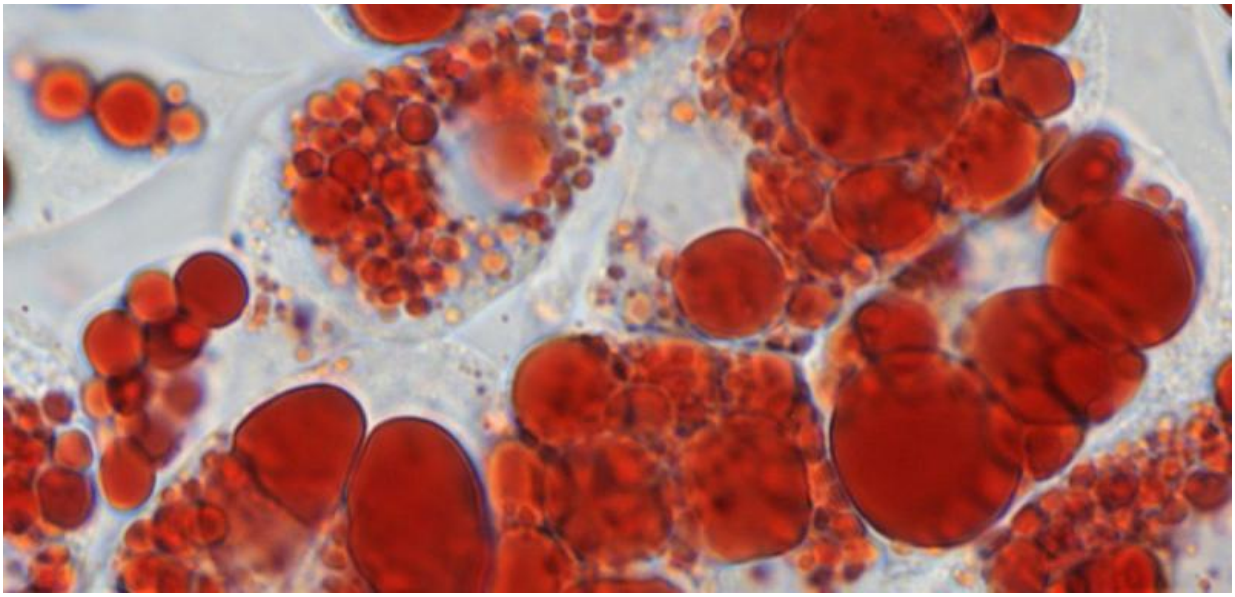
MedicalXpress

New function of obesity gene revealed

April 17 2015



Scientists have discovered a previously unknown mechanism behind how the fat mass and obesity associated (FTO) gene promotes obesity. Their findings may have important implications for future therapeutic strategies to combat obesity.

Using mice, the researchers from the University of Oxford and MRC Harwell assessed how FTO affects the development of fat cells in response to nutritional excess.

In humans, genetic variants in the FTO gene have been linked to obesity more frequently and strongly than those of any other known gene. The vast majority of studies aimed at understanding how FTO functions have tended to focus on its regulation of food intake in the brain. These studies suggested that FTO promotes weight gain by stimulating food intake. The new study, led by Professor Roger Cox at MRC Harwell and Dr Dyan Sellayah and Professor Frances Ashcroft at the University of Oxford's Department of Physiology, Anatomy and Genetics, is the latest in a growing number of studies that have served to address how FTO functions in fat itself.

'Fat is a major regulator of metabolism,' explains Professor Frances Ashcroft, one of the paper's senior authors. 'It not only serves as an energy store but also secretes hormones that communicate with other organs to regulate energy balance. FTO is very highly expressed in fat tissue but its function there was previously obscure. We therefore set out to understand the role played by FTO in fat. What we found was that FTO seemed to promote the production of new fat cells following a high fat diet'.

The study looked at the involvement of FTO in the production of fat cells from stem cells, a process known as adipogenesis using mice genetically engineered to either lack FTO or have twice the normal amount of FTO (overexpressed). The researchers found that cells in which FTO was overexpressed had a high propensity to become fat cells whereas those in which the FTO gene was removed were less likely to become fat cells. Furthermore, mice in which FTO was overexpressed produced more new fat cells on a high fat diet than control animals.

Dr Dyan Sellayah, a senior author on the paper, says: 'What we know about obesity is that both lean and obese people produce fat cells after prolonged periods of excessive eating, which act as energy storage reservoirs. Obese people, however, produce many more fat cells than

lean people do. Our research has shown that if an individual has high levels of the FTO gene, they may be prone to obesity due to enhanced fat cell production, thereby expanding the storage capacity available, and favouring energy deposition rather than energy burning.'

FTO was shown to influence adipogenesis by regulating a very early stage of adipogenesis, known as mitotic clonal expansion. Mitotic clonal expansion involves several rounds of cell division during which stem cells acquire the molecular machinery that enable them to become fat cells. The researchers showed that this proliferative capacity was blunted when the FTO gene was absent, and was enhanced when FTO was overexpressed.

'Because fat acts as a storage reservoir for excess energy, having more fat cells increases energy storage capacity. This increased storage capacity is likely to worsen the effects of FTO's known role of appetite stimulation', says Dr Myrte Merkestein, a co-first author of the paper. The study's findings may therefore help to explain why some people are prone to gain weight after prolonged overeating while others seem to be resistant.

Future work is focussed on how FTO gene variants may influence the interaction of genes in the vicinity of FTO. 'The process by which FTO gene variants cause obesity is rather more complex than we previously thought. It is becoming increasingly clear that the FTO gene variant affects not only FTO, but also neighbouring genes in that region of the chromosome. We now need to look at how these other genes may interact with FTO to promote obesity,' explains Professor Roger Cox, of the Medical Research Council's Mammalian Genetics Unit at Harwell, one of the senior authors of the study.

Samantha Laber, a DPhil student at MRC Harwell and co-first first author on the study concludes by saying: 'It has emerged that a number

of genes in the FTO locus may co-ordinately be involved in determining obesity, but our work and that of others clearly shows a central role for FTO in adipogenesis'.

The study is published in *Nature Communications* and was funded by the Wellcome Trust and MRC.

Provided by Oxford University