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# When immune cells are coached by intestinal microbiota

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**Commentary on ‘Microbial metabolites control the thymic development of mucosal-associated invariant T cells’, by F. Legoux et al., *Science*, 2019;366:494–499.**

The microbiota is in constant contact with animal hosts including humans. This relationship begins at the very first steps of life and development. Somehow, the hosts succeeded in living in a world fully occupied by trillions of microorganisms that influenced or damaged our health. In fact, the microbiota, their metabolites, and compounds deeply contribute to the development and modulation of the immune system of the hosts. However, how this interaction works remains poorly understood.

Legoux *et al.*<sup>1</sup> unveiled new roles for microbial metabolites in the immune T-cell biology through a recent study published in *Science*. They found in mice and humans, that intestine bacteria and their secretion are essential to train T-cells that migrate from the thymus to the intestine itself. Those cells, named mucosal-associated invariant T (MAIT) cells, remain immature in the thymus. They finally migrate and get involved in maintaining the intestinal homeostasis and mucosal barriers. Intestinal epithelial cells make these physical barriers reliable by insuring a symbiotic relationship between the gut microorganisms and the host that should be separated. The authors of this work discovered that immature intrathymic MAIT cells recognize a blood circulating bacterial secretion named 5-(2-oxopropylideneamino)-6D-ribitylamouracil (5-OP-RU) that acts as an antigen and stimulator for the MAIT cells. The vitamin B2 precursor derivative 5-OP-RU is a ligand, trafficking from the mucosal surfaces to the thymus to be recognized by MAIT cells via a major histocompatibility complex Class Ib molecule MR1. The recognizing and immature MAIT cells then mature, proliferate, and make the epithelial barrier stronger, which eventually reinforces the cohabitation and symbiosis between the intestinal bacteria and T-cells. This fascinating life together is of reciprocal interest. While the bacteria benefit from the nutrients present in the gut, the MAIT cells become mature and reinforce the intestinal microbiota by restricting damage caused by the bacteria. This could be called mutual benefit as a definition of symbiosis. One of the most important and novel findings from this work is the capability of the T-cells to be coached by the microbiota and their immunostimulatory secretions.

This is a training that basically controls the development of the immune cells migrating from the thymus to the gut. While our understanding of the immune system made the self-antigens major actors for its development, the present findings turn upside down this concept by demonstrating that bacterial exogenous secretions can drive the maturity and the faith of mammal immune cells. They brought new findings of the immune system that could potentially be of high interest to cure inflammatory digestive disorders and colorectal cancer in which microbiota involvement should have a say.

This study feeds the growing body of evidences on the role of the gut microbiota in secreting metabolites into the blood circulation which modulate or affect the host organs remotely. The question is whether alteration of the intestinal microorganism homeostasis has any consequences on the host. Thus, alterations of the gut microbiota and chronic inflammation have been reported in some cardiovascular diseases (CVD).<sup>2,3</sup> High plasma levels of trimethylamine-oxide (TMAO) was reported to be responsible for damaging the cardiovascular system in patients with heart failure.<sup>4</sup> While TMAO results from the gut bacterial product (trimethylamine or TMA) that is oxidized by the liver, its blood level increases with food containing choline that can be found in red meat, eggs, fish, or seafood.<sup>5</sup> Another fact is about a late breaking-research presented at the 2019 European Society of Cardiology congress. A study compared the gut microbiota in 30 patients with acute coronary syndrome and 10 patients with stable angina. Patients with acute coronary syndrome further carry microbes with pro-inflammatory properties such as Firmicutes, Fusobacteria, and Actinobacteria when compared to Bacteroidetes and Proteobacteria present in patients with stable angina. The chemicals and metabolites secreted by the pro-inflammatory microbes may affect the plaque destabilization and increase the risk of heart attack onset.<sup>6</sup>

The interplay between nutrient intake, gut microbiota, and neurodegenerative disorders such as Parkinson's and Alzheimer's diseases was described in the Braak's hypothesis and intestinal microbiota-dependent synucleinopathies in which some loops of communication between the enteric and central nervous systems were involved.<sup>7-9</sup> Knowing the close proximity between the underlying molecular mechanisms triggering the neurodegenerative disorders and CVD, similar mechanisms might occur in the heart and vessels.<sup>8</sup>

Can gut microbiota also play a role in drug toxicity and their side effects? Does it contribute to explain the patient-dependent response to therapeutic drugs? These challenging questions were originally approached by Zimmermann *et al.* Based on the fact that the vast majority of genes in human body are not human but bacterial, they employed a computational method and compared some gnotobiotic (sterile) mice with engineered microbiota unable to transform three tested therapeutic drugs. Hence, they tested a first drug namely Brivudine, an anti-viral compound that is broken down by the liver to result in bromovinyluracil (BVU) a toxic metabolite. They observed that the common gut bacteria *Bacteroides thetaiotaomicron* and *Bacteroides ovatus* can also break down Brivudine and release BVU using a specific bacterial gene. Mice lacking this bacterial gene produced less toxic BVU in the intestine and blood. Similar profiles were obtained with another anti-viral drug (Sorivudine) and an anti-anxiety drug (Clonazepam). The quantification of the microbiota and host involvement in the metabolism of these therapeutic molecules indicated that the gut bacteria produce 20–80% of the circulating derived toxic metabolites.<sup>10</sup> Such work may have a real importance to further anticipate the side effects and toxicity of a given therapeutic compound and to target the pertinent drug in patients and/or to purposely modulate the gut microbiota.

Finally, should we now consider the human gut microbiota as a novel risk factor and/or pathological biomarker? The recent advances reinforce the concept that targeting the communication between host and gut microorganisms may prevent or treat some CVD. However, the causal relation between the gut microorganisms and host needs to be better established.

## Author



**Biography:** Albano C. Meli received his PhD in Neurobiology at the Faculty of Pharmacy in Montpellier (France) in 2007. He then worked as a postdoctoral research scientist at Columbia University Medical Center in New York City (USA) for 4 years where he got mainly trained in basic cardiology. He was granted a European Marie-Curie Fellowship (2011) and a European Society of Cardiology grant (2012) to build up a team on human pluripotent stem cell-derived cardiomyocytes at Masaryk University Faculty of Medicine in Brno (Czech Republic). Albano was recruited as a permanent researcher by the French National Institute for Health and Medical Research (INSERM) in 2014. He has experience in basic cardiac physiology, calcium handling, ion channel biophysics, as well as in human pluripotent stem cell-derived cardiomyocytes to model inherited cardiac arrhythmias. He is also a nucleus member of the Scientist of Tomorrow of the European Society of Cardiology.

**Conflict of interest:** none declared.

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