New pathway of the energy metabolism in peripheral tissues regulated by cytokine GDF15
15 September 2021

A study published in the journal Cell Reports describes a new pathway related to the activity of receptors that are associated with several metabolic or cardiovascular diseases such as diabetes, obesity and hypertension. According to the conclusions, many antidiabetic effects of the activators of the PPAR?/? receptors —potential therapeutic targets for the treatment of type 2 diabetes— are regulated by cytokine GDF15, a protein expressed under conditions of physiological stress.

The study contributes to find new therapeutic pathways for the treatment of metabolic dysfunctions and it is led by Professor Manuel Vázquez-Carrera, from the Faculty of Pharmacy and Food Sciences, the Institute of Biomedicine of the University of Barcelona (IBUB), the Research Institute Sant Joan de Déu (IRSJD) and the Diabetes and Associated Metabolic Diseases Networking Biomedical Research Centre (CIBERDEM).

Cytokine GDF15, a factor that regulates the energy metabolism

PPARs (peroxisome proliferator activated receptors) are transcription factors of the superfamily of hormone nuclear receptors. The dysfunctions of these receptors are related to several metabolic or cardiovascular pathologies which have a high incidence in the population.

The paper published in Cell Reports confirms that many antidiabetic effects of the PPAR?/? activators work through the cytokine GDF15, and which is more important, independently from the activation of the GFRAL neuronal receptor, which was the most known pathway to date. The new regulation pathway works through the activation of the AMPK protein, a sensor of the energy metabolism in the cell.

"The GDF15 or growth differentiation factor 15 is a stress-response cytokine—with increased levels in many diseases such as heart failure, cancer, fatty liver, etc.—which has been suggested as potential biomarker of many diseases," notes Manuel Vázquez-Carrera, professor at the Department of Pharmacology, Toxicology and Therapeutical Chemistry.

This cytokine is expressed in multitude of cells, tissues and organs (liver, skeletal muscle, adipose tissue, kidney, heart, placenta, macrophages, etc.). Its expression increases under situations of intracellular organelle stress (mitochondrial stress...
or endoplasmic reticulum stress) and environmental factors (excess of nutrients).

"Recent studies had shown that the cytokine GDF15 shows beneficial effects on the metabolism through the activation of its GFRAL receptor in the brain. Once the GFRAL receptor is activated, the intake decreases, and as a result, there is a weight loss that can reduce obesity and would improve associated diseases such as type 2 diabetes," notes Vázquez-Carrera.

**AMPK activation route through cytokine GDF15**

The study shows how the activation of AMPK through GDF15 increases the levels of GDF15, which increases the activation of the same AMPK in the skeletal muscle and indecently the GFRAL receptor in the brain.

"We believe this pathway is a positive feedback system that would maintain the AMPK activated in a sustained manner," notes Vázquez-Carrera. "Therefore, cytokine GDF15 shows peripheral effects, not only central ones."

Specifically, AMPK is activated in situations marked by a low level of cell energy and glucose. Once activated, AMPK starts a series of catabolic processes (degradation) that generate ATP—the molecule that carries chemical energy—and at the same time it inhibits the anabolic processes (synthesis) that take ATP.

"This activation mechanism is important because AMPK is a key regulator of many processes related to the cellular energy metabolism (increase of glucose uptake and the oxidation of fatty acids, increase of mitochondrial oxidative capacity, improvement of insulin tolerance, etc.)," says the researcher.

**New therapeutic targets to fight metabolic diseases**

The activation pathway of AMPK through GDF15 is a key mechanism against type 2 diabetes because "there are currently several medicines that activate AMPK which are considered safe drugs. Regarding the GFRAL activation through GDF15, the potential effects this could cause are still unknown. An overstimulation of this neuronal receptor could involve the appearance of adverse effects we should consider," notes the researcher.

"In this context, the high levels of GDF15 produced in cancer and the following activation of GFRAL have been presented as one of the mechanisms responsible for the appearance of cachexia—i.e, the extreme malnutrition and muscle atrophy—associated with this disease. This led researchers to study the use of antibodies against GDF15 to fight against the cachexic state."


Provided by University of Barcelona