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Breakdown in the Power Plant of the Cell

A research team led by Josef Penninger examined the molecular processes that take place in the development of Type 2 diabetes. The findings turned previous beliefs of cause-and-effect upside down. The magazine Cell *devoted its cover page to the topic.*

Between five and ten percent of the world's population suffer from diabetes or obesity, two medical conditions that often go hand in hand. For those affected, this means an increased risk of cardiovascular disease and the danger of other serious complications such as renal failure or blindness. The percentage of diabetics in the population is growing rapidly – a development which is now also beginning to affect children and adolescents.

Type 2 diabetes as well as certain types of obesity are caused by an insensitivity of muscle tissue to the insulin hormone. Studies have repeatedly shown that there is a relationship between insulin resistance and the performance of mitochondria. These structures, often referred to as the cells' power plants, are responsible for metabolizing energy into a usable form for the human body. They metabolize fatty acids and sugars in food into ATP, the universal "energy currency" of life.

Under-performing Mitochondria in Diabetes

The amount of ATP produced by the mitochondria in living tissue can be measured by using magnetic resonance spectroscopy. In patients with insulin resistance, it becomes apparent that the mitochondria work in a highly inefficient manner. In order to produce the same amount of energy, they need a lot more "fuel" than does healthy muscle tissue. Studies have confirmed this phenomenon time and time again. In metabolic research circles, the view was therefore adopted that under-performing mitochondria are the cause of insulin resistance, diabetes and obesity. However, this causal link was never experimentally proven.

The IMBA, the Institute of Molecular Biotechnology of the Austrian Academy of Sciences, tried to get to the bottom of the cause and effect question and found startling results. Physiologist Andrew Pospisilik from Josef Penninger's team succeeded in genetically altering the mitochondria in muscle cells of mice so that their performance slowed down. This was achieved by the elimination of the protein AIF, a mitochondrial regulator. The induced disruption in the cell's power plant precisely resembled the defect in cells in humans prior to the manifestation of diabetes. Thus the researchers managed

to develop an animal model in which the central paradigm – that a defect in mitochondrial energy production might lead to obesity and diabetes – could be experimentally examined.

Slim despite Fast Food

When these mice were tested for signs of diabetes and obesity, the researchers involved were in for a surprise: the animals were slim and extremely insulin-sensitive. When placed on a fast food-like diet with high levels of fat, they were even protected against diabetes and obesity. Andrew Pospisilik explained this apparent paradox by declaring that the inefficient mitochondria burn much more “fuel” than properly functioning ones. The young postdoc concludes from his research that: “The under-performance of the mitochondria as observed in diabetes and obesity appears not to be a cause but rather a compensation mechanism of the body.”

“We actually wanted to deliver experimental proof that dysfunctional mitochondria can lead to Type 2 diabetes, as suggested by many correlative studies”, comments lead author Josef Penninger. “To our surprise the results proved the exact opposite of what the experts had expected. Of course one shouldn’t immediately assume that the results on mice apply directly to human beings too. The correlation between energy generation, mitochondria, obesity and diabetes is much more complex than assumed.”

The work, in which the researchers describe their new findings, will be published as a cover story in the magazine *Cell* on November 2nd, 2007.

IMBA

The IMBA – Institute for Molecular Biotechnology of the Austrian Academy of Sciences, combines basic and applied research in the field of biomedicine. Interdisciplinary research groups work on function-related genetic issues, particularly in relation to the manifestation of certain diseases. The aim is to use the gained knowledge with an innovative approach to prevent, diagnose and treat diseases.

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