

these stars orbit the black hole within a single disk (4–6), and their IMF appears to contain many more massive stars than would be expected from normal star formation (7).

One idea proposed to explain why young stars are found so close to a black hole is that they initially formed in a normal environment before subsequently spiraling inward. The S-stars may have formed within binaries that were disrupted during black hole flybys, leaving one star in a short-period orbit while the other was ejected from the galactic center (8). Promisingly for this scenario, a handful of hypervelocity stars that may originate from the galactic center have recently been identified elsewhere in the Milky Way (9). To explain the disk stars, an analogous model suggests that an entire cluster of stars spiraled into the galactic center, losing stars along the way and finally depositing the massive stars of the cluster core in the disk (10). To date, though, no sign has been seen of the stellar trail that a dissolving cluster would leave in its wake.

A rival model postulates that a thin disk of gas once orbited the black hole before fragmenting into a stellar disk (11). It has long been known that gas disks orbiting black holes at these radii are unstable to star formation (12). The new aspect that Bonnell and Rice

have addressed is how an unstable disk could form in the first place. Their numerical simulations show that an ordinary molecular cloud—formed at distances large enough to be immune from the black hole’s dangerous tidal forces—could survive the inward plunge to deposit a fraction of its gas into an eccentric disk from which the stars subsequently form. Turbulent support within the gas cloud is the key ingredient in their model, sustaining it against premature collapse long enough to permit disk formation. During the infall, the gas is heated as it is compressed and torn apart by the black hole, promoting the top-heavy IMF observed for the disk stars.

As satisfying as the new results are, the case for disk fragmentation as the origin for the disk stars remains unproven. We do not know whether the initial conditions assumed by Bonnell and Rice are realized in the galactic center. Most of the molecular gas in the inner 100 light-years avoids the very center (13), and future work will need to assess whether a fraction of that gas can be occasionally diverted into a plunging trajectory. Another interesting avenue will be to explore the implications for other galactic nuclei. A rather older disk of massive stars is seen in the nucleus of Andromeda (14), the nearest galaxy comparable to the Milky Way, but the

frequency of similar phenomena remains poorly constrained. There is an obvious potential trade-off with black hole growth, because star formation at these small radii consumes gas whose fate would otherwise be to feed the black hole. Black hole growth is known to be slowing over cosmic time, and it is tempting to speculate that the exquisite observations of the galactic center may be affording us a glimpse of one of the mechanisms responsible for that trend.

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## DEVELOPMENTAL BIOLOGY

# How Now, Brown Fat?

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Obesity, the condition of excess fat storage in adipose tissue, is harmful to health and epidemic in modern society (1). Adipocytes, or “fat cells,” are specialized cells that store this fat in triglyceride-containing droplets. Until recently, it was thought that all adipocytes are derived from a common precursor. It seemed almost obvious that different types of fat cells are closely related. However, this week, a study by Seale *et al.* (2) provides compelling evidence against this doctrine.

Not all adipocytes have the same physiological function. Those in white adipose tissue constitute the major energy storage depot in mammals. When nutritional sources of energy are scarce, triglyceride breakdown in white

adipocytes generates fatty acids that are exported and used as fuel by other tissues, including muscle. In obesity, where energy expenditure is matched, and usually exceeded, by caloric consumption, both the size and the number of white adipocytes increase. White adipose tissue is often classified on the basis of its location as subcutaneous and abdominal (or visceral) fat. Secretions from visceral fat pass through the liver before entering the general circulation, and this has been implicated in the pathogenesis of type 2 diabetes and insulin resistance (3). Visceral adipocytes differ from subcutaneous adipocytes in their gene expression profiles (4), although there is no evidence that the precursors of white adipocytes in visceral and subcutaneous depots are fundamentally different.

In contrast to white adipose tissue, brown adipose tissue plays an active role in energy expenditure, oxidizing fatty acids produced by triglyceride hydrolysis to generate heat. As

**Brown adipose tissue is, surprisingly, more related to skeletal muscle than to white adipose tissue.**

the name suggests, brown adipose tissue appears different from white adipose tissue, largely because of the increased number of mitochondria (cytochromes within the mitochondria account for the color) that function in oxidative metabolism. Also, brown adipocytes contain multiple small lipid droplets, whereas white adipocytes usually have a single large lipid droplet. The thermogenic oxidation of fatty acids is facilitated by uncoupling protein-1, which is expressed specifically in brown adipocytes. In rodents, brown fat is characteristically found in the interscapular region, and is critical for thermoregulation throughout life. By contrast, humans have proportionally more brown fat at birth than in adulthood, when it can be difficult to locate. Nevertheless, recent studies point to the existence and conserved function of brown adipose tissue in humans (5).

Although brown and white adipocytes look different and have different physiological

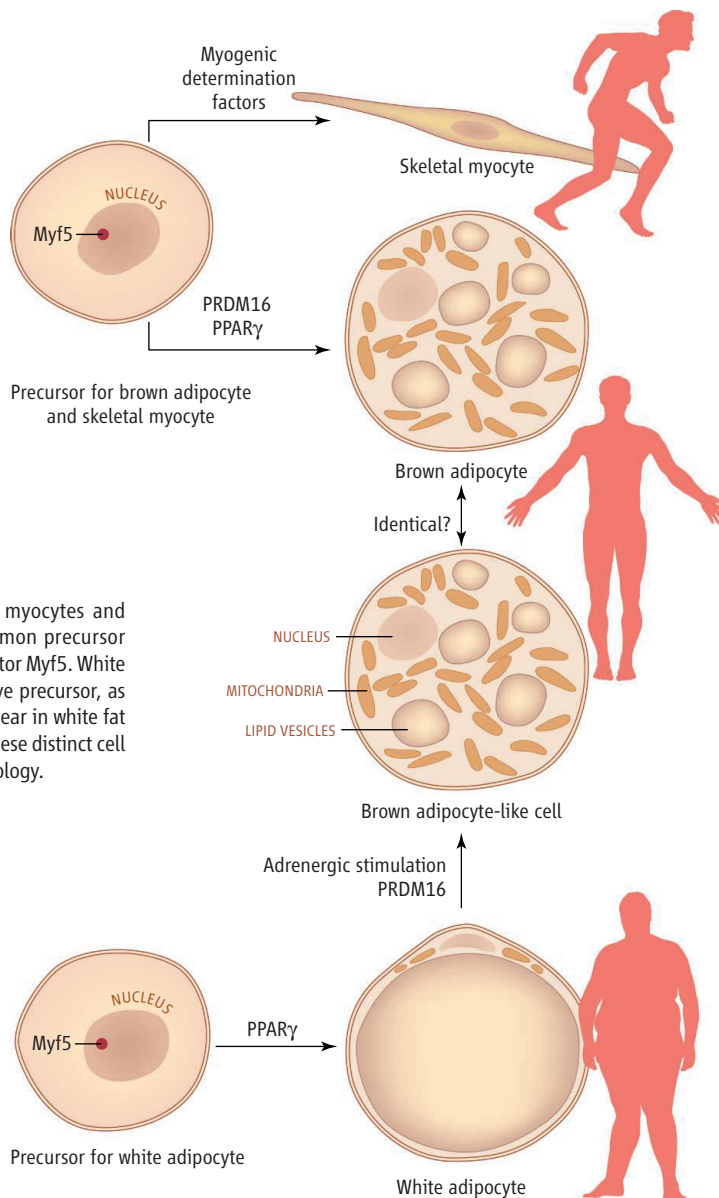
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functions, they are considered to have derived from a common precursor cell. One reason is that the transcription factor peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ), which is the master regulator of adipogenesis, is required for differentiation of both white and brown adipocytes (6). In addition, conversion of white to brown adipocytes is induced by  $\beta$ -adrenergic stimulation—that is, stimulation of white adipose with hormones (catecholamines) that are released in situations of stress or low blood sugar concentration (7).

**Paths to muscle and fat.** Skeletal myocytes and brown adipocytes derive from a common precursor cell that expresses the transcription factor Myf5. White adipocytes derive from a Myf5-negative precursor, as do brown adipocyte-like cells that appear in white fat depots after adrenergic stimulation. These distinct cell types play very different roles in physiology.

The factors that mediate conversion of white to brown adipose tissue have been extensively investigated, motivated, in part, by the hope that expansion of the brown-fat compartment, leading to increased energy expenditure, would be a novel way to treat obesity (8). Ten years ago, PPAR $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) was identified as a transcriptional coactivator that is enriched in brown adipocytes (9). Since then, PGC-1 $\alpha$  has emerged as a major metabolic regulator in brown fat, as well as other tissues, although it is not required for the expression of other brown fat-specific genes, including uncoupling protein-1 (10). About a year ago, in a more systematic search for brown-fat transcription factors, Seale *et al.* found that a previously unsuspected protein, PRDM16, is required to maintain the brown-fat phenotype, including the expression of uncoupling protein-1 (11).

The implication that PRDM16 and PGC-1 $\alpha$  are involved in the generation and function of brown adipocytes advanced the field, but did not alter the basic notion that brown and white adipocytes derive from a common precursor. Therefore, the new finding from Seale and colleagues is a real surprise: Brown adipocytes actually derive from a cell that oth-



erwise gives rise to skeletal muscle but not to white adipocytes (2). This conclusion is supported by evidence that forced expression of PRDM16 leads cultured mouse skeletal muscle cells to differentiate into brown adipocytes and, conversely, that brown adipocytes depleted of PRDM16 take on the look and function of skeletal muscle cells. Independent of genetic manipulation of PRDM16, lineage-tracing studies indicate that brown adipocytes are derived from cells that express the transcription factor Myf5, a molecular marker of skeletal muscle precursors. Importantly, white adipocytes did not derive from these cells, demonstrating that the developmental pathways of white and brown adipocytes diverge before the switch between brown fat and skeletal muscle (see the figure).

The link between brown fat and skeletal

muscle was presaged by the observation that gene-expression profiles of brown adipose tissue share features characteristic of skeletal muscle (12). Indeed, in retrospect, the oxidative metabolism of brown fat, as well as its color and mitochondrial content, is more similar to those of skeletal muscle than to those of white adipose tissue. The relationship between brown adipose tissue and skeletal muscle is likely to extend to humans, where brown adipocyte precursors have recently been identified in skeletal muscle (13).

The close connection between brown adipose tissue and skeletal muscle raises several questions. How does adrenergic stimulation convert white to brown adipose tissue? Seale *et al.* report that these brown adipocyte-like cells, although they express PRDM16, are not derived from Myf5-expressing precursors. Hence, there must be an alternative pathway to brown adipocyte formation that is more highly related to that of white adipogenesis. Are the brown adipocyte-like cells that emerge in white fat depots distinguishable, molecularly or functionally, from the adipocytes in brown fat depots? Will understanding the origin of brown adipocytes lead to novel therapeutic approaches to obesity? Confronted with a seemingly inexorable rise in obesity

and its dire medical consequences, our society may well benefit from new developments.

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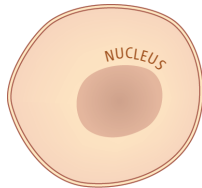
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## ERRATUM

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**Perspectives:** "How now, brown fat?" by M. A. Lazar (22 August, p. 1048). The cell identified as "Precursor for white adipocyte" should not have been labeled with "Myf5." The corrected illustration of the cell is shown here.



Precursor for white adipocyte