Sorbonne Université/China Scholarship Council program 2021

Thesis proposal

Title of the research project: Role of microbiota in leukaemogenesis

Keywords: microbiota, acute myeloid leukemia, leukemogenesis, relapse

Joint supervision: yes (name/surname) : Mohamad Mohty

Joint PhD (cotutelle): no

Thesis supervisor: Florent Malard

Email address of the thesis supervisor: florent.malard@inserm.fr

Institution: Sorbonne Université, Hôpital Saint-Antoine AP-HP, INSERM UMRS_938

Doctoral school (N°+name): ED 394 Physiologie, Physiopathologie et Thérapeutique

Research laboratory: INSERM UMRS_938 Centre de recherche Saint-Antoine, Team “Graft versus host reactions after allogeneic stem cell transplantation”

Address of the laboratory: Faculté de médecine Sorbonne Université – Site Saint-Antoine – 10ème étage

27, rue Chaligny – 75571 PARIS cedex 12

Name of the laboratory director: Bruno Feve

Email address of the laboratory director: bruno.feve@inserm.fr

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Subject description (2 pages max):

1) Study context

Over the last few years, the understanding of the role of the microbiota in health and disease has rapidly expanded thanks to the possibility of performing a comprehensive metagenomic analysis of the human gut microbiome via evaluation of the bacterial 16S ribosomal RNA (rRNA) gene. Perturbation of the gut microbiota, hereafter referred to as dysbiosis, has been associated with multiple and varied diseases, including infection, atherosclerosis, inflammatory and metabolic disease, mental illness, neurological disease and cancer. In the field of hematologic malignancy, microbiota research has mainly focused on allogeneic hematopoietic cell transplantation (allo-HCT). Therefore, diversity of the gut microbiota of patients have been associatedwith the occurrence of medical complications after allo-HCT, including graft-versus-host diseases, and bloodstream infection but also with relapse of the underlying disease[1]. Importantly, low microbiota diversity during allo-HCT has been associated with a lower overall survival in a large multicenter study[2]

In the setting of acute leukemia, the role of infectious agents in acute lymphoblastic leukemia (ALL) promotion, both perinatally and in infancy, has long been observed. Furthermore, a mouse model has recently shown that genetic predisposition to precursor B-ALL shaped a distinct gut microbiome, and microbiome deprivation by antibiotic treatment can trigger ALL in predisposed genetic carriers in the absence of infectious stimuli, suggesting that it is the lack of commensal microbiota rather than the presence of specific bacteria that promotes leukemia in genetically predisposed mice[3].Regarding acute myeloid leukemia (AML), baseline diversity of the gut microbiome has been significantly associated with infection risk during induction chemotherapy (IC) for AML. Furthermore, we conducted a proof-of-concept study (Phase 1b/2a) evaluating autologous fecal microbiota transplant (auto-FMT) in 25 AML patients[4]. There was a marked disruption of the microbiota induced by intensive chemotherapy and antibiotics but after auto-FMT the microbiome was restored to 90% of its initial richness, overall microbial diversity, and Simpson diversity index. Furthermore, in this trial, auto-FMT showed an excellent safety profile and there was on average a reduction of 43% of genes coding for anti-microbial resistance[4].

The incidence of AML is rising, and, while the increasing prevalence of therapy-related AML (as more patients with cancer treated with cytotoxic chemotherapy are cured of their primary malignancy), may partly explain this increase, other explanations remain to be identified. Similarly, in addition to the established role of microbiota dysbiosis in multiple myeloma and ALL pathogenesis, we hypothesize that microbiota dysbiosis also contributes to AML pathogenesis.

Although leukemogenesis is still incompletely understood, AML is believed to originate from the oncogenic transformation of a haemopoietic stem cell or of progenitors that have reacquired stem cell-like properties of self-renewal. Progenitors from leukemic stem cells undergo further genetic events, leading to karyotypic and molecular heterogeneity of the bulk leukemic population, with multiple coexisting, competing clones present at the time of diagnosis. Therefore, similarly to what has been reported in ALL, gut microbiota dysbiosis may contribute to the oncogenic transformation. In fact, alteration of gut microbiota with aging is well established, and may contribute to AML promotion given the incidence of AML in older patients. Furthermore, several studies have revealed that the intestinal bacterial microbiome plays an important role in the regulation of hematopoiesis. Germ-free mice have smaller hematopoietic stem and progenitor cell (HSPC) populations, abnormal splenic myeloid counts, and impaired T-cell function compared with their specific-pathogen-free (SPF) counterparts[5, 6]. Similarly, oral antibiotics deplete intestinal bacteria and have suppressive effects on hematopoiesis[5, 7]. Importantly, biologically relevant concentrations of antibiotics are not toxic to HSPCs under *in vitro* culture conditions[7], arguing against a direct antibiotic effect on hematopoiesis. Instead, several recent studies indicate that antibiotics impair normal hematopoiesis by

depleting intestinal bacteria[5-8]. Finally, in humans, cytopenias, including neutropenia, anemia, thrombocytopenia, and pancytopenia, have been reported for a wide range of antibiotics, suggesting a similar effect of antibiotics on HSPC.

2) Details of the proposal

Objective:

Work package 1.

- Compare microbiota of patients with AML at diagnosis, with patients with clonal hematopoiesis of undetermined signification and with age matched control.
- Evaluate the existence of a correlation between microbiota composition and AML molecular abnormalities evaluated by NGS.
- Compare microbiota evolution under treatment and AML history (response, relapse, clonal evolution)

Work package 2.

Evaluate the impact of microbiota on leukemogenesis in mouse models.

Expected results:

Our result will help us to understand the pathogenesis of AML and the impact of the microbiota on AML onset, response to treatment and relapse. This may offer the opportunity to develop the use of microbiota manipulation, and more particularly FMT as a therapeutic tool for AML patients.

3) References

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4°) Profile of the Applicant (skills/diploma…)

The applicant should follow a MD PhD or PharmD PhD program.

Contacts:

Thesis supervisor

Florent Malard

Email address of the thesis supervisor: florent.malard@inserm.fr