FTO and Obesity: The Missing Link

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DOI 10.1016/j.cmet.2010.12.016

Genome-wide association studies revealed that variants within *FTO* (fat-mass- and obesity-associated) are strongly associated with obesity susceptibility. A recent study in *Nature Genetics* (Church et al., 2010) demonstrates that mice overexpressing *fto* exhibit a dose-dependent increase in body weight, confirming a role for FTO in the development of obesity.

Evidence shows that the variance in body mass index (BMI) within a population that shares the same environment is strongly genetically determined. Genome-wide association studies (GWAS), conducted in population-based cohorts assessed for BMI or in obese cases versus normal weight controls, have identified several genetic regions where single-nucleotide polymorphisms (SNPs) are associated with an increased risk of obesity. The strongest association with BMI in Caucasians has consistently been found with SNPs in the first intron of a gene named fat-mass- and obesity-associated gene (FTO) (Frayling et al., 2007), an association replicated in many population-based cohorts of adult- and childhood-onset obesity and in several different ethnic groups. Studies have consistently demonstrated that carriers of the most common obesity-associated risk allele have an increased energy intake with no evidence for an effect on energy expenditure (Cecil et al., 2008). Therefore, there has been considerable interest in establishing whether FTO or another gene in the same locus is involved in energy homeostasis. In a recent paper in *Nature Genetics*, Cox and colleagues provide a key piece of evidence strengthening the candidacy of the FTO gene product in the development of obesity (Church et al., 2010).

FTO was previously found to be an AlkB-like 2-oxoglutarate-dependent nucleic acid demethylase (Gerken et al., 2007). Resequencing studies have been performed in large numbers of obese and lean subjects, but heterozygous loss-of-function mutations in FTO were found at a comparable frequency in these groups (Meyre et al., 2010). A rare homozygous missense mutation in *FTO* that inhibits catalytic activity was found in a consanguineous family in association with a complex severe polymalformation syndrome and postnatal lethality, with no obvious body weight phenotype (Boissel et al., 2009).

In rodents, *fto* is widely expressed in a number of regions important for energy balance, including skeletal muscle, liver, adipose tissue, and the brain, where hypothalamic mRNA levels are influenced by nutritional state (Gerken et al., 2007). Knockdown of *fto* in the hypothalamic arcuate nucleus of rats increased food intake, while overexpression decreased it (Tung et al., 2010). These effects were not seen when *fto* was manipulated in the paraventricular nucleus, suggesting that effects may differ depending on the brain region, tissue, and/or stage of development. Mice lacking *fto* show increased postnatal lethality, postnatal growth retardation, reduced fat mass, increased energy expenditure, and a relative increase in food intake (Fischer et al., 2009).

In this study, Cox and colleagues provide direct evidence for the role of FTO in obesity by generating mice that globally expressed either one or two additional copies of the *fto* gene (Church et al., 2010). FTO-3 and FTO-4 mice (which had either three or four copies of *fto*) displayed increased *fto* expression in multiple tissues. Notably, there was wide variation in tissue expression levels compared to wild-type mice (FTO-2); for example, *fto* mRNA was increased 8-fold in the pancreas in FTO-3 mice and 11-fold in skeletal muscle in FTO-4 mice. Mice carrying additional copies of the *fto* gene were obese, predominantly due to an increase in fat mass. FTO-3 and FTO-4 mice had increased food intake compared to FTO-2 mice. FTO-4 mice showed a significant increase in energy expenditure on a standard diet, but there were no differences in respiratory exchange ratio or locomotor activity. While hyperleptinemia is a robust and reproducible feature of obesity in mice and, indeed, humans, Church et al. observed a reduction in circulating leptin levels in male and female FTO-4 mice compared to FTO-2 mice at 8 weeks. This finding is intriguing and suggests that *fto* overexpression may alter leptin expression or secretion from adipose tissue. It is plausible that these lower leptin levels may contribute to the hyperphagia of FTO-3 and FTO-4 mice. Additional studies of the leptin response in these mice will be of interest.

This study provides critical evidence to support FTO as the gene underlying the obesity association signal in several GWASs. Another closely located gene, *RPGRIP1L* (retinitis pigmentosa GTPase regulator-interacting protein-1-like gene) is a component of the basal body of the primary cilium, but so far the balance of evidence lies with FTO. The next challenge is to determine a direct connection between genetic variants in the first intron of the FTO gene and increased expression of FTO, as the studies of Church et al. suggest that a gain of function contributes to weight gain. A small study of five individuals heterozygous for the most common obesity-associated SNP (rs9939609) found that FTO transcripts containing the A (risk) allele were more abundant than those with the T allele in RNA preparations from blood and fibroblasts (Berulava and Horsthemke, 2010), but further studies will be needed to confirm these observations.

These studies pave the way for further work on FTO, which, given its ubiquitous expression in the embryo and adult organism, will need to be studied in models of tissue-specific overexpression, possibly at different developmental stages. One critical question is whether

the effects of FTO overexpression on obesity are mediated via the brain or other tissues. Deletion of *fto* in the brain recapitulates the reduced body weight of *fto* nulls, indicating that central mechanisms are likely to play a major role (Gao et al., 2010).

Finally, studies of the FTO association signal have taught us that understanding the biology underlying these genetic associations can be a complex and challenging task. As more common variants and, indeed, rare variants emerge from hypothesis-free genetic approaches, collaborative work across disciplines will be needed to link these genes to physiological and pathophysiological processes and thus to explore their utility as potential molecular targets for intervention in patients with obesity and associated metabolic diseases.

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The Tumor Suppressor LKB1 Emerges as a Critical Factor in Hematopoietic Stem Cell Biology

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DOI 10.1016/j.cmet.2010.12.015

How cellular metabolism regulates stem cell function is poorly understood but is an emerging field of study. In a recent issue of *Nature*, three independent groups demonstrate that LKB1 promotes hematopoietic stem cell (HSC) quiescence and metabolic homeostasis. Surprisingly, these effects on HSCs occur independently of AMPK/mTOR and FoxO signaling.

LKB1 is a tumor suppressor that is inactivated in the Peutz-Jeghers familial cancer syndrome. Best characterized as a serine/threonine kinase acting upstream of the adenine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) pathways, LKB1 is currently viewed as a master regulator of cellular metabolism that restricts cell growth under energetically unfavorable conditions (Shackelford and Shaw, 2009). Increased cellular AMP/ATP ratios result in enhanced AMPK phosphorylation and activation by LKB1. Activated AMPK in turn phosphorylates the tuberous sclerosis complex (TSC), which inhibits mTOR complex 1 (mTORC1), resulting in reduced mRNA translation and cell growth. LKB1 also modulates metabolism via other AMPK targets (such as the FoxO transcription factors) or additional substrates, like the 14 AMPK-related kinases. Although the role of LKB1 in regulating metabolic activity in cancer is well established, its impact on stem cells has yet to be fully explored. Accordingly, three recent reports in *Nature* (Gan et al., 2010; Gurumurthy et al., 2010; Nakada et al., 2010) demonstrate that LKB1 plays a critical role in hematopoietic stem cell (HSC) quiescence.

The hematopoietic system functions to replenish multilineage blood cells from early embryonic development throughout adulthood. Multipotent HSCs give rise to all mature blood lineages and must maintain a delicate balance between quiescence, self-renewal, and differentiation. Complex regulatory mechanisms, both cell intrinsic and cell extrinsic, modulate this balance and have profound influence