** TransDeath
- **TITLE:** Programmed Cell Death of transient neurons in normal and pathological development of cortical circuits

LABORATORY

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LABORATORY PRESENTATION AND RESEARCH TOPICS

- **SUPERVISOR HDR:** Alessandra Pierani, alessandra.pierani@inserm.fr

- **SPECIFY THE TEAM NAME:** Genetic and Development of Cerebral Cortex

- **WEBSITE OF THE TEAM:** http://www.institutimagine.org/en/research/259

DESCRIPTION OF THE PROPOSED PROJECT

- **KEYWORDS:** programmed cell death, transient neurons, cerebral cortex, development, epilepsy

ABSTRACT

Abnormal brain development participates to the etiology of neurological and psychiatric disorders including epilepsy and schizophrenia (SCZ). While cellular processes like neurogenesis, migration, synaptogenesis or myelination are recognized building bricks for circuit formation, an emerging player is programmed cell death (PCD)1. Indeed, proper cortical development also depends on the action of cell types, in particular Cajal-Retzius (CRs), subplate and cortical plate transient (CPTs) neurons, that stay transiently during the construction of neural circuits and completely disappear shortly after birth in mice. The persistence of CRs and SPs in adults is detected in epilepsy and SCZ. However, whether and how alterations of transient neurons development and PCD might represent a shared mechanism in the aetiology of neurodevelopmental disorders remain unknown.

Our proposal aims at deciphering the role and molecular mechanisms of transient cells PCD in the construction of cortical circuits in normal development and pathological conditions.

DESCRIPTION OF THE PROJECT

Abnormal brain development participates to the pathophysiology of multiple neurodevelopmental disorders. Neurogenesis, migration, synaptogenesis or myelination are recognized building bricks for circuit formation. Programmed cell death (PCD) is also emerging as a key player in the wiring of cortical circuits. In the developing cerebral cortex, 20-30% of neurons are overproduced and eliminated by PCD. However, only three populations of neurons are present during the construction of neural circuits and completely disappear shortly after birth in mice, namely Cajal-Retzius (CRs) (which come in 3 distinct subtypes), Cortical Plate Transient (CPTs) and Subplate (SPs) neurons. CRs are among the first born cortical neurons and reside in the most superficial layer of the developing cerebral cortex from where they coordinate multiple crucial steps in the construction of functional circuits including neuronal migration, dendritic arborization and synaptogenesis. CRs completely

undergo programmed cell death at the end of brain maturation in mice. Persistence of CRs during postnatal life has been detected in pathological conditions such as Temporal Lobe Epilepsy, Ammon's horn sclerosis, polymicrogyria and focal cortical dysplasia, and that of SPs in pharmaco-resistant epilepsy, thereby opening the intriguing possibility that the lack of disappearance of transient cell populations contributes to epilepsies.

Recent work from our laboratory have shown that although all CR subtypes undergo cell death they do so at least through two molecularly distinct pathways. We produced the first mouse model in which one CR subtype survives to adulthood (Ledonne et al., Cell Reports 2016). These animals display neuronal hypertrophy and imbalanced excitatory/inhibitory (E/I) ratio leading to dysfunctional cortical circuits (Riva et al., Elife 2019) and behavior in addition to increase susceptibility to epileptic seizures (Riva et al. in preparation). However, it remains to be determined which pathway mediates the other CR subtypes demise and the relevance of this demise in the construction of functional and dysfunctional cortical circuits. Further, how abnormally persistent CR affect the maturation of cortical networks remains unclear.
The aim of the PhD project is to investigate new molecular pathways involved in CR subtype-specific PCD during post-natal development. We will perform an unbiased approach using FACS purification and single-cell transcriptomic analysis of genetically labeled CRs at different post-natal stages. Then functional studies will be done on the potential candidate genes involved in PCD to study their biological effects on CRs survival using mouse genetics and in vitro assays. In parallel, since recent data in the laboratory already established a link between PCD and neuronal excitability (Riva et al., 2019), we will also examine how cortical network activity and two molecular pathways already identified in the lab. mediate CR subtype-specific death. Finally, we will study the relevance of aberrant migration/distribution and survival of transient neurons (CRs and CPTs) to pathological conditions by the analysis of pathological human tissues. The proposed project will be achieved through a multidisciplinary approach combining mouse genetics, single-cell transcriptomics, pharmacological manipulation in embryos, cell culture, electrophysiology and behavioral phenotyping in addition to studies on human tissues and molecular genetics.

This project will provide new mouse models for cortical abnormalities and contribute to the understanding of whether and how altered PCD might represent a shared mechanism in the etiology of neurodevelopmental disorders, in particular epilepsy.

- **REFERENCES**

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Underligned publications were signed as corresponding author; # : equal contribution, * reviews

EXPECTED PROFILE OF THE CANDIDATE

- **EXPERIENCE REQUIRED**
  Knowledge on brain development.