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Scientists discover in studies with mice that an anti-cancer gene also fights obesity

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Researchers from the Spanish National Cancer Research Centre working with mice have revealed that one of the main genes protecting against cancer brings two additional health benefits by boosting longevity and combating obesity. Mice carrying extra copies of the study gene eat more than normal, but are thinner -- a novel and entirely unexpected outcome.

This result, obtained after five years' research, is published in leading journal *Cell Metabolism*. The authors, led by Manuel Serrano (CNIO), believe it will open the door to new therapeutic options not only against cancer, but against obesity and even the ageing process.

The team has also demonstrated that a synthetic compound developed in-house produces the same anti-obesity benefits in animals as the study gene.

Their findings add new weight to a hypothesis that is gaining currency among researchers in the field; namely that cancer and ageing, and now obesity too, are all manifestations of the same global process that unfolds in the body as its tissues accumulate more damage than natural repair mechanisms are able to cope with.

Prominent among these natural repair mechanisms are a small set of genes noted primarily for their protective effect against cancer. In recent years, some of these genes have also been shown to promote longevity – again by researchers from the CNIO – and to play a significant role in

other high-incidence conditions like diabetes and cardiovascular diseases.

The Serrano team set out to test whether the Pten gene, one of the four most potent anti-cancer genes, could be linked to other beneficial effects, particularly longevity.

And it turns out the answer is yes. The CNIO researchers created transgenic mice with double the standard levels of the Pten protein. The animals, as anticipated, proved far more resistant to cancer than their non-transgenic fellows. But they also lived an average of 12% longer.

This effect is independent of cancer resistance. It is not that the mice die of cancer later than otherwise, but that those that never develop cancer also live longer and exhibit fewer ageing-related symptoms. As the researchers put it, "Pten has a direct impact on length of life."

A "real surprise"

But the "real surprise" – say the authors of the Cell Metabolism paper – was another strange fact that caught their attention. Mice with the double dose of Pten were significantly thinner – by 28% on average – even though they were eating more. They were also more sensitive to the insulin hormone, therefore at less risk of developing diabetes, and their livers stood up better than normal to a fatty diet.

Serrano and his group looked for the cause in a higher energy expenditure, probing the animals' metabolism and fatty tissue, among a series of other factors. And they found the answer in brown fat, a kind of tissue which, paradoxically, helps the body to burn off the fat stored around its midriff and is increasingly the focus of worldwide research into obesity. It was Pten's ability to activate brown fat, they were able to show, that explained the thinness of the mice carrying extra copies of the

gene.

Moreover, the same effect could be achieved with brown fat cells cultured in vitro.

"What we are seeing is that tumour suppressor genes not only protect against cancer but also against the damage that builds up in the body over time," Serrano explains.

Obesity, and related conditions like diabetes, are linked to the metabolic damage caused by overeating or simply by ingesting more food, for longer, than is optimised for the human species. Evolution has equipped human beings with mechanisms which look after them until their offspring can survive alone. But after that, evolution loses interest, and declines to select repair mechanisms to offset the damage built up over time. That is why "when we are young we are protected against cancer and diseases that are, in fact, regarded as ageing-related," he remarks.

A synthetic compound with the same effect

How does Pten work? Its main mode of action is to inhibit the activity of the PI3K protein, which is capable of setting off a complex biochemical cascade. In order to establish whether Pten too employs this mechanism to act on brown fat, researchers used a synthetic molecule developed at CNIO. The CNIO-PI3Ki molecule inhibits the PI3K protein in the same way as Pten and – the team confirmed – also activates brown fat.

We thus have a synthetic compound, CNIO-PI3Ki, with the same effect as Pten. And researchers believe that with this molecule and their recent findings, there is now a good chance of obtaining a drug that achieves the same effects as the extra dose of Pten in transgenic mice.

For Serrano, it is now possible to imagine "a pill that boosts our tumour

suppressors or one that makes us burn off excess nutrients."

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