Nantes Université

Offre de stage M2 Cursus Master/Doctorat
Ecole Universitaire de Recherche Sciences et Technologies de la Santé
et Master 2 Biologie et Médicaments
UE XMS2BU100&101 – (2 pages max.)

FORMATION CONCERNEE

☐GP Immunologie et Immuno-Intervention (I^3)
☐GP Oncologie, Hématologie et Médecine Nucléaire (OHNU)
☒**GP Microbiote, Intestin, Cerveau, Alimentation, Santé (MICAS)**
☐GP Innovation for CArdiovascular, metabolic and REspiratory diseases (InnoCARE)
☐GP Médecine 4R, Réparer, Remplacer, Régénérer, Reprogrammer (M4R)

TITRE DU STAGE :

THE ENTERIC NITRERGIC PATHWAY, A TARGET OF MICROBIOTA EXTRACELLULAR VESICLES IN AUTISM-RELATED GASTROINTESTINAL DISORDERS

LABORATOIRE D'ACCUEIL :

INSERM UMR 1235 TENS - The Enteric Nervous System in Gut and Brain Disorders

EQUIPE D'ACCUEIL :

Axe 1 Neurodéveloppement

RESPONSABLE(S) SCIENTIFIQUE(S) ET ADRESSE(S) MAIL :

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TITRES ET TRAVAUX DE L'EQUIPE D'ACCUEIL (5 PUBLICATIONS LES PLUS SIGNIFICATIVES) :

- The regulation of enteric neuron connectivity by semaphorin 5a is affected by the autism-associated s956g missense mutation. LE DREAN ME, LE BERRE-SCOUL C, PAILLE V, **CAILLAUD M**, OULLIER T, GONZALES J, HULIN P, NEUNLIST M, TALON S, BOUDIN H. ISCIENCE. 2024
- A functional network of highly pure enteric neurons in a dish. **CAILLAUD M**, LE DREAN ME, DE-GUILHEM-DE-LATAILLADE A, LE BERRE-SCOUL C, MONTNACH J, NEDELLEC S, LOUSSOUARN G, PAILLE V, NEUNLIST M, BOUDIN H. FRONT NEUROSCI. 2023
- Fecal supernatant from adult with autism spectrum disorder alters digestive functions, intestinal epithelial barrier, and enteric nervous system. GONZALES J, MARCHIX J, AYMERIC L, LE BERRE-SCOUL C, ZOPPI J, BORDRON P, BUREL M, DAVIDOVIC L, RICHARD JR, GAMAN A, LEJUSTE F, BROUILLET JZ, LE VACON F, CHAFFRON S, LEBOYER M, BOUDIN H, NEUNLIST M. MICROORGANISMS. 2021

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RESUME DU PROJET PROPOSE ET TECHNIQUES ENVISAGEES (MAXIMUM 1 PAGE) :

Autism spectrum disorder (ASD) is a neurodevelopmental pathology with several comorbidities, including gastrointestinal disorders. Gastrointestinal disorders significantly affect the quality of life of these patients, and can exacerbate behavioral symptoms. Gastrointestinal disorders have been associated with intestinal dysbiosis, but remain poorly understood pathophysiologically. The transfer of microbiota from ASD patients to mice results in behavioral as well as digestive symptoms, apparently affecting the enteric nitrergic pathway. However, the mediators of communication between microbiota and gut are still largely unknown, but they could involve extracellular vesicles (EVs). EVs are signaling cargoes that mediate intercellular and inter-organ communication. Their potential role in microbiota-host interactions has never been studied in the context of ASD. The hypothesis is that fecal EVs (f-EVs), which contain EVs produced by the microbiota, are mediators between the microbiota and enteric neurons, targeting the nitrergic pathway and contributing to gastrointestinal disorders in autism.

We isolated f-EVs from the stool of controls and ASD patients and applied them to cultured rat enteric neurons. Their impact on neuronal activity, connectivity and the nitrergic pathway was assessed by Ca^{2+} imaging and protein expression/distribution respectively.

Our initial results show a significant difference in the size, number and metabolite composition of f-EV between the control and ASD patients. Then, acute treatment with f-EVs from ASD patients induced in enteric neurons an immediate increase of intracellular Ca^{2+} that was more sustained than with f-EVs from controls. After 48h of treatment, we found an increase in the number of PSD95 synaptic clusters in neurons treated with f-EVs from ASD patients compared to controls. PSD95 is a scaffolding protein involved in the recruitment of the neuronal nitric oxide synthase (nNOS), an enzyme responsible for nitric oxide (NO) production. Interestingly, an increase in nNOS expression and in the number of nNOS neurons was observed with f-EV from ASD patients, associated with an increase in NO production and nitrosative stress.

The aim of the internship will therefore be to confirm these results by analyzing nitrosative stress on enteric neuron cultures. In addition, to confirm the in vitro observations, an in vivo study will be envisaged. Animals will receive f-EV by gavage, and behavioral and digestive tests will be carried out. Finally, to investigate the potential effect of f-EVs on enteric nervous system remodeling, histological analyses will be performed on the intestines of treated mice.

TECHNIQUES ENVISAGEES :

CELL CULTURE (ENTERIC NEURONS), BIOCHEMISTRY (WESTERN BLOT) HISTOLOGY (IMMUNOFLUORESCENCE), CALCIUM IMAGING, DAF-FM IMAGING (NITRIC OXIDE PRODUCTION), BEHAVIORAL AND DIGESTIVE TESTS.

FAMILIARITY WITH ANIMALS AND A DIPLOMA IN ANIMAL EXPERIMENTATION IS HIGHLY DESIRABLE.