Sorbonne Université/China Scholarship Council program 2021

Thesis proposal

Title of the research project: The gut microbiota as an actor in immunometabolism: impact in inflammatory bowel diseases

Keywords: gut microbiota, tryptophan and immunometabolism

Joint supervision: ~~yes (name/surname) /~~no

Joint PhD (cotutelle): ~~yes (name/surname)~~ /no

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Institution: Sorbonne Université, APHP, INSERM

Doctoral school (N°+name): ED394 Physiologie, Physiopathologie et Thérapeutique

Research laboratory: Microbiota, Intestine and Inflammation

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SORBONNE UNIVERSITÉ

Subject description (2 pages max):

1) Study context

Host-microbiota interactions are now recognized as a significant factor in the maintenance of health and in onset of several diseases, and particularly inflammatory bowel diseases (IBD). IBD, including Crohn's disease and ulcerative colitis, are chronic, relapsing inflammatory conditions of the gastrointestinal tract that can have a major impact on patients' health and quality of life. Classical host-microbe interaction concepts rely on the recognition of conserved microbial motifs by innate immunity sensors, or on the effect of microbial molecules on a host cell receptor. However, energy metabolism has a crucial role in mounting the appropriate cellular response (called immunometabolism in immune cells), and the studies investigating how the gut microbiota directly affects it remain scarce. Yet the gut microbiota has a special relationship with metabolism, notably via the mitochondria due to their common origin. Mitochondria share a large part of their genome with bacteria, so communication and regulation can be evoked between these entities.
Understanding the bidirectional impact of gut microbiota and host cells metabolisms in health and disease is crucial to identify preventive and therapeutic targets that will be actionable through metabolic modulation.

2) Details of the proposal

An alteration in intestinal cells energy metabolism has been suspected in IBD for a long time. Notably, an energy deficient state associated with alterations in epithelial cells oxidative metabolism has been pointed out in ulcerative colitis [1] and an activated mitochondrial unfolded protein response (MT-UPR) has been observed in intestinal epithelial cells from patients with IBD and colitic mice [2]. Interestingly, Paneth cell abnormalities in patients with Crohn's disease correlate with alterations in both microbiota composition and oxidative phosphorylation in ileal tissue [3]. Mitochondrial function is required to maintain the good functioning of intestinal stem cells and Paneth cells and its impairment has been suggested to play a role in Paneth cells dysfunctions in Crohn's disease and intestinal inflammation in mice [4]. The emerging field of immunometabolism demonstrates that immune cells behavior is strongly impacted by their energy metabolism [5]. It is thus likely that mitochondrial dysfunction in IBD affects other cell types involved in IBD pathogenesis and particularly immune cells. The role of cellular energy metabolism defect in IBD pathogenesis is supported by the numerous genetic risk loci affecting mitochondrial functions that are associated with IBD [6].
The gut microbiome represents a significant biomass with a strong metabolic activity involved in the normal mammalian physiology. The metabolites it produces, contribute massively to the physiology of the host and, when altered, to disease pathogenesis [7]. Some data demonstrate its role in host cells energy metabolism, with the role of gut microbiota-derived short chain fatty acids (SCFA) butyrate as the main energy source for colonic epithelial cells [8]. However, the involvement of the gut microbiota in host cells energy metabolism has been poorly explored until now although there are major arguments suggesting a crucial role [9].

Given these data, **we hypothesize that the altered gut microbiota contributes to the impairment of host cells energy metabolism in IBD**.

The aim of this phD project is to determine the effects of gut microbiota metabolites on host cell energy metabolism and its alteration in IBD pathogenesis.

Here are the main tasks of the project:

(1) Identify *in vitro* the microbiota-derived metabolites impacting epithelial and immune cells energy metabolism. A collection of microbiota-derived metabolites (including SCFA, tryptophan metabolites, bile acids) will be screened using custom designed reporter cell lines (already available in the host lab and allowing for example glycolysis or Krebs cycle studies). Follow up experiments will be performed with a maximum of 3 metabolites to identify the mechanisms, using notably human ex-vivo intestinal culture systems. In parallel, the effects of fecal microbiota supernatant from healthy subjects and IBD patients will be compared using the same systems.

(2) Establish *in vivo* the consequences of altered microbiota on host immunometabolism. Consequences of gut microbiota alterations on host cells metabolism will be explored in mice. Conventionally raised as well as germ-free and antibiotics treated mice will be studied at baseline and in chemically induced-colitis context. Energy metabolism in intestinal epithelial cells and immune cells (both in the gastrointestinal tract and at the systemic level) will be studied using Scenith system [10] and metabolomics approach. Metabolites identified in task 1 will be also tested *in vivo*.

3) References

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2. Rath, E. *et al.* Induction of dsRNA-activated protein kinase links mitochondrial unfolded protein response to the pathogenesis of intestinal inflammation. *Gut* **61**, 1269–1278 (2012).
3. Liu, T.-C. *et al.* Paneth cell defects in Crohn's disease patients promote dysbiosis. *JCI Insight* **1**, e86907 (2016).
4. Khaloian, S. *et al.* Mitochondrial impairment drives intestinal stem cell transition into dysfunctional Paneth cells predicting Crohn's disease recurrence. *Gut* **69**, 1939–1951 (2020).
5. O'Neill, L. A. J., Kishton, R. J. & Rathmell, J. A guide to immunometabolism for immunologists. *Nat. Rev. Immunol.* **16**, 553–565 (2016).
6. Barrett, J. C. *et al.* Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat. Genet.* **40**, 955–962 (2008).
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8. Donohoe, D. R. *et al.* The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. *Cell Metab.* **13**, 517–526 (2011).
9. Michaudel, C. & Sokol, H. The Gut Microbiota at the Service of Immunometabolism. *Cell Metab.* **32**, 514–523 (2020).
10. Argüello, R. J. *et al.* SCENITH: A Flow Cytometry-Based Method to Functionally Profile Energy Metabolism with Single-Cell Resolution. *Cell Metab.* **32**, 1063-1075.e7 (2020).

4) Profile of the Applicant (skills/diploma…). Master degree in Biology. An experience in the gut microbiota research field would be a plus.

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