demands were high, possibly causing acute cognitive and behavioral abnormalities. If so, the greater tolerance to stress (latency to behavioral despair and agoraphobia) in heteroplasmic mice could be interpreted as a consequence of energy deficit. In fact, mice with a lysine codon deletion in the deubiquitinating enzyme USP46 exhibit a striking "loss of behavioral despair" in forced swim tests, as well as abnormalities in circadian rhythms (Zhang et al., 2011). As the ubiquitination system is sensitive to energy availability and associated with respiratory dysfunction in Parkinson's disease, it is not implausible that a respiratory deficit could affect deubiquitination, leading to the observed alterations in behavior. Whether subtle bioenergetic deficits play an important role in human psychiatric disorders and learning difficulties deserves serious consideration.

Although such behavioral changes are restricted to animals, their underlying cause may have played a wider role in organisms, including plants and fungi. By showing that heteroplasmy causes an energy deficit, Sharpley et al. (2012) just added another dimension to the long-standing questions of how and why uniparental inheritance of mitochondria arose and its relation to the evolution of two sexes.

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Turning on Brown Fat and Muscle Metabolism: Hedging Your Bets

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Developmental genes are essential in the formation and function of adipose tissue and muscle. In this issue of *Cell*, Teperino et al. demonstrate that noncanonical hedgehog signaling increases glucose uptake into brown fat and muscle. Modulation of developmental pathways may serve as a potential target for new treatments of diabetes and other metabolic disorders.

Obesity results from an imbalance between energy intake and energy expenditure. In obesity, the excess energy is stored as triglyceride in white adipose tissue (WAT). Mammals, including humans, also have active brown adipose tissue (BAT), which is specialized for energy expenditure. BAT has also been shown to share some common developmental origins with skeletal muscle, the other major tissue involved in thermogenesis (Kajimura et al., 2010).

Over the past two decades, the mechanisms underlying the differentiation of WAT and BAT have been elucidated and have been shown to involve a transcriptional cascade beginning with C/EBPβ, C/EBPδ, and Krox20, which induce C/EBPα and PPARγ, the major transcriptional regulators of adipose differentiation. In the case of brown fat, additional coactivators are involved, including PGC1α and PRDM16 (Kajimura et al., 2010). These pathways are regulated positively by a number of growth factors and hormones, especially insulin, IGF-1, and the BMPs, and negatively by the Wnt pathway (Fournier et al., 2012; Christodoulides et al., 2009). Recently, fundamental developmental genes, including several Hox and T-box genes, have also been shown to be involved in programming adipose development and function and contribute to differences in WAT and BAT, as well as differences between WAT in different anatomical

Figure 1. The Signaling Pathways Linking Hedgehog Signaling to Energy Storage and Expenditure

depots (Gesta et al., 2011; Mori et al., 2012) (Figure 1).

In this issue of *Cell*, Teperino et al. (2012), demonstrate a novel, noncanonical hedgehog signaling pathway, a pathway in which Smoothened (Smo) activates the AMP kinase (AMPK) pathway in brown fat and muscle, leading to an increase in insulin-independent glucose uptake and energy expenditure (Teperino et al., 2012). This extends previous studies by this group, which showed that fat-specific disruption of Suppressor of Fused, which normally activates the canonical hedgehog signaling pathway, leads to loss of white, but not brown, fat mass by blocking differentiation of white adipocytes through repression of early adipogenic factors (Kajimura et al., 2010). This also adds to studies that have shown that hedgehog signaling can inhibit adipogenesis of WAT and that repression of this pathway can lead to an increase fat development. In white fat, this involves the canonical hedgehog pathway and is dependent upon Gli transactivation of target genes, whereas the current paper shows activation of a Smo-Ca^{2+}-AMPK pathway in brown fat and muscle. The uncoupling of canonical and noncanonical hedgehog signaling represents a paradigm shift that has several important clinical implications. On one hand, activation of the Smo pathway can explain many of the adverse side effects, including muscle spasms and weight loss, observed during cancer treatment with hedgehog "inhibitors." On the other hand, this study suggests that the development of selective agonists of this alternative pathway may hold therapeutic promise for the treatment of obesity and diabetes.

Like hedgehog, the activation of the Wnt signaling pathway stimulates myogenesis and largely inhibits adipocyte differentiation, whereas expression of negative regulators of Wnt signaling such as secreted frizzled-related proteins (Sfrps) stimulate adipogenesis (Christodoulides et al., 2009). Interestingly, activation of Wnt signaling in mature brown adipocytes drives their conversion into white adipocytes. Likewise, whereas TGF-β itself inhibits adipogenesis, the closely related bone morphogenetic proteins (BMPs) are positive regulators of this process. Both BMP2 and BMP4 have been shown to promote adipogenesis of WAT while inhibiting myogenesis, whereas BMP7 promotes differentiation of brown preadipocytes (Tseng et al., 2008). Inhibition of the Activin receptor IIb also results in an increase in the mass of the interscapular BAT and skeletal muscle without affecting WAT (Fournier et al., 2012).

Several T-box (Tbx) and Hox genes have been shown to control adipose and muscle function. Tbx15 is differentially expressed between different WAT depots and regulates oxidative metabolism (Gesta et al., 2011), whereas Tbx1 has been shown to be preferentially ex-

pressed in the inducible pool of brown adipocytes present in white fat (Wu et al., 2012). Hox gene expression clearly demarcates brown and white adipose tissue, and decreasing HoxC8 expression by overexpressing its targeting micro-RNA, miR-196a, leads to an increase brown adipocytes within white adipose tissue (Mori et al., 2012).

Numerous potential mechanisms could link developmental genes to control of adipogenesis. MicroRNAs, pocket proteins (necdin and Rb proteins), phosphatases, and matrix proteins have all been shown to have important roles in adipose tissue biology. The study of Teperino et al. demonstrates that hedgehog acts via a cilia-dependent, noncanonical pathway that leads to activation of AMPK and glucose uptake (Teperino et al., 2012). Cyclopamine, a classical hedgehog antagonist, activates this pathway, increasing glucose uptake in an insulin-independent manner in brown adipose tissue and muscle. Other regulators of adipose and muscle function also converge on the AMPK pathway. Alterations in Wnt signaling have been shown to alter AMPK activity and glucose metabolism in muscle. Furthermore, expression of constitutively active β-catenin in preadipocytes can lead to the generation of an uncharacterized mediator that activates AMPK and enhances glucose uptake in an insulin-independent manner in both brown fat and skeletal muscle (Zeve et al., 2012).

Bmp8b treatment of brown adipocytes has also been shown to lead to an increase in AMPK activation (Whittle et al., 2012). Though pharmacological activators of AMPK, especially metformin, are already in clinical use, activators of the noncanonical hedgehog pathway and modulators of these other developmental gene pathways may serve as targets for new therapeutics for diabetes and obesity.

The current study from Teperino et al. adds to the burgeoning body of data that developmental genes and signaling pathways play integral roles not only in the formation, but also in the function, of brown fat, white fat, and muscle. Thus, these pathways regulate not only development of these tissues, but also the metabolism of the fully differentiated cells. These findings suggest that modulation of these developmental genes and their signaling pathways has therapeutic implications across a wide array of disease states, including cancer and metabolic disorders.

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A Circuit Mechanism for Neurodegeneration

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How deficiency in SMN1 selectively affects motoneurons in spinal muscular atrophy is poorly understood. Here, Imlach et al. and Lotti et al. show that aberrant splicing of Stasimon in cholinergic sensory neurons and interneurons leads to motoneuron degeneration, suggesting that altered circuit function may underlie the disorder.

Neurological disorders with a genetic basis usually involve the degeneration of distinct cellular subpopulations within the central nervous system (CNS). The factors shaping the differential sensitivity of neurons to the same genetic insult are poorly understood. Sensitivity to disease may be cell autonomous, with the particular molecular makeup of one subpopulation of neurons being responsible for the phenotype. In an alternative scenario that has received much less attention so far, a subpopulation of neurons might be prone to degeneration due to alterations in the function of the neuronal circuits that impinge onto those neurons. In the latter view, degenerating neurons might represent the "weakest link" within a circuit, although they are not primarily affected by the genetic mutation. The circuit scenario further implies that distinct dysfunction pathways affecting the same circuit might produce comparable patterns of neurodegeneration. In this issue of Cell, Imlach et al. (2012) and Lotti et al. (2012) provide evidence in a Drosophila model of spinal muscular atrophy (SMA) that motoneuron dysfunction is in fact due to impairments in the function of sensory neurons and interneurons (Figure 1).

SMA is a frequent autosomal-recessive motoneuron disorder characterized by the degeneration of α motoneurons due to inactivation of the survival of motor neuron 1 (SMN1) gene. SMN1 protein is critically involved in the biogenesis of small nuclear ribonucleoproteins (snRNPs), and SMN1 loss extensively