Master de Sciences et Technologies
Mention Biologie Intégrative et Physiologie
Parcours : Neurosciences
Responsable : Professeur Régis Lambert

Internship Proposal
Academic Year 2019-2020

1. Host team :

Research Unit (e.g. Department or Institute): Center for Interdisciplinary Research in Biology
Research Unit Director : MH Verlhac
Research Team Director : N Rouach
Team name : Neuroglial Interactions in Cerebral Physiopathology

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2. Internship project title: Gliomas: effects on the oncometabolite D2HG on glutamatergic signaling.

3. Internship Description:

Gliomas are brain primary tumors with variable growth and epilepsy potencies. Approximately 80% of low-grade gliomas have a mutation in the enzyme Isocitrate DesHydogenase (IDH) and are then associated with increased survival and a higher prevalence of epilepsy. Among various effects, IDH mutations result in the overproduction of D2 HydroxyGlutarate (D2HG) which is released by glioma cells, accumulates extracellularly and acts as an oncometabolite. D2HG structure is close to glutamate, suggesting it may affect glutamatergic signaling. Our team has already shown that in vitro, D2HG has paradoxical anti-epileptic effects, especially in human tissues obtained from patients surgically treated for gliomas. Studies in HEK cells expressing AMPA and NMDA receptors have shown that high concentrations of D2HG had agonistic effects on AMPA and NMDA glutamatergic receptors. However, when co-applied with glutamate, D2HG was rather antagonist. D2HG therefore seems to have a weak glutamatergic agonist effect, becoming, in the presence of glutamate, a competitive antagonist, in particular for AMPA glutamate receptors.

These data are consistent with the positive effects of IDH mutations on survival, glutamate being released by glioma cells and acting as a growth promoter on the same cells witch express glutamate receptors. In peritumoral tissues, the effects of D2HG on neuronal activities, including epileptic discharge, will depend on the glutamate / D2HG local balance.

This M2 project aims to explore deeper the effects of D2HG on glutamatergic AMPA and NMDA signaling and its effects on neuronal excitability. The study will be performed directly on postoperative human cortical tissues. Electrophysiological (extracellular recording by MultiElectrodeArray) recordings will allow testing the effects of co-applications of D2HG and

glutamate mimicking those measured in patients in vivo. The effects of D2HG on glutamatergic signaling will be assessed by patch clamp-recording in order to calculate IC50 both for AMPA and NMDA receptors in human tissue slices.