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RESEARCH HIGHLIGHT

When BAT is lacking, WAT steps up

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Brown adipose tissue (BAT) has evolved to generate heat to maintain core body temperature, but it is also of great importance for the regulation of energy balance. In addition to BAT, mammals can induce the formation of "brown adipocyte-like" or "beige" fat cells in white adipose tissue and understanding their regulation could have implications for the treatment of metabolic diseases.

All homeotherms depend on the maintenance of their core body temperature for survival. Brown adipose tissue (BAT) has evolved specifically to meet this demand, providing additional heat beyond that produced by basal metabolism. In mice and rats, BAT is located primarily between the scapulae and its thermogenic activity is under the control of the sympathetic nervous system and mediated by activation of the mitochondrial uncoupling protein, UCP1. When the brain senses a reduction in temperature, sympathetic nerves in BAT release norepinephrine. This triggers the oxidation of fatty acids and glucose, and the recruitment of additional brown adipocytes [1]. In addition to interscapular BAT, "brown-like" cells can be recruited to white adipose tissue (WAT) depots following prolonged cold exposure, which have since been termed "brite" or "beige" adipocytes [2]. Treating cultures of white adipocytes with PPARγ agonists recapitulates this browning phenomenon and interrogations of beige adipocytes has shown that whilst they share many thermogenic markers with constitutive BAT (cBAT), they are devoid of any of the myogenic transcripts usually detected in cBAT [3]. This is perhaps to be expected, as brown adipocytes are derived from a myogenic precursor cell lineage that expresses the transcription factor Myf5, whereas white adipocytes and thus beige adipocytes are not [4].

A recent *Nature* paper by Schulz *et al*. [5] makes interesting observations about how these two populations of thermogenic cells are regulated and the findings may have implications for exploiting brown and beige adipose tissues for therapeutic use in human obesity. Following the observation that bone morphogenetic proteins (BMPs) regulate both the formation and function of BAT [6, 7], Schulz and colleagues generated a mouse lacking the BMP receptor BMPR1A only in cells that expressed Myf5. The resulting Myf5-BMPR1A-KO mice demonstrated a marked impairment in interscapular BAT formation that persisted into adulthood, confirming the importance of BMPR1A in brown fat development. However, a more interesting finding concerned what occurred in their subcutaneous and epigonadal WAT. Although these mice had obvious problems at birth with heat production, they adapted by increasing the number of UCP1-expressing beige cells in fat depots that are usually predominantly white in nature.

The most likely explanation is that Myf5-BMPR1A-KO mice sensed the deficit in heat production by BAT and mounted a compensatory sympathetic stimulation of their white fat depots to drive browning therein. Remarkably, this adaptation "primed" the WAT to be more sensitive to adrenergic stimulation than a wild-type mouse, inducing higher thermogenic gene expression in response to a given dose of β-adrenergic receptor agonist. This could purely be due to an expansion of the beige cell progenitor pool, or perhaps enhanced cellular responsiveness to adrenergic stimulation. Regardless of the mechanism, so pronounced is the expansion of the thermogenic capacity of WAT in these mice that after 8 days of cold exposure the core body temperature and whole body maximal thermogenic capacity of the Myf5-BMPR1A-KO mice was equal to that of their wild-type littermates. This finding demonstrates the huge degree to which specific WAT depots under the right conditions, in particular the subcutaneous depot, can display enough flexibility to meet the thermogenic needs of the organism.

A second observation by Schulz *et al*. also bears potential importance for the application of thermogenesis to the treatment of metabolic disease. The Myf5-BMPR1A-KO mice, when housed at temperatures where no additional heat production was required to maintain core body temperature (thermoneutrality), were no more susceptible to weight gain when fed a high-fat diet. This is of interest because mice devoid of any UCP1-mediated thermogenesis do get fat at thermoneutrality, as they lack any capacity for diet-induced thermogenesis (DIT) [8]. DIT is a physiological response that acts to a lesser degree but in a similar manner to cold exposure as a stimulus for BAT heat production, contributing to the maintenance of energy balance. Unfortunately, the paper does not contain a detailed analysis of the tissues of the mice raised in this setting. However, one can postulate that the increased numbers

of beige cells in WAT may also be able to respond to nutritional stimuli for heat production. This could be promising news when hoping to apply the use of brown fat, or techniques that brown WAT, to human disease.

The interest in BAT has flourished in recent years, thanks to the confirmation that adult humans possess measurable amounts of BAT and that its activity responds to ambient/perceived environmental temperature [9, 10]. Furthermore, the BAT amounts detected inversely correlate with age, BMI and diabetic status [11], suggesting that having more BATs promotes metabolic health. What makes the findings from the Myf5-BMPR1A-KO mice doubly relevant is the fact that humans lose much of the BAT that is comparable to the interscapular depot in mice soon after birth, and that the brown fat found in adult humans seems to share more molecular characteristics in common with murine beige fat cells [12]. Perhaps due to our greater body size and ability to control our environment close to thermoneutrality, traditional BAT does not prevail into adulthood to the extent that it does in mice. However, given the findings to date and the knowledge that low levels of UCP1 expression can be detected in human WAT, it is likely that we might retain the capacity to increase the thermogenic cell content of these fat depots following the right signals. The data of Schultz *et al*. suggest that if this can be achieved, beige cells are likely to respond to daily nutrient intake and contribute to the maintenance of energy balance. These recent findings support the idea that beige cells can be highly physiologically relevant and the coming years are certain to yield additional exciting findings into the specific mechanisms by which we may target this intriguing cell population.

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