Brown Fat and Skeletal Muscle: Unlikely Cousins?

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Although the functions of white fat and brown fat are increasingly well understood, their developmental origins remain unclear. A recent study published in *Nature* (Seale et al., 2008) identifies a population of progenitor cells that gives rise to brown fat and skeletal muscle but not white fat.

Obesity and its associated metabolic disorders, type 2 diabetes and cardiovascular disease, have reached epidemic proportions. Humans have two types of adipose tissue—white fat, which stores energy as triglycerides, and brown fat, which burns lipids to generate heat (thermogenesis). Brown fat and white fat have much in common, including the capacity to store and metabolize lipids and the expression of many of the same adipocyte-specific proteins. Yet, brown fat also shares features with skeletal muscle: both use oxidative phosphorylation to expend energy, have abundant mitochondria, and are capable of adaptive thermogenesis. A new study by Seale et al. (2008) in *Nature* demonstrates the strongest link yet between brown fat and skeletal muscle—the existence of a common progenitor cell. Using in vivo fate mapping in mice, these investigators show that brown fat and skeletal muscle develop from a common progenitor that expresses the transcription factor myf5. Although this newly discovered progenitor population makes both brown fat and skeletal muscle, it fails to give rise to white fat.

Until recently, it was thought that brown adipose in humans is only active in newborns. However, PET scans have identified active brown fat in the cervical, supraclavicular, paravertebral, mediastinal, para-aortic, and suprarenal regions of adults, introducing the notion that brown adipose tissue contributes to energy balance in humans and is therefore a therapeutic target to combat obesity-associated morbidities (Nedergaard et al., 2007). In small mammals, brown adipose tissue exists within distinct depots, most notably within the interscapular regions innervated by the sympathetic nervous system. The release of catecholamines from the sympathetic nervous system induces lipolysis of triglycerides in the lipid droplets of individual brown adipocytes, leading to accelerated oxidation of the fatty acids (Cannon and Nedergaard, 2004).

Like brown fat, oxidative skeletal muscle is specialized for lipid catabolism rather than storage. Skeletal muscle is also innervated by the sympathetic nervous system, contains abundant mitochondria, and facilitates adaptive thermogenesis. Unlike brown adipocytes, skeletal myocytes do not express uncoupling protein-1 (UCP-1), a proton transporter unique to brown fat that uncouples electron transport from ATP production, allowing energy from the oxidized lipids to dissipate as heat. Skeletal muscle develops from myogenic progenitors of the dorsal epithelium of the somites (the dermomyotome) through a complex process requiring the participation of multiple transcription factors, including Pax3/7 and myf5 (Buckingham, 2006). The recent study by Seale et al. using in vivo fate mapping demonstrates that brown but not white fat cells arise from precursors that express myf5, providing evidence for a close relationship between brown adipose tissue and skeletal muscle in development. These results are supported by earlier studies that identified a myogenic gene expression signature in brown fat precursor cells (Timmons et al., 2007). Additionally, Atit et al. (2006) used lineage-tracing techniques to demonstrate that some interscapular brown fat bundles originate from cells of the central dermomyotome that express *engrailed-1* (*En1*).

The studies of Seale et al. additionally show that the transcriptional regulator PRDM16 appears to specify the brown fat lineage from the myf5-expressing progenitors through mechanisms that involve activation of PPARγ and suppression of myogenic factors. Specifically, loss of PRDM16 from brown fat precursors in vitro and in vivo disrupts their differentiation into brown fat and enhances expression of muscle genes rather than enhancing white fat differentiation, as might have been anticipated. In contrast, ectopic expression of PRDM16 in myoblasts in culture induces brown fat adipogenesis through mechanisms that involve enhanced expression of PPARγ. Moreover, the studies demonstrate a direct interaction between PRDM16 and PPARγ that appears to activate the transcriptional function of PPARγ. It is also interesting that these authors found that PPARγ alone can convert myogenic cells into adipocytes (presumably white), whereas conversion into brown fat cells requires the additional expression of PRDM16.

These data are consistent with the notion that skeletal muscle and some depots of brown fat share a common myf5-expressing progenitor that diverges along separate developmental lineages to give rise to brown adipoblasts (preadipocytes) and myoblasts. PRDM16 likely functions at an early stage to influence this lineage deci-

sion (Figure 1). The expression of PRDM16 is likely regulated by various extracellular effectors including bone morphogenetic proteins (BMPs) and Wnts (Gesta et al., 2007). In addition to inducing and activating PPARγ, PRDM16 also is likely to interact with other coregulators that have been similarly induced in response to developmental factors that control the brown fat lineage. Coregulators would include repressors that suppress the myogenic lineage within the progenitors of brown fat. Other studies by Spiegelman and collaborators have shown that PRDM16 does have the ability to simultaneously repress and activate genes through a mutually exclusive interaction with either CtBP corepressors or PGC-1α/β coactivators, respectively (Kajimura et al., 2008).

Chronic cold exposure or catecholamine stimulation can induce expression of many brown-specific markers in depots of white adipose tissue (Guerra et al., 1998). However, Seale et al. show that the brown fat cells that emerge in white adipose tissue in response to β-adrenergic stimulation are not derived from myf5-expressing progenitors. These data suggest that the emergence of brown fat cells in white adipose tissue is likely due to induction of expression of brown fat genes in white adipocytes that are already in existence. However, the question still remains as to whether there are separate progenitors for the different depots of brown fat and whether some brown fat cells can arise from the same lineage as white fat cells. On the basis of the observations of Seale et al., it is likely that brown adipocytes arise from myogenic precursors in response to unknown effectors that enhance PRDM16 expression. In this regard, brown adipocytes have been identified in skeletal muscle, and their abundance in different strains of mice correlates with energy expenditure and resistance to obesity (Almind et al., 2007). It is quite possible that these brown adipocytes in muscle develop from myf5-expressing satellite cells (myogenic precursors) that principally function to repair damaged muscle tissue. An alternative function of these satellite cells might be to enhance the oxidative capacity of skeletal muscle. Hence, the ability of some individuals to expend energy might be due to the size of this pool of brown adipocyte progenitors within skeletal muscle.

Future studies will include extensive fate mapping to trace the source of the other brown fat depots and a delineation of the many factors (extracellular as well as intracellular) regulating the fate of the individual progenitors. Several recent studies have suggested that different white fat depots have distinct functions in regulating overall metabolism, most notably the link between visceral white fat and metabolic disorders. Consequently, identification of the origins of these depots and the factors responsible for their unique functions will provide insight into obesity and its comorbidities.

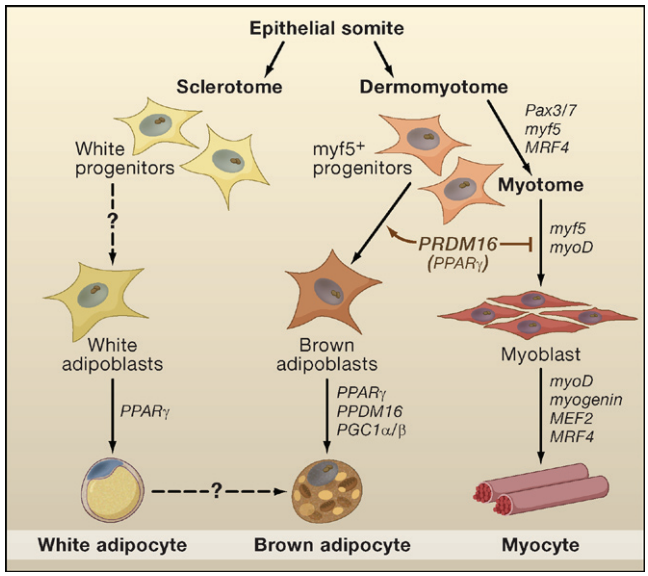

Figure 1. Developmental Pathways for Brown Fat, White Fat, and Skeletal Muscle

Seale et al. (2008) show that progenitor cells expressing the transcription factor myf5 (myf5+) develop into brown adipocytes as well as skeletal myocytes. This population of progenitors likely arises within the developing dermomyotome or myotome, where additional factors, most notably Pax3, contribute to induction of myf5; myf5 then induces expression of other myogenic factors. The transcription factor PRDM16 is induced at this early stage in a subpopulation of progenitors by unknown factors and activates expression of the nuclear hormone receptor PPARγ. Together, PRDM16 and PPARγ suppress myogenesis and initiate development of brown adipocytes. The mechanism of early development of white adipocytes is not known, although progenitors may arise from the developing somites, possibly the sclerotome. In addition to controlling the development of brown fat, PPARγ also controls white fat formation. The mechanisms regulating emergence of brown adipocytes in white depots are also unknown.

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