SORBONNE UNIVERSITÉ

CHINA SCHOLARSHIP COUNCIL

Appel à projets
Campagne 2022
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Title of the research project :

Competition between intestinal bacteria: mechanisms, roles and therapeutic pote

Thesis supervisor (HDR) :

Name : ROLHION Surname : Nathalie

Title : doctor in microbiology, CRCN INSERM

email : nathalie.rolhion@inserm.fr

Professional adress :
(site, dresse, bulding, office…)
entre de Recherche de Saint-Antoine Equipe 13 « Microbiote

Research Unit

Name : Centre de recherche saint Antoine

Code *(ex. UMR xxxx)* : UMRS 938

Doctorate School

Thesis supervisor's doctorate school (candidate's futur doctoral school) : ecole doctorale 394

PhD student currently supervised by the thesis supervisor (number, year of the first inscription) :

none

Title of the project: Competition between intestinal bacteria: mechanisms, roles and therapeutic potential in inflammatory bowel diseases.

Proposal's context: The intestinal microbiota describes the large and diverse microbial community that inhabits our intestine. In recent years, knowledge of the gut microbiota has grown exponentially but the link between intestinal microbiota and human health is mainly based on correlatives studies and functional studies are now needed to decipher the mechanisms and offer new therapeutic approaches. In the laboratory, we are interested in inflammatory bowel disease (IBD), which include Crohn's disease (CD) and ulcerative colitis, and develop as a result of a combination of genetic predisposition, altered immune responses, environmental influences and alteration of the gut microbiota[1]. There is no cure for IBD, and treatments based on immunosuppressants are not always effective and have only suspensive effects. Interestingly, high-throughput sequencing analyses of microbiota from several hundred individuals indicate that the presence of some micro-organisms is very strongly correlated with the presence or absence of other micro-organisms[2], suggesting functional cooperation between micro-organisms or, conversely, competition. Despite the knowledge of the existence of complex interactions between bacteria in several ecosystems, there are few studies in the intestinal ecosystem on these interactions, their roles, the molecular mechanisms governing them and their importance in human health. In patients with CD, a high level of *Escherichia coli* (and more specifically *E. coli* strains belonging to the pathovar AIEC (Adherent Invasive *E. coli*) with pro-inflammatory properties[3]) is associated with a strong decrease in *Faecalibacterium prausnitzii* (an anti-inflammatory commensal bacterium[4]) while a high level of *F. prausnitzii* and a lower level of *E. coli* are observed in healthy subjects. These data therefore suggest direct or indirect competition between *E. coli* and *F. prausnitzii* with an impact on host metabolism and immune response, which may therefore play an active role in the development or chronicity of IBD.

Project objectives: **The aim of this phD project is to characterize and decipher the interplays between intestinal bacteria.** The project will focus on the interactions between *E. coli* and *F. prausnitzii*, but other microbial interactions may be investigated depending on the results obtained.

Here are the main tasks of the project:

- **characterize the interactions between *E. coli* and *F. prausnitzii*.** Co-cultures in liquid and anaerobic medium will be set and the numbers of bacteria after mono-culture or co-culture will be compared on agar plates and by molecular biology. We will determine if this putative competition is direct and depends on a competition for substrate, contact and/or secretion of molecule(s). We will then test the interaction between *E. coli* and *F. prausnitzii* in human microbiota using a system of human artificial digestive tract SHIME®[5] (available in the laboratory), which mimic the entire digestive tract.

- **identify the molecular mechanisms governing these interactions** by screening for example transposon libraries of mutants of bacterial strains (available in the laboratory) for their loss of capacity to inhibit the bacterial growth.

- **analyse the biological effects on the bacterial interactions on the host**. Depending on progress made during the PhD, the effect of micro-organisms will also be tested on cells in culture and *in vivo* (in mice). Molecular mechanisms identified in axis 2 will be tested by using bacterial mutants and/or molecules of interest.

Expected results: This project will deepen our knowledge of (i) intestinal microbial interactions, and more particularly the potential competition between *E. coli* and *F. prausnitzii* which are among the main bacteria whose abundance is altered in CD and (ii) the consequences on the host. Furthermore, it will open up new therapeutic strategies for IBD aimed at modulating these interactions.

References

Reference involving the PhD supervisor is indicated in blue and references involving the host laboratory are underlined.

[1] Ananthakrishnan. Epidemiology and risk factors for IBD. Nat Rev Gastroenterol Hepatol 2015 Apr;12(4):205-17.

[2] Pascal, Pozuelo, Borruel, Casellas, Campos, Santiago, Martinez, Varela, Sarrabayrouse, Machiels, Vermeire, Sokol, Guarner & Manichanh. A microbial signature for Crohn's disease. Gut 2017 May;66(5):813-822.

[3] Rolhion & Darfeuille-Michaud. Adherent-invasive *Escherichia coli* in inflammatory bowel disease. Infl Bow dis 2007 Oct;13(10):1277-83

[4] Sokol, Pigneur, Watterlot, Lakhdari, Bermúdez-Humarán, Gratadoux, Blugeon, Bridonneau, Furet, Corthier, Grangette, Vasquez, Pochart, Trugnan, Thomas, Blottière, Doré, Marteau, Seksik & Langella. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 2008 Oct 28;105(43):16731-6.

[5] Van de Wiele, Van den Abbeele, Ossieur, Possemiers & Marzorati. The Simulator of the Human Intestinal Microbial Ecosystem (SHIME ®). The Impact of Food Bioactives on Health: in vitro and ex vivo models. Cham (CH): Springer; 2015. Chapter 27.

Profile of the Applicant : Master degree in Biology. An experience in the gut microbiota research field would be a plus.