IN THE NEWS

Fighting fat

Scientists working at The Rockefeller University in New York City, and the Joslin Diabetes Center in Boston, have identified a gene that counteracts obesity. The gene, *Foxa-2*, which is expressed in immature fat cells (pre-adipocytes) and in mature adipocytes of genetically and diet-induced obese mice, prevents pre-adipocyte differentiation and increases metabolism in mature adipocytes. The findings are reported in *The Journal of Clinical Investigation*.

"We know a lot about the various molecular pathways that stimulate or promote fat production, and the focus has been on trying to block these pathways to fight obesity" says Markus Stoffel, of Rockefeller University, the lead investigator in the study. "This pathway is one of only a few that we know of that naturally work to counteract obesity" (*ScienceDaily,* 16 July 2003).

Overexpressing Foxa-2 in cultured pre-adipocytes inhibits differentiation by activating transcription of *Pref-1*. This, in turn, prevents the adipocyte maturing. In mature adipocytes, as well as activating *Pref-1*, Foxa-2 also seemed to activate other genes that are involved in fat and glucose metabolism and so might feature in diet-induced insulin-resistance and benefit type 2 diabetic patients, too.

"It is now apparent that when we overfeed a mouse and it becomes obese, Foxa-2 is induced, which then activates a set of genes that work against obesity," says Stoffel. "Obviously that's not sufficient to prevent obesity, but it is sufficient to slow it down. Without this force, the mice accumulate more fat." (*Yahoo News,* 21 July 2003). The next challenge is to identify what induces *Foxa-2* expression in humans.

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PROTEIN SORTING

Over to you, SAM

Most mitochondrial proteins are made in the cytosol, so to reach their final destination they need to be transported through the TOM (translocase of the outer mitochondrial membrane) and TIM (translocase of the inner mitochondrial membrane) complexes. In addition to protein transport, it has been thought that these translocases also sort proteins to their sub-mitochondrial destination. However, in *Nature*, Meisinger and colleagues now reveal that another complex — SAM — functions after TOM to sort and assemble complex outer membrane proteins.

The Tom components of the TOM complex are encoded in the nucleus, so they are imported into mitochondria through TOM. The biogenesis of Tom40 — which forms the TOM channel — requires nearly all of the TOM subunits, and Meisinger and co-workers began their work by showing that the outer mitochondrial membrane protein Mas37 is also involved in Tom40 biogenesis. Previously, Mas37 had been proposed to be an import receptor and a Tom protein, but it was subsequently found to be neither.

To clarify the role of Mas37, Meisinger and colleagues studied the import of a ^{35}S-labelled precursor of Tom40 into isolated wild-type and *mas37Δ* yeast mitochondria. They found that Tom40 assembly into the core TOM complex occurs through Tom40 assembly intermediates I and II in wild-type mitochondria and that, in *mas37Δ* mitochondria, the formation of all three complexes was strongly inhibited. The latter effect was also observed after incubating wild-type mitochondria with anti-Mas37 antibodies. They further showed that the level of the outer mitochondrial membrane protein porin was reduced in *mas37Δ* mitochondria, whereas protein markers of the mitochondrial matrix or inner membrane were unaffected. Mas37 is therefore needed for Tom40 biogenesis, but not for protein import to the inner membrane.

Next, Meisinger and co-workers studied the import and assembly of three other outer mitochondrial membrane proteins. They found that the assembly of porin and Mdm10 — integral proteins with predicted β-strands — was strongly inhibited in *mas37Δ* mitochondria, whereas the assembly of Ugo1, which has a single transmembrane segment, occurred normally. This indicates that Mas37

STEM CELLS

Taking new orders

Nuclei that are transplanted from differentiated somatic cells to enucleated eggs of frogs or mammals take on the properties of the acceptor eggs. The molecular mechanisms that underlie this process of nuclear reprogramming are poorly understood, but involve new transcriptional instructions. Now, reporting in *Current Biology*, John Gurdon and colleagues show that a stem-cell marker is expressed in the nuclei of differentiated adult mouse and human cells after transplantation, and that this reprogramming does not require DNA replication.

An important activity of eggs is to induce replication, so to study the transcriptional reprogramming activity in eggs, Gurdon and colleagues chose *Xenopus* oocytes (growing egg cells), as they are nonreplicating but have a high transcriptional activity. *Xenopus* oocytes were injected with the nuclei of mouse fetal fibroblasts, and tested for the presence of *Oct4* messenger RNA — a stem-cell marker — using reverse transcriptase (RT)-PCR. Mature, spliced *Oct4* transcripts could be detected in oocytes that had been cultured at 18°C. The level of the transcript was 5–10 times higher when nuclei were injected into the oocyte nucleus (germinal vesicle, GV) than when nuclei were deposited in the cytoplasm.

To see whether the reprogramming activity of *Xenopus* oocytes was also effective for nuclei of adult mouse cells, mouse thymocyte nuclei were injected into the GV of oocytes. Fully spliced *Oct4* transcripts could be detected in oocytes that had been incubated for less than 2 days at 18°C. As the levels of *Oct4* transcripts increased, the thymus-specific differentiation marker *Thy1* decreased and became undetectable by day 5.5. Crucially, the oocyte's reprogramming activity is highly efficient, as the number of *Oct4* transcripts in GV-injected oocytes after 5.5 days of incubation was comparable to that of cultured mouse embryonic-stem cells. The cross-species reprogramming activity of *Xenopus* oocytes even extended to differentiated adult human cells, as the human *OCT4* gene was activated in oocytes 4–6 days after GV injection with human lymphocyte nuclei.

It will be interesting to study the expression of other genes in this