Discovery of new gene called Brd2 that regulates obesity and diabetes

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The chance discovery of a genetic mutation that makes mice enormously fat but protects them from diabetes has given researchers at Boston University School of Medicine, USA, new insights into the cellular mechanisms that link obesity to Type 2 diabetes. Dr Gerald Denis and his colleagues report their findings in the current issue of *The Biochemical Journal*.

The researchers were studying the gene, called Brd2, which had not previously been linked to body energy balance. While complete absence of the gene was fatal, Dr Denis found that in mice where there had been a single, genetic change in the Brd2 gene, fortuitously reducing its expression, the mice became severely obese - but did not go on to develop Type 2 diabetes. This result was very surprising because in both 'mice and men', chronic obesity commonly leads to Type 2 diabetes, with its life-threatening consequences, including heart disease, kidney and nerve damage, osteoporosis, blindness and circulation problems in the feet that can require amputation.

If the mice had been human their weight would be equivalent to approximately 270 kilograms (600 pounds); despite this, they exercised at the same levels as normal mice and, in comparison, lived for a surprisingly long time.

Obesity is linked to the development of Type 2 diabetes, and as obesity levels soar - it is predicted that there will be around 366 million diabetic individuals worldwide by 2030 - there is an urgent need for a much

deeper biological understanding of the forces that link obesity and diabetes, in order to design new drugs and therapies for treatment.

However around 20 - 30% of the adult obese population remain relatively healthy despite their obesity. These are populations with a healthy metabolism but who are obese (MHO) while others are metabolically obese but are at a normal weight (MONW).

Dr Denis said, "Studies have shown that these individuals have a reduced 'inflammatory profile'. Inflammation caused by normal immune cells called macrophages leads to insulin resistance and Type 2 diabetes - this inflammation is typically seen in connection with obesity but it is the inflammation that is a trigger for diabetes, not the obesity itself. The mechanisms that explain this protection from diabetes are not well understood."

He went on to add, "Much like these protected obese humans, the Brd2-deficient mice have reduced inflammation of fat and never develop failure of the beta cells in the pancreas that is associated with Type 2 diabetes".

The researchers suggest several mechanisms by which the Brd2 gene mutation may protect against the development of diabetes.

These mice have impaired production of inflammation molecules that are normally seen in infections, but that also contribute to Type 2 diabetes. This impairment has the surprising benefit of protecting them from obesity-induced diabetes.

Commenting on the findings, Dr Denis said, "The strong influence of Brd2 levels on insulin production and action suggest that Brd2 is likely to be a promising target for diabetes treatment, but also imply that overactive Brd2 might cause diabetes. The ways in which Brd2 affects

the immune system may also play a part in Type 1 diabetes, further studies to determine this are needed."

More information: "Brd2 disruption in mice causes severe obesity without Type 2 diabetes" by Fangnian Wang, Hongsheng Liu, Wanda P. Blanton, Anna Belkina, Nathan K. LeBrasseur and Gerald V. Denis, will be published in The Biochemical Journal (2009) Vol 425, part 1, pp 71-83 at www.biochemj.org on 14 December 2009.

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