whether a tissue-specific clock exists in joint tissue would help to determine whether disease-associated impairments in clock function also occur in other tissues and disease processes.

The important findings described by Gibbs *et al.*[10] elucidate mechanisms that underpin well-recognized clinical phenotypes in patients with inflammatory lung disease[2,3,15] and provide avenues to developing new therapeutic approaches to tackle neutrophil-dominant inflammation.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Lightening up a notch: Notch regulation of energy metabolism

Thomas Gridley & Shingo Kajimura

Inhibiting Notch signaling induces adipose browning, improves systemic glucose tolerance and insulin sensitivity, and suppresses weight gain in mice.

A fundamental concept of obesity is the lack of balance between energy intake and energy expenditure. Currently, all US Food and Drug Administration–approved antiobesity medications aim to limit energy intake, either through appetite suppression or inhibition of lipid absorption by the intestine[1]. Although these medications are effective in the short term, several adverse effects, such as depression or steatorrhea, are often associated with long-term treatment, and new avenues are required.

All mammals harbor two types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT). WAT functions mainly in the storage of excess energy, whereas BAT specializes in dissipating energy in the form of heat and functions as a defense against cold and obesity through the BAT-specific protein uncoupling protein 1 (Ucp1). Although BAT was formerly considered to be restricted to infants and small animals, the recent discovery of BAT in adult humans led to the exciting notion that increasing energy expenditure by activating BAT thermogenesis could provide a novel approach to modulating energy balance[2]. Recent studies indicate that adult humans and rodents[3–6] have a 'recruitable' form of thermogenic adipocytes, termed 'beige adipocytes', whose development can be induced by certain environmental stimuli (termed 'browning' of white fat), such as chronic cold exposure. In this issue of *Nature Medicine*, Bi *et al.*[7] describe a new role for the Notch signaling pathway[8], a pathway known to have multiple roles in development but not previously known to play an important role in regulating adipose browning and energy homeostasis in mammals. Thus, the authors identify a potential new therapeutic avenue for treatment of obesity by modulating this important developmental pathway.

The authors initially carried out gene expression analyses of white adipose tissue depots in mice and found that an inverse correlation existed between the expression levels of Notch family receptors and targets (such as the transcriptional repressor Hes1), and the expression of the BAT-specific gene *Ucp1* and two transcriptional regulators crucial for brown adipocyte development, *Ppargc1a* and *Prdm16* (ref. 2). To assess whether there was a direct relationship between levels of Notch signaling and the differentiation of BAT, the authors selectively deleted in adipocytes either the gene encoding the Notch1 receptor or the gene encoding the primary transcriptional effector of the Notch signaling pathway, *Rbpj*. Mice in which Notch signaling was selectively reduced in adipocytes exhibited morphological browning of subcutaneous white fat depots, upregulated expression of BAT-selective genes and elevated thermogenesis. These mice also exhibited an improvement in glucose homeostasis and insulin sensitivity and had higher rates of whole-body energy expenditure than wild-type mice. Strikingly, these mice with selective Notch signaling reduction were protected from high-fat diet–induced obesity (**Fig. 1**).

Bi *et al.*[7] then analyzed mice in which Notch signaling was selectively increased in adipocytes through expression of a constitutively active form of the Notch1 receptor. Compared to wild-type mice, these mice in which Notch1 was overexpressed in adipocytes exhibited impaired glucose homeostasis and insulin sensitivity, lower metabolic rate and core body temperature, and reduced expression of the Ucp1 and Pgc1-α (encoded by Ppargc1a) proteins in WAT.

The authors then further investigated the molecular mechanisms of the Notch signaling-regulated adipose browning effects. They showed that the transcriptional repressor Hes1, whose transcription is induced by Notch signal reception, directly bound in cultured mouse adipocytes to consensus Hes1 binding sites that are present in the proximal promoter regions of both human and mouse *Prdm16* and *Ppargc1a* genes. Furthermore, they showed that the Hes1 protein could suppress transcription of the *Ppargc1a* gene. In turn, Notch1-deficient mouse adipocytes, or wild-type adipocytes in which Notch signaling had been suppressed by an inhibitor of γ-secretase (an enzyme complex required for proteolytic processing and signal transduction by Notch family receptors), had elevated levels of BAT-selective proteins, such as Ucp1, Pgc1-α and Prdm16, and increased cellular respiration. These results suggest that the browning effects resulting from inhibition of Notch signaling are cell autonomous.

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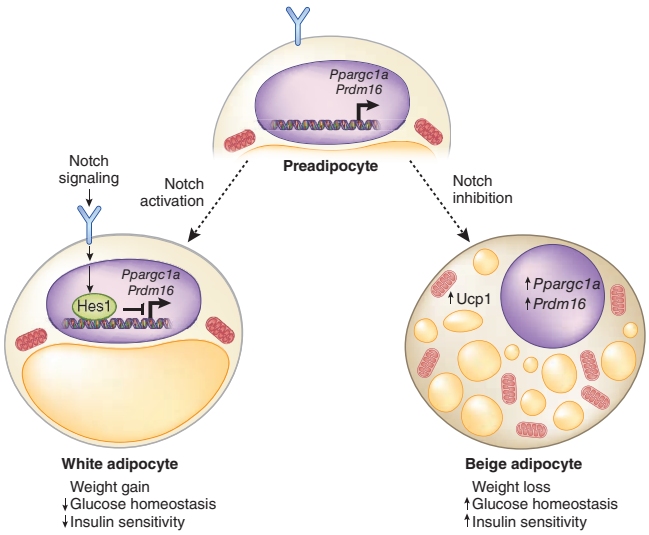

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Figure 1 Notch signaling inhibition promotes adipose browning and improved energy homeostasis. The study by Bi *et al.*[7] demonstrates that selective inhibition of Notch signaling in mice induces a BAT-selective gene program most likely acting in preadipocytes that promotes differentiation into beige adipocytes, leading to an increase in energy expenditure, a decrease in body weight gain and an improvement in systemic glucose homeostasis and insulin sensitivity. Alternatively, Notch signal reception induces expression of the Notch target protein Hes1, which binds directly to the promoter regions of the *Prdm16* and *Ppargc1a* genes, suppressing their transcription and promoting white adipocyte differentiation.

Importantly, the authors tested the ability of pharmacological inhibition of the Notch pathway to reduce obesity in mice *in vivo* by administering a γ-secretase inhibitor to wild-type mice, as well as to obesity-prone mice homozygous for a null mutation of the leptin gene (*ob/ob* mice). Treatment of wild-type mice with the inhibitor increased glucose tolerance, insulin sensitivity and UCP1 expression and reduced leptin expression and adiposity. In *ob/ob* mice, γ-secretase inhibition almost entirely prevented the weight gain observed in control, vehicle-treated mice.

An important question to address in the future is whether Notch signaling also regulates browning in adult humans, given the differences between humans and mice. Although several studies indicate that beige adipocytes may exist in adult human BAT[3,4,6], the cellular and molecular mechanisms of adult human brown adipocyte development are currently poorly understood. However, the work of Bi *et al.*[7] suggests that pharmacological inhibition of Notch signal transduction in adipocytes may have beneficial metabolic effects in humans. The potential benefits of doing so, however, must be balanced against the many biological roles played by the Notch pathway, as well as by the fact that Notch pathway components can act as either oncogenes or tumor suppressors, depending on the type of mutation and the particular tissue affected[9,10].

Numerous Notch pathway antagonists have been developed and are being tested in preclinical studies and clinical trials[11–13]. However, serious side effects have been observed in clinical trials in which these therapies have been tested for treatment of Alzheimer's disease or several types of cancer. Inhibition of the ligand-receptor interaction in Notch signaling may provide improved specificity compared to inhibition of receptor processing, although neither the cellular source nor the identity of the Notch ligand(s) signaling to Notch receptor–expressing preadipocytes are currently known. Much work remains before Notch pathway inhibition might be realized as an effective therapeutic intervention for obesity. However, the study of Bi *et al.*[7] represents an exciting first step toward this goal.

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