'Sensor' protein could help fight against obesity and diabetes

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(L-R are) Mr. Man Lee (Baker IDI), Dr. Andrew Murphy (Baker IDI), Dr. Helene Kammoun (Baker IDI), Ms. Dragana Dragoljevic (Baker IDI), Dr. Seth Masters (Walter and Eliza Hall Institute). Credit: The Walter and Eliza Hall Institute of Medical Research

Melbourne researchers have identified an internal 'sensor' that helps fight obesity by instructing cells to burn their fat stores. The finding could play a major role in the fight against obesity and metabolic diseases, including type 2 diabetes.

In the study, researchers showed a protein called NLRP1 is switched on when increased dietary energy (food) intake triggers the cell to become 'unstable'. Activating the protein sets off a chain of events that instructs cells to use up their energy or fat stores to prevent excess fat accumulating.

The research, led by Dr Seth Masters from Melbourne's Walter and Eliza Hall Institute and Dr Andrew Murphy and Dr Michael Kraakman from the Baker IDI Heart and Diabetes Institute, with obesity expert Mark Febbraio from the Garvan Institute, was published today in the journal *Cell Metabolism*.

Dr Masters said NLRP1 was a biological sensor that could hold the key to developing new ways of treating obesity and type 2 diabetes.

"NLRP1 is a biological sensor that can respond to and prevent obesity and metabolic syndrome, which are causing a dramatically increasing burden of disease throughout the world," Dr Masters said.

"The sensor is activated if it detects that the body's energy intake is too high. When the sensor is activated, it tells cells to burn fat stores to prevent excess build up of fat. We showed that without NLRP1, fat stores continue to build up, especially with a high-energy diet, leading to obesity."

Dr Masters said NLRP1 was more commonly known for its role in the immune system. "However it is becoming increasingly clear that immune signalling proteins also have an important role in regulating metabolism."

Dr Murphy said the collaboration between two of Australia's leading institutes in immunology and metabolism research provided new insights into obesity. "This study provides compelling evidence that the immune system is activated not only during infection, but also in response to the loss of metabolic 'equilibrium' associated with a high-energy diet," Dr Murphy said.

"In order to combat the world-wide obesity epidemic it is essential to understand the immune mechanisms the body uses to prevent obesity, insulin resistance and development of type 2 diabetes."

The key to NLRP1 and its anti-obesity effects is how it controls an important lipid-regulating hormone called interleukin-18 (IL-18), Dr Murphy said. "We showed for the first time that NLRP1 is the key to IL-18 production, explaining how it acts to reduce obesity."

"Our long-term goal would be to develop a small molecule that activates the pathway to produce IL-18. In people who are obese, this would help the body to switch on this system and burn existing fat stores."

However the investigators cautioned that the treatment would have to be tightly controlled to avoid potential side-effects, Dr Masters said. "Our research showed that activation of NLRP1 could be exacerbated by some diets, and identified that there is a fine balance between increasing the cell's fat burning abilities and causing harm."

"This shows us just how active the pathway is, which is important if you are looking at it in a therapeutic sense. It suggests that treatment would be most safe if given in small doses over a long period of time, which is less likely to have potentially negative consequences."

Provided by Walter and Eliza Hall Institute

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