COLLEGE ED BIOLOGIE DOCTORAL SANTE PAYS DE LA LOIRE

Année 2022/2023

FICHE SUJET DE THESE

Sujet N° (à remplir par l'ED) :	**FINANCEMENT :** ☒ **Demandé** ☐ **Acquis**	**Origine du financement :**
Titre de la thèse : **Role of T cell / enteric glial cell interactions in the development of postoperative recurrence..**		3 mots-clés : Crohn Disease Enteric nervous system Neuro-immunology
Unité/équipe encadrante : **INSERM UMR1235, TENS**		
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Contexte socioéconomique et scientifique (env. 10 lignes)

Despite a large therapeutic arsenal, many patients with Crohn's disease (CD) require, after several years of treatment, surgical resection, and the risk of postoperative recurrence (POR) is high. One of the risk factors for early postoperative recurrence is the presence of myenteric plexitis at the level of the proximal resection margin. It is therefore important to understand the mechanisms underlying the formation of these plexites, which are characterized by an accumulation of immune cells in the nerve ganglia of the intestine. Advances have recently been made in this area since our laboratory revealed a selective increase in interactions between enteric glial cells (EGC) and T lymphocytes (LT) in patients with Crohn's disease (Pabois J et al. J Neuroimmunol 2020).

Hypothèses et questions posées (env. 8 lignes)

Our preliminary results show that in vitro interactions between EGCs and T lymphocytes of human or murine origin are favored by pro-inflammatory conditions and that these interactions involve the adhesion molecules ICAM-1/LFA-1. The involvement of ICAM-1/LFA-1 in CGE-T cell interactions has been confirmed in vivo in mice. It remains to characterize the impact of these interactions on the phenotype of EGCs and T cells in order to understand how plexitis can promote postoperative recurrence in Crohn's disease. In particular, we will study the impact of CGE-T cell interactions on the production of pro- or anti-inflammatory molecules by CGE as well as on the orientation of T cells.

Grandes étapes de la thèse (env. 12 lignes)

First, we will analyze the production of chemokines and cytokines in single cultures of CGE and murine CD4 T lymphocytes, which we will compare to their production in co-cultures carried out in direct contact or separated by a permeable membrane (Transwell). The impact of co-cultures on the orientation of CD4 T lymphocytes (Th1, Th17, Th22, Treg) will be studied thanks to the analysis of the expression of transcription factors and cytokines specific to the different phenotypes. The analyzes will be carried out by flow cytometry, ELISA, western blot or qPCR. Secondly, the results obtained on murine cells will be invalidated or confirmed on cultures prepared from T lymphocytes of human origin and EGCs from control patients or patients suffering from Crohn's disease. Depending on the results obtained on cultures of murine or human origin, we will study the most relevant regulatory mechanisms. The last step will be based on the analysis of transmural sections of the ileum from control patients or patients with Crohn's disease. In particular, we will search for and quantify the molecules and cellular subtypes of interest within myenteric plexitis in order to highlight the differences between control patients and Crohn's patients, but also between patients who have or have not relapsed after ileocolic resection. This work will provide a better understanding of the pathophysiological consequences of interactions between CGE and T cells, particularly in the case of Crohn's disease.

Compétences scientifiques et techniques requises par le candidat (2 lignes)

The candidate must have basic knowledge of the digestive nervous system and the immune system. From a technical point of view, he/she should have knowledge of immunohisto/cytochemistry, western blot, qPCR and flow cytometry techniques. Knowledge of cell culture methods of neural and immune cells is desirable.

Trois publications de l'équipe d'accueil relatives au domaine (cinq dernières années)

- Belarif L*, Danger R*, Kermarrec L*, Nerrière-Daguin V, Pengam S, Durand T, Mary C, Kerdreux E, Gauttier V, Kucik A, Thepenier V, Martin JC, Chang C, Rahman A, Guen NS-L, Braudeau C, Abidi A, David G, Malard F, Takoudju C, Martinet B, Gérard N, Neveu I, Neunlist M, Coron E, MacDonald TT, Desreumaux P, Mai H-L, Le Bas-Bernardet S, Mosnier J-F, Merad M, Josien R, Brouard S, Soulillou J-P, Blancho G, Bourreille A, Naveilhan P*, Vanhove B*, Poirier N*. 2019. IL-7 receptor influences anti-TNF responsiveness and T cell gut homing in inflammatory bowel disease. J Clin Invest 130. * equal contribution

- Pabois J, Durand T, Le Berre C, Gonzales J, Neunlist M, Bourreille A, Naveilhan P, Neveu I. 2020. T cells show preferential adhesion to enteric neural cells in culture and are close to neural cells in the myenteric ganglia of Crohn's patients. Journal of Neuroimmunology: 577422.

- Durand T, Paul-Gilloteaux P, Gora M, Laboudie L, Coron E, Neveu I, Neunlist M*, Naveilhan P*. 2023. Visualizing enteric nervous system activity through dye-free dynamic full-field optical coherence tomography. Commun Biol 6:236. * equal contribution

Collaborations nationales et internationales

Grégory Bouchaud, INRAE-BIA, Nantes, Fr ; Michalina Gora, Wyss center, Genève, Ch ; Kulmira Nurgali, Victoria University, Melbourne, Au.