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Laboratory: Inserm UMR 1034, Biology of cardiovascular diseases, Pessac/University of Bordeaux
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Title: **Dll4 at the Glia Limitans, a key player of neuro-inflammation pathophysiology**

Context

Neuronal cell loss, defined as neurodegeneration, is the major cause underlying behavioral and psychological abnormalities, notably in multiple sclerosis and dementia. It represents a major public health issue as life expectancy increases. One common feature of neurodegeneration is vascular impairment: the Central Nervous System (CNS) vasculature represents a physical blood brain barrier (BBB) which separates blood components from the parenchyma. However, during neuropathology, two interconnected and interdependent processes are observed: BBB breakdown leading to parenchymal inflammatory infiltration and abnormal angiogenesis. Increased angiogenesis is a common feature of several neurological conditions, notably multiple sclerosis where angiogenesis contribute antagonistically to disease progression and remission after relapse.

Importantly, a wealth of literature has recently enabled a change in the vision of the BBB structure and integrity which has expanded to include contributions from all components of the neurovascular unit, among which endothelial cells, pericytes, microglia and astrocyte endfeet (Glia Limitans). Strikingly, our group just published a paper highlighting the capacity for bidirectional signaling between endothelial cells and astrocytes from the neurovascular unit; however, how these signals participate to cerebrovascular impairment, notably BBB dysfunction and neuro-inflammation remains unclear and is of considerable translational interest to the field of neuro-immunology.

Literature showed that, during neuropathology, astrocytes described as reactive, on one hand produce pro-inflammatory and pro-permeability factors and on the other hand, neuro-protective factors. Interestingly, we recently identified delta-like 4 (Dll4) as highly expressed by reactive astrocytes during neuro-inflammation. Dll4 is primarily known to play a role in the regulation of angiogenesis via the Dll4-mediated Notch signaling but it also controls the CD4+/CD8+, Th17/Treg balance during neuro-inflammation.

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Objective of the Thesis

The fundamental aim of our project is to unravel the contribution of Dll4-Notch signaling at the Glia Limitans to neuro-inflammatory disease progression. Our hypothesis is that astrocytes communicate with neighboring cells from the neurovascular unit during neuropathology to regulate (1) angiogenesis at the BBB through juxtacrine communication between astrocyte endfeet and mural cells and (2) T-cell behavior within the CNS through juxtacrine communication between astrocyte endfeet and immune T-cells. The project is built around 3 objectives:

(A) To identify Dll4 critical effect on BBB angiogenesis and immune T-cell parenchymal infiltration in condition of multiple sclerosis.
(B) To explore Notch signalling in cells responding to astrocyte Dll4 during neuro-inflammation.
(C) To explore Dll4 signalling blockage as a pre-clinical tool for therapeutic strategy in condition of multiple sclerosis.

Methodology

The project relies on a novel mouse model knocking down Dll4 specifically in astrocytes, on human multiple sclerosis cortical lesion samples and on primary human cell co-culture models. The methodology associates classic neurovascular and molecular biology to more challenging technics such as neurovascular unit isolation, RNA sequencing, live imaging and light sheet microscopy to analyze angiogenesis and lymphocyte infiltration, as well as Doppler and angiography to measure brain and retina vascular function.

Qualification requirements

The applicant is expected to hold or soon to complete a Master degree in Cell biology or Neurobiology (To be classified in the first half of the class is highly recommended).
Only serious and highly motivated students are encouraged to apply.
Experience in mouse handling, imaging, cell culture, cell transfection/transduction, western blot and RT-qPCR is recommended.

References from the group:

Mora, P., Hollier, P.L., Guimbal S., Abelanet, A., Diop, A., Cornuault, L., Couffinhal, T., Horng, S., Gadeau, A.P., Renault, M.A., **Chapouly, C**. (2020) "Blood brain barrier genetic disruption leads to protective barrier formation at the Glia Limitans." Plos Biology.

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