2023-12-20

International PhD Program IC-PhD

PhD thesis project

2024 Call for application

Mechanisms controlling stemness, epithelium-to-mesenchyme transition and genomic stability in neural crest cell development and melanoma

General information

Call	2024
Reference	2024-07-MONSORO-BURQ_BARDOT
Keyword(s)	Epithelial-to-mesenchymal transition; neural crest; melanoma; metastasis; single cell spatial transcriptomics

Director(s) and team

Thesis director(s)	Anne-Hélène Monsoro-Burq & Boris Bardot
Research team	Signaling and Neural Crest Development
Research department	UMR3347 / U1021 - Signaling, radiobiology and cancer

Description of the PhD thesis project

Abstract

Neural crest cells (NCC) are a transient stem-like population of cells that are induced as an epithelial cell type, and that subsequently undergo an epithelium-to-mesenchymal transition (EMT) to migrate away from their source, invade the developing embryo, colonize various locations, and differentiate into diverse cell types such as melanocytes, peripheral sensory neurons, or cells of the craniofacial skeleton. Our recent single cell (SC) transcriptomic analysis in Xenopus embryos point at specific gene co-expressions at the individual cell level to control these processes and uncovers micro-heterogeneities in otherwise similar cells. These micro-heterogeneities could prefigure patterning transitions or cell behaviors such as EMT and cell migration. They also suggest that migrating NCC results from the selection of cells able to maintain both their differentiation potential and their genomic integrity. This Ph.D. project will test this hypothesis by establishing a temporal single cell map of co-expression of genes involved in these processes using spatial transcriptomics (Aim 1) and by genetic perturbations in Xenopus embryos (Aim 2). Relevance of our discoveries to human melanoma metastasis will be tested on a zebrafish xenograft model (Aim 3). It will be conducted at Curie Institute with secondments and co-supervision of academic (USA) and industrial (France) supervisors.

Background

Our team "Signaling and Neural Crest Development" deciphers the gene regulatory network controlling neural crest formation, an essential embryonic cell population with stem cell properties and highly migratory capacities (Dev. Cell 2005, PNAS 2013, PLOS Biol 2017, Cell Reports 2021…). Cell emigration is an essential behavior to shape embryos during development and the initial step for cancer metastasis in adults. The molecular mechanisms involved in the acquisition of cell motility and cell ability to leave its epithelium of

origin (by EMT), are conserved in evolution and between embryos and adults (Science Advances 2020, Life Science Alliance 2022…). Recently, we have described gene programs in single cells predicted to preside to fate choices in the developing ectoderm and activate EMT and migration programs (BioRxiv 2022, in revision). These new data open the possibility to understand the control of cell migration at an unprecedented resolution and identify possible stochastic mechanisms, gene combinations and other parameters controlling cell migration in embryos. In cancer, activating or blocking these new programs will be tested on melanoma metastasis in vivo using a patented new model of human cell migration in zebrafish larvae. We thus have gathered an international and intersectoral team dedicated to development of novel strategies to describe, manipulate, and explore the molecular dynamics of gene expression in vivo in cell EMT and migration.

Objectives

This Ph.D. project is fully integrated in the team's larger project and benefits from preliminary data and well-established approaches mastered by the team or the collaborators. This project will focus specifically on a key patterning branching event defined from our recent single cell (SC) analyses, identifying an important cell state transition in neural crest cells, and potentially driving their highly invasive character (they massively populate long-distance tissues forming our vertebrate head). This program involves several neural crest derivatives (pigment, neurons, bone...), and the interplay between fate choices, migratory behaviors and genomic stability will be explored. The first objective will establish the spatial molecular map of gene co-expressions at SC level, by integrating a highly structured team steered by our group (funded ANR project), which establishes spatial transcriptomics to detect multiple gene co-expressions during early development. This map will reveal the spatial organization of the cells undergoing fate and behavior decisions, driving hypotheses for experimental perturbations in vivo. Second objective will use experimental embryology tools to understand the logic of these regulations in the controlled context of embryonic EMT. Third objective will use human melanoma cell lines well characterized in the team to evaluate if the identified gene co-expressions are reactivated in those cells and if they are involved in cell invasiveness in vivo.

Experimental approaches

- Obj. 1: Spatial validation of the gene co-expressions predicted to be critical will use the best spatial transcriptomic approach optimized for our samples (techniques recently established in the team, Hybridization Chain Reaction and Merscope).
- Obj. 2: Uses the team's long-standing expertise in building gene-regulatory networks in vivo, based on perturbing/rescuing gene expressions in a targeted manner in Xenopus laevis embryos, a model respecting ethics rules (3R) and ideal to study early development (e.g. morpholino or Crispr-based multiplexed gene depletions, in vivo micro-grafting, metabolic and biochemical assays adapted to embryonic tissues, organoid model of neural crest induction).
- Obj. 3: Uses the patented zebrafish model of our collaborators (Azelead, France) to challenge human metastatic melanoma cells invasiveness when the new regulators of cell migration are disrupted. This approach involves high content in vivo advanced imaging.

International, interdisciplinary & intersectoral aspects of the project

International co-supervision by Prof. Leon Peshkin, Harvard Medical School, Systems Biology Department, with whom we have a long-standing collaboration (article on single cell transcriptomics in developing neural crest currently in revision, second article being written). The PhD student will visit for one month secondment and do analysis of SC data.

Collaboration and secondment at industrial (SME) partner (Azelead, Montpellier, France) who has a patented model of in vivo metastasis for melanoma cells in zebrafish. We have an on-going collaboration with them

and two current collaborations with current PhD students in the lab. PhD candidate will do two one-month secondments in the industrial partner.

PhD student will be trained in Biology (in vivo and in vitro cell and developmental biology), in advanced imaging (in vivo spatial transcriptomics and cell migration) and in bioinformatics and statistics. Moreover, advanced imaging analysis will involve collaboration with mathematicians for quantitative analysis.

Recent publications

1. Fajac et al., BioRXiv https://doi.org/10.1101/2023.10.13.562180

2. Kotov et al., BioRXiv https://doi.org/10.1101/2022

3. Sittewelle M, Kappès V, Zhou C, Lécuyer D, **Monsoro-Burq AH***. PFKFB4 interacts with ICMT and activates RAS/AKT signaling-dependent cell migration in melanoma. Life Sci Alliance 2022, PMID: 35914811.

4. Alkobtawi M, Pla P, **Monsoro-Burq AH***. BMP signaling is enhanced intracellularly by FHL3 controlling WNT-dependent spatiotemporal emergence of the neural crest. Cell Rep. 2021, PMID: 34161771.

5. Scerbo P-L and **Monsoro-Burq A**.* The vertebrate-specific VENTX/NANOG gene empowers neural crest with ectomesenchyme potential. Science Advances 2020; 6: eaaz1469 29

Expected profile of the candidate

Candidates will demonstrate:

- An excellent academic background, including cell biology, molecular biology, genetics and epigenetics, with theoretical and practical training.
- A background in stem cell and developmental biology, in advanced microscopy, or bioinformatics will be a plus.
- At least one long laboratory internship, and practical experience in cell biology, molecular biology or biochemistry.
- The candidate will demonstrate a strong motivation for the field, supported by previous experience. Letters of recommendation from previous supervisors or professors will be requested.