cold, is less effective in inducing the formation of beige adipocytes in the inguinal WAT depot of *Ehmt1*^{adipo} knockout mice than in wild-type mice. Since Ohno et al. (2013) mainly studied the effect of EHMT1 on classical brown adipocytes derived from *Myf5*$^+$ precursors, it is an open question as to whether the molecular machinery underlying this effect in beige adipocytes is similar to that in classical brown adipocytes. Another question relates to the bipotential precursor cells described by Lee et al. (2012), which can develop into either white or brown adipocytes depending on the type of stimulation: activation of β3-adrenergic receptor leads to the formation of brown adipocytes, while a high-fat diet stimulates the differentiation of white adipocytes. Are such cells derived from a population of precursors that avoided a muscle destiny by appropriately regulating EHTM1? One more exciting issue is how the early B cell factor 2 (Ebf2) relates to EHTM1. Ebf2 also regulates PPARγ activity and acts as a key transcriptional regulator of brown fat cell fate and function (Rajakumari et al., 2013). This factor may act synergistically with EHTM1 since it recruits PPARγ to BAT-selective target genes (Rajakumari et al., 2013), an action that appears to be complementary to the inhibition of muscle gene expression mediated by EHMT1.

The recent findings deciphering the transcriptional and chromatin code that regulates brown fat formation and function are important not only from a biological science perspective. They also provide new pathways and molecules that can be tested and targeted for therapeutic purposes so that the beneficial effects of having ample amounts of brown fat can be harnessed and made available to the many who suffer from obesity and obesity-related maladies, such as type 2 diabetes.

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Synaptic Plasticity and the Warburg Effect

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Functional brain imaging studies show that in certain brain regions glucose utilization exceeds oxygen consumption, indicating the predominance of aerobic glycolysis. In this issue, Goyal et al. (2014) report that this metabolic profile is associated with an enrichment in the expression of genes involved in synaptic plasticity and remodeling processes.

Aerobic glycolysis (AG), also known as the Warburg effect, is a metabolic hallmark of cancer cells (Warburg, 1956). It consists of production of lactate from glucose in the presence of oxygen. As it turns out, some brain areas and cell types can also process glucose in this way. Studies at the whole organ level have shown already decades ago (for Review, see Allaman and Magistretti, 2013) that glucose utilization by the brain is in excess of oxygen consumption by about 10%, implying a nonoxidative use of glucose entering the brain. Functional brain imaging studies have identified in the adult brain areas such as the dorsolateral prefrontal cortex, superior and medial frontal gyrus, precuneus and posterior cingulate cortex, in which AG predominates, accounting for 25% of glucose utilization, whereas in other areas such as the cerebellum AG is virtually nonexistent (Vaishnavi et al., 2010). As far as cell types are concerned, astrocytes (glial cells) are the major sites of AG in the brain (Bélanger et al., 2011).

The question then arises of the function of AG in these specific locales. In an

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attempt to address this question, Goyal and colleagues report in this issue a thorough meta-analysis of the developmental pattern of whole brain AG by comparing glucose utilization and oxygen consumption throughout the human life span (Goyal et al., 2014). During early developmental stages, aerobic glycolysis levels are highest, with a peak at 5 years of age, when it accounts for nearly 30% of glucose utilization. Interestingly, glucose utilization at this age is twice as high as during adulthood, whereas oxygen consumption does not increase as much, indicating a considerably high lactate production rate by AG during this critical period of brain development. Given that during adulthood AG becomes restricted to the specific brain areas mentioned earlier, the authors reasoned that processes that are very active during early development are likely to persist in these brain areas, a process defined as neoteny (Petanjek et al., 2011). To test this hypothesis, Goyal and colleagues compared AG with a neotenic index in 16 brain regions. This index, which essentially indicates the persistence of developmental genes in adulthood, was derived from a data set of gene expression in the human brain, the BrainSpan Study, a publicly available, gene-expression microarray data set spanning the human life span (http://www.brainspan.org). The authors found a remarkable correlation between AG and the neoteny index, supporting the hypothesis that the regional distribution of AG observed in the adult brain reflects the persistence of a developmental character. Extending the analysis to gene-expression patterns from the Allen Human Brain Atlas (http://www.brain-map.org), the authors identified 116 genes that are strongly associated with AG. The gene with the highest association is EPHB6 (ephrin type B receptor 6), a gene involved in a variety of developmental and remodeling functions, including regulation of axon guidance and dendritic dynamics. Furthermore several other genes involved in synaptic transmission and plasticity were also highly associated with aerobic glycolysis. Interestingly, all 116 genes associated with AG display a particular pattern of expression across the life span, being highly expressed throughout the brain during early childhood, with expression becoming restricted to AG-active brain regions in adulthood. More importantly, these data indicate that aerobic glycolysis is associated in the adult brain with the expression of genes that are involved in plasticity and synaptic remodeling processes.

An important question that the study was not designed to address is the nature of the mechanism(s) that underlie the correlation between aerobic glycolysis and synaptic plasticity and turnover. One lead comes from the product of aerobic glycolysis, namely lactate. Indeed, previous studies reported the ability of lactate to stimulate gene expression in several cell types of culture including vasculogenic stem cells though the activation of specific transcription factors (Milovanova et al., 2008). Furthermore, astrocyte-derived lactate is necessary for induction of the gene *Arc*, a key element of synaptic plasticity such as long term potentiation, and for the consolidation of long-term memory (Suzuki et al., 2011). Thus, aerobic glycolysis may well modulate the expression of synaptic plasticity through lactate, its metabolic product.

Interestingly, the regions displaying high AG in the adult map onto what is now known as the Default Mode Network, a group of brain regions more active in the absence of a task-specific activation (Raichle et al., 2001). The AG-active areas also correspond to those regions that are most vulnerable to β-amyloid deposition (Vlassenko et al., 2010).

The relationship between aerobic glycolysis and the Default Mode Network along with the associated vulnerability to β-amyloid deposition remains to be determined. However, the main message of the work of Goyal et al. is the fact that the Warburg effect, namely aerobic glycolysis, is associated with synaptic remodeling. Since AG can easily be visualized using PET imaging for glucose utilization and oxygen consumption, one can agree with the authors' conclusions that in vivo measurement of AG may provide information concerning ongoing synaptic plasticity and turnover in normal and pathological conditions.

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