# Adipose Tissue Flexes Its Muscles

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**How brown and beige adipocytes activate UCP1-dependent thermogenesis has been studied in great detail. In *Cell Metabolism*, Tharp et al. (2018) have recently added another interesting dimension to this by demonstrating that actinomyosin-mediated elasticity regulates the thermogenic capacity of UCP1+ adipocytes, opening up new ways by which UCP1-dependent thermogenesis can be stimulated.**

Brown adipose tissue (BAT) is an interesting tissue since it has the capacity to activate several "futile" cycles that instead of generating ATP dissipate stored chemical energy as heat. This is potentially an important feature that can be used in the treatment of obesity-linked conditions such as type 2 diabetes. Even though we have recently learned that thermogenic adipocytes can use several different ways to generate heat, e.g., creatine cycling (Kazak et al., 2015) and SERCA2b-mediated calcium shuttling (Ikeda et al., 2017), UCP1 expression and ucp1-mediated thermogenesis are features that have defined the uniqueness of brown and beige adipocytes. Hence, activation of UCP1-mediated thermogenesis is a topic that has been intensively studied. Most aspects of signaling and activation have been covered, from cell surface-located β3-adrenegic receptors and subsequent activation of downstream signaling targets and complexes such as PKA, to transcriptional regulation of UCP1 and, more recently, posttranslational modification of UCP1 itself with sulfenylation of Cys253 (Chouchani et al., 2016).

Tharp et al. (2018) have taken a fresh approach to the study of UCP1 activation by using parallel plate rheometry on intact tissues such as BAT and white adipose tissue (WAT). This enabled the authors to measure mechanical properties including tissue stiffness. Notably, BAT has more stiffness than WAT, and when mice are cold exposed (4°C), their BAT is stiffer than that of mice kept at room temperature (23°C). Moreover, using atomic force microscopy (AFM) on brown adipocytes to directly measure cellular stiffness, the authors found that isoproterenol, a non-selective β-adrenoreceptor agonist, induces a contractile-like response in brown fat cells. Interestingly, isoproterenol is in clinical use to stimulate cardiac-myocytes to contract in conditions marked by a low heart rate (bradycardia). These muscle-like properties of brown fat cells are not too surprising since it is known that the transcriptional regulator PRDM16 controls a bidirectional cell fate switch between skeletal myoblasts and brown fat cells (Seale et al., 2008), indicating a close relationship between these two cell types. In line with this notion, the authors point out that muscle-specific type II myosin heavy chains (MyH), known to regulate intrinsic cellular forces, are expressed in brown fat cells. Thus, the brown fat cell seems to be well equipped for engaging in contractile-like activities.

Using type II myosin inhibitors, blebbistain and 2,3-butanedione monoxime, the authors found downregulation of UCP1 and reduced cytoplasmic stiffness. This effect was subsequently linked to activation of a calcium-sensitive smooth muscle isoform of the myosin light chain kinase (MYLK) family. Reduction of this kinase led to a seemingly specific loss of UCP1 expression. When the authors instead used a potentiator of MyH (omecamtiv mecarbil) together with isoproterenol, there was a significant enhancement of UCP1 expression levels compared with isoproterenol alone. Thus, it appears that actinomyosin-mediated tension is critical for thermogenic capacity of adipocytes and that targeting this pathway might be an interesting way to induce thermogenic UCP1 expression. Aided by RNA sequencing (RNA-seq) data to evaluate global transcriptome changes in response to actinomyosin inhibition, the authors identified downregulation of several YAP/TAZ (transcription factors known to act as sensors and mediators of mechanical cues) target genes, which in turn implies that the hippo signaling network and mechanosensing pathways are involved. Confirming involvement of YAP/TAZ *in vivo*, mice with a reduced level of YAP/TAZ in UCP1-expressing cells featured significantly reduced BAT depots.

These findings link β-adrenoreceptor stimulation, mechanosensing, and cellular mechanical properties to the regulation of UCP1-dependent thermogenesis. Experiments using other types of activation of BAT such as adenosine (Gnad et al., 2014) would be interesting to determine if this is a general effect that applies to all types of UCP1-mediated thermogenesis or a phenomenon specifically linked to β-adrenoreceptor stimulation. The authors have carried out experiments showing that both cellular stiffness and tissue stiffness are affected and regulated in a similar way. Does this reflect a dual function in thermogenesis, one that facilitates thermogenesis in the cell and one that enhances the thermogenic capacity of the tissue as such? It has previously been shown in humans that, while at room temperature, insulin stimulates BAT glucose uptake to a similar extent to that of cold-exposed humans. However, the glucose removal rate of the tissue is significantly higher after cold exposure (Orava et al., 2011). This is due to a concomitant increase of BAT perfusion in the case of cold exposure not seen in the case of insulin stimulation at room temperature. Since cold exposure elicits a β-adrenergic response in BAT, it is tempting to speculate that induction of tissue stiffness might be linked to upregulation of

perfusion. Relatedly, reduced renal tissue stiffness was found to be related to impaired renal perfusion (Guo et al., 2018). Furthermore, in an innovative three-dimensional imaging approach, Chi et al. (2018) have shown that PRDM16-expressing UCP1+ subcutaneous beige adipocytes have a higher density of sympathetic neurites as compared to white adipocytes. Since it is known that mechanosensing is also critical for axon growth (Koser et al., 2016), it would be interesting to see if BAT innervation is regulated by cellular or tissue stiffness. Finally, why is actinomyosin involved in cellular thermogenesis at all? Is it primarily to achieve the mechanical properties induced by activation of actinomyosin, or do actinomyosin microfilaments confer other functions to brown fat cells that promote thermogenesis?

These new findings provide new pathways and molecules that can be tested and targeted for therapeutic purposes so that the beneficial effects of activated BAT may 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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