Proposition de sujet de thèse à l’appui d’une demande de contrat doctoral 2016-2017

Renseignements relatifs à l'Unité de Recherche :
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Titre du sujet proposé :
Effets combinés des mutations génétiques et de l’inflammation neurale sur la pathophysiologie des troubles du spectre autistique

Combinatorial effects of genetic background and neuroinflammation in the pathophysiology of autism spectrum disorders

Département (cocher le département correspondant au sujet de thèse qui n’est pas obligatoirement le vôtre) :

- Biologie Cellulaire et moléculaire, Physiologie et Physiopathologie
- Immunologie
- Développement Génétique Neurobiologie et Vieillissement
- Infectiologie, Microbiologie

Summary (5 lines maximum) :

Autism spectrum disorders (ASDs) manifest early in childhood. Their causes may be either environmental, with a major impact of inflammation, or genetic. Despite observations that these causes do not exist in isolation, models combining the two are still lacking. Here, we will develop ASD model animals to understand neuroinflammation-induced neuronal defects and causes of ASD by unravelling, for the first time, the links between an environmental perturbation, peri-and post-natal inflammation, with strong clinical relevance to human disease.
Proposition de sujet de thèse à l'appui d'une demande de contrat doctoral 2016-2017

Nom, prénom du directeur de l'unité de recherche : GRESSSENS Pierre, MD, PhD
Numéro de l'unité de recherche (et établissement de rattachement) : UMR1141 Inserm/Paris Diderot
Nom, prénom du responsable de l'équipe d'accueil (EAD) : BAUD Olivier, MD, PhD
Nom, prénom du directeur de thèse : DOURNAUD Pascal, PhD

Titre du sujet de thèse proposé : **Combinatorial effects of genetic background and neuroinflammation in the pathophysiology of autism spectrum disorders**

key words : neuroinflammation ; autism ; microglia ; gene-inflammation interaction ; prematurity

Candidat pressenti : ☒ OUI ☐ NON

Contenu scientifique du programme de la thèse (en anglais)

Epidemiological studies showed that genetic background and inflammation contribute to the ontogeny of neurodevelopmental disorders including autism spectrum disorders (ASD). Despite of these observations, there is a lack in literature of data collected from models combining both of these factors. A general consensus regarding neurodevelopmental disorders including ASDs is that they originate from early development defects in brain formation, leading to altered neuronal circuitry responsible for the pathological behavior. Despite studies on genetic implication in ASDs, a causal relationship between genomic alteration and ASD has been difficult to explain in many cases, suggesting environmental factors might be involved. In fact, preterm birth is often linked to the occurrence of inflammation and preterm infants have a ten times higher risk of developing ADS-like symptoms than infants born at term. Moreover, some clinical studies reported ongoing neuroinflammation processes in different brain regions in autistic infants. The major relay of the environmental response in the brain, including inflammatory responses, is microglia cells (MG), the brain resident macrophages that continuously survey their local environment. In an inflammatory context, MG are activated and participated to the local release of pro-inflammatory cytokines. In adult functioning brain, MG contribute to synapse elimination and plasticity by the engulfment of pre- and post-synaptic components and also a fine-tune neurotransmission. Previously several genes have been reported as synaptic genes mutated in ASDs. Both gene mutations and neuroinflammation are associated with the occurrence of ASDs, however the concept of pure genetic or pure inflammatory-driven causes for neurodevelopmental disorders is unlikely to cover all individuals' presentations of ASDs. One hypothesis is, therefore, that the combination of susceptibility gene mutations with exposure to prenatal inflammation generates additive and/or synergistic effects that triggers or impacts on neurodevelopmental disorder symptoms.

Thus, this project aims to i) determine how postnatal inflammation primed by inflamed MG in mouse deregulates cortical function relevant to ASDs; ii) elucidate underlying molecular mechanisms; iii) study interactions between inflammation factors and ASDs specific susceptibility genes on synaptic dysfunctions and ASD-like behaviors caused by neuroinflammation and ASD separately. This innovative project has as objective to identify potential diagnosis markers to facilitate an early detection in premature infants based on inflammatory indicators and genetic background.

Indiquez les cinq meilleures publications récentes de l'équipe :


