

Researchers develop novel solutions to fight the obesity gene

October 20 2014



This is an image of a weight scale. Credit: CDC/Debora Cartagena

Individuals who are genetically predisposed to obesity may soon have a therapeutic solution to combat their condition. A research team led by scientists from the National University of Singapore (NUS) has identified several potent inhibitors that selectively target FTO, the common fat mass and obesity-associated gene. These FTO-specific inhibitors pave the way for the development of novel anti-obesity drugs

and treatments.

The research, led by Assistant Professor Esther Woon from the Department of Pharmacy at the NUS Faculty of Science, along with colleagues from the Institute of Molecular and Cell Biology (IMCB) at the Agency for Science, Technology and Research (A*STAR), as well as the Nanyang Technological University, is the first to look at potential treatment of obesity from a genetic perspective.

The findings were first published online in the journal *Chemical Science* on 22 September 2014.

Obesity: A heavy problem

Obesity is not merely a cosmetic problem; it predisposes the individuals to a host of medical conditions such as Type 2 diabetes, cardiovascular diseases and certain cancers. It is estimated that by 2030, about 58 per cent of the world's population will be obese. Singapore shares similar alarming statistics, with 40 per cent of its adult population, aged between 18 and 69, being either overweight or obese.

Despite an urgent need to combat the [obesity epidemic](#), there is currently no safe and effective treatment for obesity. Healthy eating habits and active lifestyle remain important measures in our battle against obesity. However, these efforts are frequently insufficient by themselves due to underlying genetic influences which 'programme' a person's size and appetite.

Among the genetic influences, the FTO gene is one that is strongly linked to obesity, with genome wide studies showing that people with certain variations of the FTO gene are 70 per cent more likely to become obese. This has been shown for both children and adults, as well as across all major ethnic groups, including Chinese, Malay and Indian

populations in Singapore.

Currently, there is no safe and effective drug for the long term-treatment of obesity. To address this huge therapeutic gap in medicine, and to explore whether FTO is a probable therapeutic target for obesity, the researchers started to look at developing specific inhibitors of the FTO protein.

"Fat" hope: Potential drug against common obesity gene

In their experiments, the researchers discovered several novel and potent FTO inhibitors, with the strongest being the 4-[N'-(4-Benzyl-pyridine-3-carbonyl)-hydrazino]-4-oxo-but-2-enoic acid. Many of the inhibitors are also able to selectively target FTO over other proteins that are very similar structurally. This discovery was done through an innovative drug discovery strategy called Dynamic Combinatorial Mass-Spectrometry, a method which combines the permutation power of dynamic combinatorial chemistry and the sensitivity of protein mass-spectrometry.

Explained Asst Prof Woon, "Such remarkable selectivity is rarely achieved and is the 'holy grail' in drug discovery, as it potentially translates to significantly reduced side effects. This is demonstrated by the promising activities and low cytotoxicity of some of these inhibitors in cells."

Development of drugs and treatments for obesity and other metabolic diseases

The research team's findings open doors for the development of novel anti-obesity drugs and treatments. They are currently working closely

with Associate Professor Tai E Shyong and Assistant Professor Sue-Anne Toh, who are from NUS Yong Loo Lin School of Medicine, as well as Dr Liu Mei Hui of the Food Science and Technology programme at the NUS Faculty of Science, to study the molecular mechanisms and effects of the FTO inhibitors on other closely-related metabolic diseases, such as diabetes. They also hope to secure funding to further their research.

Said Asst Prof Woon, "Recognising a genetic, or even epigenetic, component in obesity certainly changes the way in which we approach to the treatment of the disease. What is so exciting about these FTO inhibitors is that they represent a potential new class of anti-obesity drugs, which target one of the most common genetic causes of obesity."

"Conceivably, if this research comes to fruition, it should benefit a large majority of the population. However, there is still a lot to learn about the actual mechanistic link between FTO and [obesity](#). The challenge now is to uncover the mystery through the use of these selective FTO inhibitors," she added.

The researchers have filed a patent for the [inhibitors](#) through the NUS Industry Liaison Office, which is part of NUS Enterprise.

Provided by National University of Singapore

Citation: Researchers develop novel solutions to fight the obesity gene (2014, October 20)
retrieved 5 May 2024 from <https://medicalxpress.com/news/2014-10-solutions-obesity-gene.html>

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