



NATIONAL PRESS RELEASE | PARIS | 9 MARCH 2015

MAIT cell alterations involved in obesity and T2 diabetes

Scientists at Institut Cochin (CNRS/Inserm/Université Paris Descartes) and ICAN – Institute of Cardiometabolism And Nutrition (Inserm/UPMC/AP-HP) have discovered that a class of inflammatory cells, MAIT lymphocytes¹, is deregulated in patients suffering from type 2 diabetes and obesity. In these patients, bariatric surgery (or a *gastric bypass*)², which relieves inflammation, can restore the normal functioning of MAIT cells. Already known to be activated by certain bacterial populations and to favor inflammation, these cells may explain the link between alterations that affect the intestinal flora (microbiota) and the inflammatory nature of these diseases. These findings are published on 9 March 2015 in *Journal of Clinical Investigation*.

Type 2 diabetes³ and obesity are severe and intimately related pathological conditions whose incidence is increasing in France⁴ and throughout the world. These diseases with multiple causes (dietary changes, sedentary lifestyle, combined with genetic predispositions) are associated with chronic inflammation, induced by the immune system, which is abnormally activated. This inflammation is present not only in the blood but also in the organs involved in metabolic control of the body, such as the liver and adipose tissue. It also contributes to a loss of glycemic control. Furthermore, recent studies have shown that the gut flora of diabetic and obese patients is modified to a significant degree.

However, the link between the alterations of the gut flora and the chronic inflammation observed in these pathologies is poorly understood. But some inflammatory cells — specific T-lymphocytes called MAIT — are activated by certain bacteria. Research teams coordinated by Karine Clément and Agnès Lehuen thus tried to determine whether these cells were modified in patients with type 2 diabetes or obesity.

Their findings revealed a clear alteration of these MAIT lymphocytes: their levels were very markedly reduced in blood samples, and were even undetectable in a quarter of obese patients. However, adipose tissue from diabetic and obese patients contained much larger quantities of these lymphocytes than those found in healthy subjects. Indeed, their activation was enhanced, producing large quantities of cytokines (inflammatory molecules).

In addition, after bariatric surgery (*gastric bypass*), which is known to improve diabetes and inflammation, the frequency of circulating MAIT lymphocytes increased, returning to the levels observed in non-obese and non-diabetic subjects. Similarly, the production of cytokines by MAIT lymphocytes was markedly reduced after this surgical procedure.



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These results highlight a strong correlation between MAIT lymphocytes and metabolic dysfunctions. They suggest that these cells participate in the development of type 2 diabetes and obesity. The scientists propose that they might be activated by an alteration of the gut flora (microbiota) in such patients, thus increasing inflammation. The next step will be to verify the link between these MAIT cells and the microbiota. For example, do patients who no longer display circulating MAIT cells have a different microbiota from that seen in subjects in whose blood such cells can still be detected? To answer these questions, the researchers are now planning to sequence the microbiota of obese patients, before and after bariatric surgery.

This project involves the teams led by Agnès Lehuen at Institut Cochin and Karine Clément at IHU-ICAN Pitié-Salpêtrière and is receiving support from the Inflammex Labex⁵, the DHU-AUTHORS, a hospital-based clinical research program (AP-HP, Microbaria) and the European Métacardis program. It is also supported by the ANR (ObeMAIT program).

(1) MAIT: Mucosal-Associated Invariant T cells

(2) The gastric bypass technique consists in short-circuiting a large portion of the stomach, reducing it to a small pouch linked to the small intestine, which thus reduces the amount of food ingested and assimilated.

(3) Type 2, or non-insulin-dependent, diabetes, is the most common type of this disease, where hyperglycemia is caused by a loss of cellular sensitivity to insulin (insulin resistance). This notably develops under the effect of obesity or a sedentary lifestyle.

(4) In France, the most recent OBEPI survey (2012) showed that depending on the region, between 14% and 20% of people were obese and 5%-9% suffered from type-2 diabetes. The number of people affected by morbid obesity had increased three-fold over 12 years (1% of French people were morbidly obese in 2012 and 30% of these were diabetic).

(5) IHU ICAN and the Inflammex Labex (Laboratory of Excellence) were set up under the French 'Investments for the Future' (Investissements d'Avenir) program.

Bibliography

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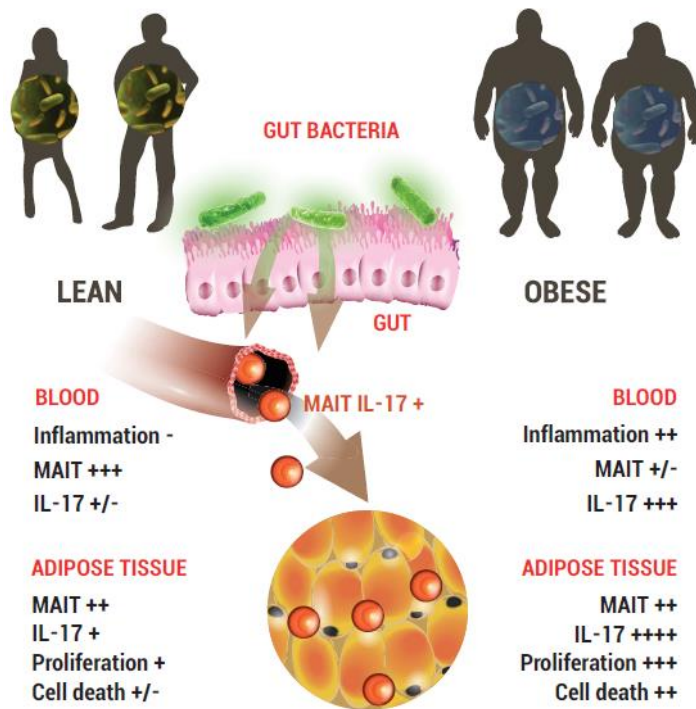
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Illustration



MAIT cells: a link between the microbiota and inflammation?

This diagram explains the scientists' hypothesis regarding the role of MAIT cells in obesity.

In obese individuals, alterations of the gut microbiota and a loss of integrity of the intestinal mucosa disturb the homeostasis and function of MAIT lymphocytes, which then produce large quantities of IL-17 cytokine, an inflammatory molecule. The MAIT cells, found in smaller quantities in the blood of obese individuals, are recruited to their adipose tissue, where they exacerbate the inflammation. The scientists also observed an increased turnover of MAIT cells in adipose tissue, indicated by high levels of proliferation and cell death.

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