PhD Project Michalakis (epigenetics, neuroscience, bioinformatics)
Role of TET-mediated 5mC oxidation for neuronal differentiation and plasticity

Scientific background. Neuronal networks show a remarkable degree of plasticity during physiological and pathophysiological processes. This plasticity goes along with major adjustments in the expression of key genes. The mechanisms controlling gene expression and neuronal plasticity are not well understood, but it is suggested that epigenetic mechanisms such as DNA methylation contribute crucially to these biological processes. Methylation of the DNA base cytosine is catalyzed by DNA methyltransferases (DNMT) and occurs at the C-5 position of the cytosine base resulting in 5-methylcytosine (5mC). Removal of the methyl group involves oxidation by TET methylcytosine dioxygenases. The overarching goal of this project is to help improving our understanding on how TET enzymes and 5mC oxidation products shape the epigenome of neurons and influence CNS function.

Specific aims and methodology. The functional role of TET enzymes in mouse brain and retina has not been fully investigated, and it will be addressed in this project. Using a combination of in vivo and in vitro models (2D neuronal cultures and 3D retinal organoids) we aim at elucidating the role of TET enzymes and their enzymatic products in neuronal differentiation and maturation. The expression level of TET3 enzyme will be manipulated using a variety of techniques in the above-mentioned models, and the effects will be analysed by the student in this project. TET enzymes act in concert with chromatin remodeling proteins and transcription factors. We identified intriguing novel TET interaction partners in mouse retina, mouse brain and/or induced pluripotent stem cell (iPSC)-derived neurons. The potential of these proteins, as well as the identification of novel interactors, to engage with the TET3 isoform and modulate its enzymatic activity will be assessed in this proposal. We are looking for a highly motivated PhD candidate with bioinformatic, genetic and epigenetic background and strong interest in neuroscience. The candidate will apply bioinformatic methods and will also have the chance to learn and apply genetic, biochemical, molecular and viral gene transfer methods in vitro and in vivo.

Further information and selected literature.

https://www.gsn.uni-muenchen.de/people/faculty/associate/michalakis/index.html

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