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OBESITY

Hipk2—an essential regulator of adipoctye differentiation

The highly conserved serine-threonine nuclear kinase, Hipk2, has been identified as a central regulator of adipocyte differentiation and white fat development in a new study using a systems genetics approach.

The rise in the prevalence of obesity and obesity-associated metabolic disorders over the past 20 years has led to increased research efforts being directed toward understanding the molecular mechanisms that underlie fat development.

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A team of researchers at the University of California San Francisco, USA, created a network view of the genetic architecture of healthy mouse tissues by measuring gene expression in skin and mammary glands from a genetically heterogeneous population of backcrossed mice, and exploiting the perturbations that were created by polymorphisms inherited by individual animals.

Previously, Hipk2 was known to interact with a number of transcription factors and other binding partners; however, its *in vivo* function was unknown. Independent analyses of the architecture of each tissue, using *Hipk2* as a seed, revealed that *Hipk2* expression correlates with gene expression patterns related to lipid metabolism, Pparγ signalling and adipogenesis, which suggests that Hipk2 might be involved in adipose tissue development. Supporting this computational prediction, *Hipk2* expression was higher in both white adipose tissue (WAT) and brown adipose tissue (BAT) than in other mouse tissues. Experiments using an *in vitro* model of adipocyte differentiation showed that *Hipk2* expression was low in undifferentiated cells but was up to 10-fold increased 8 days after induction of an adipocyte differentiation program.

Hipk2 knockout mice showed reduced WAT deposits and smaller adipocytes, as well as a 'browning' phenotype with increased expression of BAT-specific genetic markers, such as *Ucp1*, *Ppargc1a* and *Cidea*, and increased insulin sensitivity.

Studies in human populations have previously identified genomic regions close to *HIPK2* that are associated with obesity and type 2 diabetes mellitus, leading the authors to suggest that their findings might provide insights for developing new therapies for metabolic diseases.

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Original article Sjölund, J. *et al.* Identification of Hipk2 as an essential regulator of white fat development. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1322275111