Fundació
La Marató de TV3
22nd SYMPOSIUM
Diabetes and Obesity

LIPID DROPLET OVERLOADING PROMOTES PATHOGENESIS AND PROGRESSION OF TYPE 2 DIABETES: IDENTIFYING NEW THERAPEUTIC TARGETS AND APPLYING UPGRADED THERAPIES

Albert Pol Sorolla
IDIBAPS Institut d'Investigació Biomèdica August Pi i Sunyer

1. Project summary

Intracellular fat accumulation in peripheral tissues such as muscle and liver is the most obvious cellular hallmark of obesity and type 2 diabetes mellitus. Although this condition is commonly described as "ectopic fat accumulation", this definition does not reflect the cellular complexity and the physiological cost of the disorder.

The organelle in charge of storing fat is called the lipid droplet. Lipid droplets are not just accumulations of fat, but dynamic organelles that function in a wide variety of key cellular processes. Lipid droplet overload / dysfunction (which occurs during obesity) triggers a complex cellular response that could ultimately lead to or contribute to the development of insulin resistance and type 2 diabetes.

Surprisingly, although it is becoming increasingly clear that lipid droplet dysfunction / overload plays a role in the progression of insulin resistance, alleviation of organelle dysfunction has been largely neglected by existing therapies. In fact, type 2 diabetes is currently understood as a glucose-related disease and its clinical management is exclusively aimed at lowering blood glucose. In contrast, little effort has been made to simultaneously reduce intracellular dyslipidaemia or, in other words, to stimulate a controlled consumption of lipid droplets by decreasing overload, lipotoxicity, and cellular damage of intracellular organelles. This complementary strategy, which could reverse some of the root causes of type 2 diabetes, could be crucial to provide a significant advance in treating the disease.

2. Results obtained

After evaluating different experimental approaches, metabolic pathways, and molecules to modulate these pathways, to reduce the intracellular accumulation of fat, it was decided to stimulate the mitochondrial consumption of fatty acids by means of a molecule that belongs to the furan family. This molecule should function as an inhibitor of the key

enzyme in lipid synthesis and the main natural inhibitor of fat consumption by the mitochondria.

Studies in cell culture showed the effectiveness of this molecule in reducing intracellular fat accumulation and, more importantly, the toxicity associated with excess of saturated fatty acids. Studies in mice fed with high-fat diets showed that this furan not only reduces the weight of animals and the accumulation of fat in adipose tissue, muscle and liver, but it also significantly reduces liver damage and the progression of insulin resistance. and the type 2 diabetes associated with obesity.

3. Relevance with possible future implications

The initial project had the markedly basic intention of identifying new therapeutic targets to implement the current treatments for insulin resistance and type 2 diabetes. The results obtained in this project show, for the first time, that pharmacological treatments aimed at enhancing the consumption of lipid droplets represent an excellent strategy. Our studies demonstrate this in cultured cells, primary cultures and mice subjected to high-fat diets. We have not observed any adverse effects of the proposed treatments in experimental animals. The reduction of insulin resistance has been observed in just six weeks of treatment and in mice that were already obese, even maintaining the high-fat diets. Once a new target has been characterized, a second stage of work should allow exploring the possibility of applying these and other similar drugs to clinical practice.

4. Publications generated

Funding from the La Marató Foundation has been recognized in the following scientific publications:

1. Mammalian lipid droplets are innate immune hubs integrating cell metabolism and host defense. Bosch M,…, Pol A. Science. 2020 Oct 16;370(6514):eaay8085.

2. Lipid droplets, bioenergetic fluxes, and metabolic flexibility. Bosch M, Parton RG, Pol A. Semin Cell Dev Biol. 2020 Mar 4:S1084-9521(19)30052-7.

3. Non-caveolar caveolins - duties outside the caves. Pol A, Morales-Paytuví F, Bosch M, Parton RG. J Cell Sci. 2020 May 11;133(9):jcs241562.

4. Novel contact sites between lipid droplets, early endosomes, and the endoplasmic reticulum. Parton RG, Bosch M, Steiner B, Pol A. Journal of Lipid Research 2020. Nov;61(11):1364. doi: 10.1194/jlr.ILR120000876.