MASTER 2 BMC
PARCOURS GENOPATH
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Titre du sujet de stage :

Lineage reprogramming of cell identity within the brain: Unravelling the molecular mechanisms

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Sujet de stage :

Direct lineage reprogramming of cell identity has emerged as a concept for the restoration of organs with limited regenerative capacity. Lineage reprogramming consists of assigning a new cell identity to terminally differentiated somatic cells without going through a pluripotent state. Typically, successful cell-fate conversion can be achieved by forced expression of lineage-specific transcription factors. Lineage reprogramming carries great potential for applicability in vivo thereby allowing regeneration of lost cells which has profound implications for regenerative medicine.

The adult mammalian central nervous system lacks intrinsic regenerative capacity to replace lost neurons and induce functional recovery following injury/diseases. A promising approach towards brain repair is to instruct fate conversion of brain-resident non-neuronal cells (such as glial cells) into induced neurons by direct lineage reprogramming (Heinrich et al, Nat Cell Biol, 2015; Vignoles et al, Trends Mol Med, 2019). We and others have previously shown that glial cells can be efficiently converted into functional induced neurons of various

phenotypes both in vitro and in vivo (Heinrich et al, PLoS Biol 2010, Nat Protoc 2011, Stem Cell Reports 2014; Gascon et al, Cell Stem Cell, 2016). Notably, we have recently shown in the context of drug-resistant epilepsy that reactive glial cells can be converted into inhibitory neurons (typically lost in epilepsy) that integrate within epileptic networks and are capable of reducing chronic seizure activity (Lentini et al, Cell Stem Cell, 2021). Thus, our data uncovered glia-to-neuron reprogramming as a potential disease-modifying strategy to reduce seizures in therapy-resistant epilepsy.

It is now a fundamental question to unravel how reprogramming transcription factors impose on glial cells a new molecular program reassigning the novel neuronal identity. The aim of this project is to decipher the molecular mechanisms and the transcriptional alterations underlying glia reprogramming into inhibitory neurons. During his/her internship, the Master student will join forces to study these questions using techniques such as cell culture, immunostaining (culture and brain sections), confocal microscopy, pharmacological manipulations, time-lapse video microscopy and analysis of single-cell RNA sequencing datasets.

The knowledge gained within this project will contribute to further decipher the molecular mechanisms underlying glia-to-neuron reprogramming. A better understanding of this process is crucial to design innovative future therapeutic strategies to replace lost neurons in the injured brain.

Technologies utilisées :

cell culture, immunostaining (culture and brain sections), confocal microscopy, pharmacological manipulations, time-lapse video microscopy and analysis of single-cell RNA sequencing datasets

Mots clés :

Direct lineage reprogramming
Brain repair
Gia-to-neuron conversion
Regenerative medicine

Publications d'intérêt :

Lentini C, d'Orange M, Marichal N, Trottmann MM, Vignoles R, Foucault L, Verrier C, Massera C, Raineteau O, Conzelmann KK, Rival-Gervier S, Depaulis A, Berninger B, and **Heinrich C**. Reprogramming reactive glia into interneurons reduces chronic seizure activity in a mouse model of mesial temporal lobe epilepsy.
Cell Stem Cell, 2021, 28(12):2104-2121.e10 (5-year IF: 27.8)

Vignoles R, Lentini C, d'Orange M, and **Heinrich C**. Direct Lineage Reprogramming for Brain Repair: Breakthroughs and Challenges.
Trends in Molecular Medicine, **2019,** 25 (10): 897-914 (5-year IF: 15.6)

Heinrich C, Spagnoli F and Berninger B. In vivo reprogramming for tissue repair.
Nature Cell Biology, **2015**, 17 (3): 204-211 (5-year IF: 28.1)

Heinrich C, Blum R, Gascon S, Masserdotti G, Tripathi P, Sanchez R, Tiedt S, Schroeder T, Götz M and Berninger B. Directing astroglia from the cerebral cortex into subtype specific functional neurons.
PLoS Biology, **2010**, 8 (5): e1000373 (5-year IF: 10.5)