The 1D1 of Burning Calories

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You have probably daydreamed about eating as much as you want – but instead of becoming overweight or obese, you would burn the calories off effortlessly. We admit that we have dreamed of such a scenario – more than once. In the current issue of *Nature Genetics*, Chad et al. [1] show that they did a lot more than just dream; they actually report results from a series of elegant studies, suggesting that the enhanced and balanced burning of excess calories may not be impossible. They report that a loss-of-function mutation in the so-called *Tbc1d1* gene of the lean SJL mouse strain confers resistance from high-fat-diet-induced obesity, most likely by increased skeletal muscle substrate utilization.

Genome-wide linkage analysis based on cross-breeding experiments is a tedious but powerful tool to identify the chromosomal regions (quantitative trait loci; QTLs) underlying polygenic traits. More than 270 QTLs for traits related to obesity and body weight have been mapped in crosses between various mouse lines [2]. For human obesity, analyses of such mouse models are of general clinical importance: each QTL explains a part of the variance of the trait under investigation and might point to homologous regions in the human genome.

The New Zealand obese (NZO) strain is considered an ideal mouse model for the identification of obesity-related polygenes because this model reflects various features of the human metabolic syndrome, including polygenic obesity, insulin resistance, hypertension, and hypercholesterolemia [3]. In contrast, mice of the Swiss/Jim-Lambert (SJL) strain are lean, normoglycemic, and resistant to diet-induced obesity [4, 5].

In a previous genome-wide linkage study based on female mice of a NZO × F1 (NZOxSJL) backcross, Joost and colleagues [4–6] identified a major QTL (LOD score 7.9) for high-fat-diet-induced obesity on chromosome 5; this QTL was termed New Zealand obese 1 (Nob1). Along with being at an increased risk for obesity, carriers of the NZO allele at Nob1 exhibited a pronounced acceleration of the development of hyperglycemia and insulin resistance upon exposure to HFD [5, 6].

In their new report, Al-Hasani, Joost and colleagues [1] assessed the body weight gain of several other cross-bred populations (NZOxNZB and NZOxC57BL/6J). They observed neither a correlation of the Nob1 genotype with HFD-induced body weight gain, nor linkage of body weight gain to chromosome 5. These results indicated that Nob1 represents an obesity suppressor gene from the lean SJL strain. The authors narrowed down the critical region of Nob1 by introgression of a 24 Mb segment of Nob1 from SJL into a mixed NZO/C57BL/6J background. Compared to control animals, both homozygous and heterozygous carriers of the NobSJL allele showed markedly reduced body weight and blood glucose levels upon HFD exposure. Microarray and subsequent qRT-PCR analysis of various tissues further revealed that only two transcripts in the critical 24 Mb region of Nob1 were differentially expressed (>two-fold) between NZO/C57BL/6J background. Compared to control animals, both homozygous and heterozygous carriers of the NobSJL allele showed markedly reduced body weight and blood glucose levels upon HFD exposure. Microarray and subsequent qRT-PCR analysis of various tissues further revealed that only two transcripts in the critical 24 Mb region of Nob1 were differentially expressed (>two-fold) between NZO and SJL mice. Among these, *Tbc1d1*, a gene with high sequence homology to *Tbc1d4* (AS160), mapped exactly into the Nob1 peak region and was three-fold down-regulated in the skeletal muscle of lean SJL mice. Further cloning and sequencing of *Tbc1d1* led to the identification of a SJL-specific loss-of-function mutation in *Tbc1d1*. This mutation leads to a truncated protein that lacks most invariant residues of the GTPase-activating (Rab GAP) domain.

Does *Tbc1d1* underlie the Nob1 linkage peak and entail resistance to HFD-induced obesity in SJL mice? If so, how might *Tbc1d1* affect energy balance? Some evidence points to an implication of *Tbc1d1* in glucose metabolism. *Tbc1d1* comprises of two N-terminal phosphotyrosine-binding (PTB) domains, a central calmodulin-binding domain, and a C-terminal Rab GAP domain [7]. *Tbc1d1* shows high sequence homology to *Tbc1d4* (AS160), which is involved in insulin signalling. GLUT4 translocation, the insulin-induced trafficking of the...
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blood glucose levels as compared to carriers of the Nob1 NZO

weight of the Nob1SJL allele carrier.

might at least in part be a mere reflection of the lower body
circulation to be considered is that the lower blood glucose levels
indication is indeed affected by this mutation. One potential expla-
nation is that a high level of Rab GAP activity causes suppression of
GLUT4 translocation (and thus glucose uptake), whereas a decrease of Rab GAP activity does the opposite [7, 9]. In light of this observation, the identified SJL-specific loss-of-function mutation in Tbc1d1 by Chadt et al. [1] would thus be expected to contribute to decreased levels of glucose through an increased GLUT4 translocation. Indeed, as shown in their new paper, carriers of the Nob1SL allele show markedly reduced blood glucose levels as compared to carriers of the Nob1NZO allele. Even though this result points to Tbc1d1 as a missing link between GLUT4 translocation and glucose uptake, it warrants further investigation as to whether GLUT4 translocation is indeed affected by this mutation. One potential explanation to be considered is that the lower blood glucose levels might at least in part be a mere reflection of the lower body weight of the Nob1SL allele carrier. Additionally, the question remains of how a truncated Tbc1d1 protein might contribute to resistance to HFD-induced obesity. In line with earlier results [10], Chadt et al. [1] show that Tbc1d1 is predominantly expressed in skeletal muscle, a main tissue of glucose action in vivo. Skeletal muscle glucose up-
take is accompanied by increased GLUT4 translocation; both insulin and contraction independently stimulate GLUT4 translocation in vivo [10]. One of the main differences between Tbc1d1 and Tbc1d4 is the occurrence of an AMPK (AMP-activated protein kinase) phosphorylation site between the two PTB domains of Tbc1d1 [9]. The PTB domain seems to be relevant for the implication of Tbc1d1 in energy homeostasis, since a non-conservative mutation (R125W) in the PTB domain of Tbc1d1 has recently been repeatedly shown to be associated with severe familial obesity in humans [11, 12]. Moreover, in vivo stimulation by insulin, contraction, and the AMPK activator AICAR has recently been shown to increase phosphorylation of Tbc1d1 (and thus glucose uptake) in skeletal muscle [10]. In their new paper, Chadt et al. [1] further provide data which suggest that carriers of the Nob1SL allele display an elevated skeletal muscle lipid oxidation as indicated by a decreased respiratory quotient (RQ) during the dark period. Accordingly, palmitate oxidation was increased by approximately 25% in soleus muscle of 12-week-old Nob1SL/SJL mice. In line with this observation, siRNA-mediated knock-down of Tbc1d1 increased palmitate uptake and oxidation in C2C12 myotubes, whereas overexpression of Tbc1d1 in C2C12 myotubes had the opposite effect. These data indicate that Tbc1d1 might play a fundamental role in skeletal muscle substrate utilization.

The lean phenotype of the SJL mice might therefore be explained by a shift of skeletal muscle substrate utilization from glucose to fat due to the lack of Tbc1d1 activity. The scientific breakthrough by Chadt et al. [1] suggests that we may after all be able to one day loose body weight without the need to change our eating habits. However, the evidence that Tbc1d1 is implicated in the 101 of substrate utilization and glucose uptake in skeletal muscle, at least makes Tbc1d1 a hot drug target for the prevention and treatment of metabolic disease.

References


The Basics of Burning Calories

The prevalence rate for overweight obtained in the current WC had the most unfavorable cardiovascular risk profile. C-reactive protein was measured using a sensitive assay. Concentrations measured by ELISA; TNF-α, IL-6, monocyte chemoattractant protein 1 (MCP-1), C-reactive protein) in 54 females at baseline and after a 24-week weight loss intervention. The first three markers were measured using both a standard ELISA technique and a new multiplex technique, C-reactive protein was measured using a sensitive assay. Concentrations measured with the multiplex technique were poorly correlated to those obtained by ELISA; TNF-α was not detectable. Only
the ELISA-based concentrations were correlated with the independent inflammatory marker C-reactive protein. Taken together, these results suggest that caution is warranted upon interpretation of data obtained with the multiplex technique. The study suggests that circulating ELISA-based determinations of IL-6 and C-reactive protein, but not MCP-1 and TNF-α, are useful markers of obesity-related inflammation.

Several cross-sectional and longitudinal studies have linked a reduced amount of sleep with an elevated BMI in children and adults. In one of the few controlled intervention studies, Bosy-Westphal et al. [7] assessed 14 healthy women who were extensively investigated prior to and after 4 nights of consecutively increasing sleep curtailment (7 h, 6 h, 6 h and 4 h sleep/night) and after 2 nights of sleep recovery. Sleep reduction resulted in elevated energy intake, body weight, leptin/fat mass, free triiodothyronine, free thyroxine and glucose induced thermogenesis. No effect was discernible on mean resting and total energy expenditure, oral glucose tolerance, and ghrelin levels. The results add further evidence to the notion that reduced sleep causally entails an elevated BMI.

Holecki et al. [8] re-investigated the effect of vitamin D supplementation on weight loss of obese females who participated in a 3-month weight reduction program. No beneficial effect of the supplementation was observed. The authors additionally provide a synopsis of human and rodent studies: the current study further substantiates that supplementation has no additional effect on weight loss.

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References