Mission to knock out fat-storing mechanism

NUS don and team find a way to to switch off receptors that suppress the breakdown of fat

David Ee

Deep within the labyrinthine corridors of the National University of Singapore Life Sciences Institute, the talk among researchers is deadly serious. The chatter is about rising rates of obesity and how it is killing people.

More than 40 per cent of Singapore's residents are overweight or obese (with a body mass index of above 25), putting them at risk of health problems such as diabetes and heart disease that can cut years off their lives.

The same is happening worldwide.

In China, for instance, about 30 per cent of people are overweight. In the United States, the figure is 70 per cent.

At the institute, Professor Carlos Ibanez, a molecular biologist by training, lightens the mood. He whips out two familiar cartoons poking fun at how humans have regressed since evolving from apes.

In one, the sturdy, athletic Homo sapien has given way to the sorry sight of a man crouched in front of a computer. In the other, the same man, clutching a sugary soft drink, is morbidly obese.

"This is a wonderful slide," says Prof Ibanez, a professor at the Yong Loo Lin School of Medicine's Department of Physiology, and the university's neurobiology programme.

"Everybody knows, but nobody does anything about it," he says, pointing to the two main causes of obesity – a sedentary lifestyle and poor diet.

For the past five years, he has been working to uncover the molecular links between diet and obesity.

Now, Prof Ibanez and his team at the NUS may have found another way of combating weight gain that does not involve diet or exercise – by cheating evolutionary design.

They have found – and learnt how to "knock out" – one of the first mechanisms known to link diet and fat storage (others have been found that link appetite and food intake). It is governed by a receptor found in fat cells called ALK7.

The ancient mechanism is at least a few hundred million years old, says Prof Ibanez, a Spaniard who moved to Singapore two years ago. It is present in all mammals and probably conserved in one form or another in all vertebrates.

What happens is this: After meals, the body typically activates ALK7. This suppresses the breakdown and burning of fat (after the body burns what is needed for daily exertion) so that more can be stored.

This biological reaction was how early humans resisted starvation when food was scarce, he explains.

"That means depositing fat, which is energy, whenever you can... because there wasn't breakfast, lunch and dinner every day."

Today, however, in the developed world, three meals a day are the very least many people eat.

Often, people eat much, much more. Worse still, these meals tend to be laden with sugar, starch and fat.

Yet these primal fat-storing mechanisms have not evolved a single bit. "We are living in the same bodies as the Stone Age, but we... have constant access to high-calorie foods, and we have a sedentary life," says Prof Ibanez.

His team's research was done in collaboration with the Karolinska Institutet in Sweden and the Howard Hughes Medical Institute in the United States. Their findings, published last month in online science journal eLife, could one day help people lose weight simply by taking pills or having injections.

Mice on a high-fat diet, but with their ALK7 receptors shut down, gained only half as much weight as normal mice. They were leaner as they were burning more fat for energy.

If placed on a lower fat diet, they may actually lose weight, says Prof Ibanez. It is something he is keen to test on obese mice in the future.

His tests on human fat cells showed that ALK7 worked in a similar way.

He also wants to find out if different people around the world have variants of ALK7 that "make it work a little better or a little worse", to see how that affects how fat accumulates.

This could be crucial for Asians, who deposit more fat in their liver, which can cause it to fail.

Obesity is viewed as one of the most serious public health issues of the 21st century. Last year, the American Medical Association classified it as a disease.

Scientists continue to chip away at it but, for now, no effective pharmaceutical treatment exists, says Prof Ibanez. There are only questionable health store supplements that reduce a person's appetite, often causing side effects.

Bariatric surgery to reduce the size of the stomach does help obese people lose weight, but is costly and risky.

Prof Ibanez does not envision his findings – even if eventually a treatment is found – to be a panacea for weight loss.

Eating more healthily and being more active, as difficult as some may find it, are still the answers.

He adds, pointing to the cartoon where the man with his gut sticking out continues to hang on to his super-sized soft drink: "We are sitting too much – I'm sitting the whole day here – and then we eat all this type of... well, I don't... but many people do.

"There hasn't been enough time for our genes to adapt."

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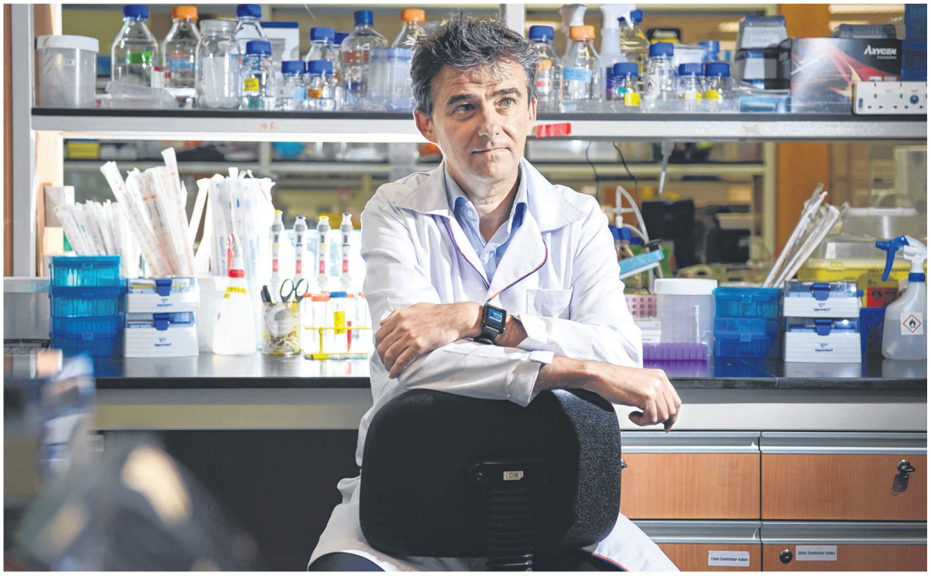

ST PHOTO: DESMOND LIM

Prof Ibanez and his team at the NUS are targeting a receptor called ALK7 in fat cells that could be the key to fighting obesity. After meals, the body activates ALK7, which suppresses the burning of fat so that more can be stored.

BATTLE OF THE BULGE

Scientists around the world are working to combat the obesity epidemic on various fronts.

Australian scientists discovered recently that obesity is an inflammatory disease, and hope to control it by controlling inflammation.

In the United States in June, researchers reported an important role for immune pathways in activating good types of body fat, called brown and beige fat, which burn stored calories, reduce weight, and improve metabolic health.

And over in Israel, scientists found that fat cells exposed to sustained, chronic pressure – such as what happens to the buttocks when a person sits – experienced accelerated growth of lipid droplets, molecules that carry fats.

One of the researchers involved, Professor Amit Gefen of Tel Aviv University, said in a statement: "This proves that you're not just what you eat. You're also what you feel – and what you're feeling is the pressure of increased weight and the sustained loading in the tissues of the buttocks of the couch potato."

But obesity is a very complex disease affected by biological, environmental, socioeconomic and behavioural factors.

US National Institutes of Health director Francis Collins, speaking on a documentary on obesity, noted: "We are not doomed to this situation. But it takes diverse and rigorous research to understand obesity and to identify interventions that work in the real world."