Adipocyte ALK7 links nutrient overload to catecholamine resistance in obesity

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Obesity is increasing in prevalence in Singapore. This is a part of worldwide phenomenon. According to world health organization, estimated 1.4 billion people above 20 years were overweight in 2008 across the globe. Of these, about half a billion were obese. In Singapore, 10.8 per cent of adults aged between 18 and 69 years were obese in 2010, almost double that in 1992.

Leading the study was Professor Carlos Ibanez from the NUS Department of Physiology and Life Sciences Institute. Professor Ibanez and his team was the first to confirm the link between diet fat storage, and its regulation by a receptor called ALK7.

ALK7 is a receptor for a subset of ligands from the TGF-β superfamily, including Nodal, activin B, and GDF-3. ALK7 is not necessary for mouse embryogenesis, suggesting alternative functions in postnatal development and adult physiology. ALK7 is highly expressed in rodent and human adipose, as well as in a few other tissues implicated in metabolic regulation, such as pancreatic islets and the arcuate nucleus of the hypothalamus.

Mice lacking ALK7 show reduced fat accumulation after a high fat diet. It has been unclear whether ALK7 affects fat accumulation cell-autonomously in adipose tissue or through other sites, and whether its effects on adult physiology are developmental or homeostatic, via acute regulation of adult cell function.

In this study, Prof Ibanez and his team developed a conditional knock-out mouse lacking ALK7 in adipose tissue and a knock-in mouse model carrying an analogue-sensitive kinase allele (ASKA) of ALK7, which can be specifically inhibited by administration of ATP competitive inhibitors. Using these animals, as well as cell culture models, the team established that ALK7 functions cell-autonomously and acutely in adult adipocytes to control energy expenditure and fat accumulation by suppressing adipocyte mitochondrial biogenesis, fatty acid oxidation, and β-AR mediated-lipolysis. Importantly, the team found that ALK7 signaling negatively regulates adipocyte β-AR expression and β-adrenergic signaling during a high fat diet, providing a link between nutrient overload and catecholamine resistance in adipose tissue.

"The discovery is the mechanistic link between the diet and the resistance of the adipose tissue to burn the fat. ALK7 is one of the first links found—a high-calorie diet enhances the signalling of this receptor," Prof Ibanez said.

The NUS team, who collaborated with the Karolinska Institutet in Sweden and the University of California, San Francisco, US, on the study, will be looking into whether obesity in mice can be reverted after administration of special chemicals.
The full paper can be accessed via
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