AAP China Scholarship Council - CSC 2024

PROJET DE RECHERCHE DOCTORALE (PRD)

Titre du PRD : Identification of MicroRNAs involved in the innate immune surveillance against infection during post-prandial metabolism.

DIRECTION de THESE

Porteuse ou porteur du projet (***doit être titulaire de l'HDR***) :

NOM : LESNIK

Prénom : Philippe

Titre : Sélectionner ou Autre : DR2 INSERM, HDR

Section CNU :

Email : philippe.lesnik@sorbonne-universite.fr

Unité de recherche : Code (ex. UMR xxx) et Intitulé : UMR-S1166

Ecole doctorale de rattachement : Sélectionner 394

Nombre de doctorants actuellement encadrés : 2

CO-DIRECTION de THESE (HDR) ou CO-ENCADREMENT (Non HDR) :

NOM :

Prénom :

Titre : Sélectionner ou Autre :

Section CNU :

Email :

Unité de recherche : Code (ex. UMR xxx) et Intitulé :

Ecole doctorale de rattachement Sorbonne Université : Sélectionner ou autre :

Nombre de doctorants actuellement encadrés :

CO-TUTELLE INTERNATIONALE envisagée : ☐ OUI X NON

DESCRIPTIF du PRD :

Identification of MicroRNAs involved in the innate immune surveillance against infection during post-prandial metabolism.

Scientific context:

At the postprandial state, the human body is exposed to inflammatory and metabolic insults associated with major alterations in the concentration of macronutrients, endocrine/hormonal signals, microbiota-derived factors, and other metabolites (xenobiotics, drugs…). These changes are characterized by specific kinetic patterns and peak or declining concentrations in serum[1],[2],[3]. Therefore, postprandial exposure can subsequently affect metabolism, inflammation, and health, especially in people in developing countries who are in a fed state for more than 16 hours a day. For example, many of the observed chronic effects of dietary carbohydrates and fats on metabolic health are underpinned by postprandial fluctuations in glucose and triglycerides, leading to postprandial inflammatory responses and the formation of reactive oxygen species (ROS) [4]. Furthermore, ingesting high-fat food results in a transient proinflammatory state via a metabolic endotoxemia pathway sustained by bacterial wall products derived from gut microbiota [5]. In contrast, the postprandial secretion of bile acids that can exert health-promoting and adverse actions is lowered in response to a high-fat diet [3]. Consequently, altered bile acid signaling might contribute to the development and/or worsening of components of the metabolic syndrome (hepatic steatosis, low-grade inflammation, hypertriglyceridemia, low levels of HDL cholesterol, or hyperglycemia).

The link between diet and innate immune function is evident not only in metabolic disease but also at homeostasis. Food intake leads to peripheral leukocyte activation and release of proinflammatory cytokines, including IL-6 and TNF-$^{\alpha}$ phenomena commonly called “postprandial inflammation” [6]. This response depends on macronutrient intake and involves the activation of inflammasomes and other pattern recognition receptors (PRRs) in peripheral blood mononuclear cells (PBMCs). Ultimately, this results in the release of cytokines, including IL-1β and IL-6, important pro-inflammatory mediators that regulate insulin sensitivity and glucose turnover. Albeit the initiating pathways of this postprandial inflammatory response are still poorly defined, innate immune receptors that recognize broadly conserved microbial molecular patterns emerge as central in metabolic and cardiometabolic diseases. Recent evidence shows that PRRs of the Toll-like receptors (TLRs) and NOD-like receptors (NLRs) family are central to metabolic and cardiometabolic diseases.

In addition, it is worthwhile to note that diet may affect intestinal miRNA expression and release in a direct and/or gut microbiota-mediated indirect manner. Tarallo et al. reported fecal miRNA profiles obtained from vegans, vegetarians, and omnivores and found miRNAs differentially expressed among different dietary habit subjects[7]. Hence, diet could affect intestinal miRNA-mediated crosstalk between the gut microbiota and the host immune system [8].

Since miRNAs are important regulators of innate immunity, we aimed to investigate the relevance of miRNA signatures in addressing nutritional challenges. Indeed, circulating miRNAs have a significant impact on infectious diseases [9] and sepsis. As biomarkers, miRNA may also help differentiate viral from bacterial infection and prognosticate sepsis. miRNAs can function at multiple levels, such as control of leukocyte development, cellular tropism of the virus, individual resistance to infection (i.e., HIV), or poor vaccine response, as well as PRR-mediated responses. To the best of our knowledge, the first study to address miRNA signature during the postprandial state analyzed the miRNA profile on peripheral blood mononuclear cells (PBMCs) between fasting and postprandial state after the consumption of a high-fat meal in humans. The authors identified several down-regulated and upregulated miRNAs, revealing specific changes in miRNA levels associated with non-fasting state [10]. Among those, some proinflammatory miRNAs are involved in the regulation of innate immunity, such as miR-155, which is induced by TLR2, TLR3, TLR4, and TLR9 signaling. Likewise, functional micro-RNA signatures in human monocytes upon stimulation with the diacylated lipopeptide lipopolysaccharide, and muramyl dipeptide were reported recently by Hasler et al. [11]. More recently, Ramzan et al. [12] demonstrated that postprandial variation of circulating-miR-15a and circulating-miR-17-5p levels differ between healthy insulin-sensible and overweight insulin-resistant women, thus revealing a possible contribution of miRNAs in the development of metabolic inflexibility [12]. Interestingly, in the context of infection, functional high-throughput screening identifies the miR-15 as a cellular restriction factor for *Salmonella* infection and as a regulator of macrophage phagocytosis after bacterial infection. Comparably, miR-17-5p has been reported to regulate autophagy in *Mycobacterium tuberculosis*-infected macrophages and as a potential antiviral against the SARS-CoV2 gene (ORF1ab).

Preliminary data:
We performed a postprandial analysis of circulating miRNAs in a cohort of healthy volunteers that were stratified based on the desirable or undesirable postprandial triglyceride response [2]. Variation of circulating miRNAs in the two groups revealed up and downregulated circulating-miRNA, which are under investigation for their potential implication in the quality of the postprandial triglyceride response. Similarly, we reported several circulating miRNAs with significant flexibility in the "desirable group" and no variation in the undesirable postprandial triglyceride group. Among these circulating miRNAs, based on the literature, we identify several potential associations and cause-and-effect relationships: (i) as potential biomarkers of sepsis diagnosis and mortality for miR-16a; (ii) as ligand for TLR7 and TLR8 and as regulator of innate and adaptive immune responses to bacterial infection by targeting interferon-gamma for miR-29a; (iii) as immunoregulator of NOD2-mediated expression of IL-23 by dendritic cells for miR-29a; (iv) as a putative causal factor on developing cases of severe COVID-19 for miR-139-5p. Using a similar post-prandial challenge, a recent study by Yaman et al. also identified a flexible postprandial response for miR-122, which is involved in hepatitis C and hepatitis B infections [13].

Thesis Objectives:
Building on these findings, we hypothesize that several identified circulating and/or fecal micro-RNAs are associated with physiological or pathological postprandial immune surveillance responses in human cohorts. These circulating miRNA candidates, as well as fecal miRNA, will be further assessed and validated (i) in a new cohort of dysmetabolic patients, and the miRNA candidates with the strongest rationale will be assessed for causality experiments (miRNA mimics and anti-miRNA) in infected mice using various models of septic shock and bacterial infections.

We hypothesize that understanding the cause-and-effect relationship of postprandial inflammation is particularly well suited for early intervention and prevention of metabolic disease, but also will provide novel insights into the diet-induced protection from infectious diseases. This project is granted by the European Union.

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AVIS de l'Ecole Doctorale :

Avis très favorable pour ce projet et cette équipe. Le taux d'encadrement du directeur de thèse lui permet d'accueillir un nouveau doctorant.

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