Weight is a prickly problem: a key role for hedgehog signalling in controlling fat storage

Obesity is a widespread condition in humans and has many serious consequences. Not only are overweight people faced with surcharges on airplanes but they also have a much higher risk of contracting a number of potentially fatal diseases. A considerable amount of research effort is currently focussed on the problem of weight control but to date genetic screens for factors that cause obesity have been hampered by the lack of an appropriate system. Putting it bluntly, yeast do not become overweight. However, fortunately (for us) flies do and this has provided scientists in Josef Penninger's group at the IMBA (Institute of Molecular Biotechnology) in Vienna with a unique handle on the process. Their initial and highly surprising results are reported in the present issue of *Cell*.

Andrew Pospisilik and Daniel Schramek in Penninger's group have designed a method that allows them rapidly to screen a large percentage of the genome of the fruit fly *Drosophila melanogaster* for genes that when mutated give rise to disorders in fat metabolism. The screen was based on the extensive fly library at the IMP/IMBA's VDRC (Vienna Drosophila RNAi Centre). Importantly, this permitted them to examine the effects of genes that had previously not been amenable to such studies because mutations in them are lethal at a very early developmental stage. Furthermore, the screen worked *in vivo* rather than in cultured cells, so there was no need to verify that the results are physiologically relevant.

Application of the screen resulted in a total of about five hundred genes that seemed somehow to be involved in fat metabolism. Many of these had been previously implicated in the process, which confirmed that the method yielded plausible results. Some of the genes identified were found to be active in neurons, suggesting strongly that fat storage in flies can be regulated by neuronal genes: it is clearly the case in mammals that feeding behaviour is under the control of neuronal genes. And some of the candidate regulatory genes worked in muscles: this too is similar to the situation in mammals.

As expected, the majority of hits from the screen related to genes showed to be active in fat tissue. A good number of them were previously unknown and the screen was thus highly successful in pointing out further areas for study. But perhaps the most significant result of the work was the finding that genes associated with the so-called "hedgehog" signalling pathway are involved in the regulation of fat storage. *Hedgehog* is one of the "pattern" genes in the fly, responsible for ensuring that developing cells assume the correct identity.

The idea that *hedgehog* also plays a part in controlling fat levels in flies was extremely interesting as it was consistent with previous findings that inhibition of hedgehog signalling protects mice from gaining weight (see Buhman *et al.* 2004, *J. Nutr.* **134**, 2979-2984). Mammals store fat in so-called adipocytes, or fat cells. Together with Harald Esterbauer at the Medical University of Vienna, and with the expert assistance of Chi-chung Hui at the University of Toronto, Pospisilik was able to show in cultured cells that hedgehog signalling blocked differentiation of pre-adipocytes to white adipocytes. To examine directly the effects of inhibiting *hedgehog* signalling in fat tissues, Pospisilik and Esterbauer generated mice in which the *Sufu* gene was inactivated solely in these tissues. (*Sufu* is a known inhibitor of hedgehog signalling.) The mice were healthy but noticeably

thin and Pospisilik found that this was because they had essentially no white adipose tissue, although their brown adipose tissues levels were unaffected. And in *in vitro* experiments on pre-adipocytes, hedgehog activation was shown to inhibit expression of a number of pro-adipogenic genes while stimulating expression of anti-adipogenic genes.

Taken together, these results confirm a role in mice – and thus presumably in man – for hedgehog signalling in the production of white but not brown adipocytes. Mammals use white adipose tissue as the major storage site for triglycerides, while brown adipose tissue is important in the regulation of body temperature (it metabolizes lipids to generate heat). Inhibiting the storage of fat in white adipose tissue ("bad" fat) could represent a way to control weight gain in humans but any such treatment could be counterproductive if it also affected brown adipose tissue. As Pospisilik says, "Anything that interferes with white fat has generally turned out to have similar effects on brown fat. Hedgehog is one of the first molecules shown to affect white and brown fat differently."

The finding that the *hedgehog* signalling pathway inhibits the formation of white adipose tissue while leaving brown adipose tissue intact is of enormous potential therapeutic importance. Pospisilik points out that "most overweight people suffer from cold because they have less brown fat and the little they do have is not active." Disrupting the hedgehog signalling pathway in a tissue-specific way (Pospisilik and Esterbauer showed that doing so did not alter glucose tolerance or insulin sensitivity) could channel more fat into brown adipose tissue, thereby helping overweight people both stay warm and lose weight. Perhaps the days of airplace surcharges may finally be numbered?

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The paper ""Drosophila genome-wide obesity screen reveals Hedgehog as a determinant of brown versus white adipose cell fate" by Pospisilik *et al.* will be published in Cell on January 7, 2010. It will be featured in Cell's new online format as "article of the future".

About IMBA

The IMBA – Institute for Molecular Biotechnology of the Austrian Academy of Sciences – opened in 2003. It combines fundamental and applied research in the field of biomedicine. Interdisciplinary research groups address functional genetic questions, particularly those related to the origin of disease. The ultimate goal is to implement acquired knowledge into the development of innovative applications for prevention, diagnosis and treatment of disease.

About IMP - IMBA Research Center

A cooperation contract links the Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA) to the Research Institute of Molecular Pathology (IMP), which has operated since 1988 and is supported by Boehringer Ingelheim. Under the name of the "IMP – IMBA Research Center", both institutes have access to a combined infrastructure in scientific and administrative areas. Together, the two institutes employ around 400 staff from 30 nations and are members of the Campus Vienna Biocenter.

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