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Perspective

White adipose tissue browning and obesity

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Obesity and metabolic disorders are major health concerns worldwide. Although a range of therapies have been developed, these pharmaceutical treatments often have adverse side effects or limited efficacy. Therefore, there is a growing need of novel therapeutics to prevent or treat obesity. Obesity is thought to be caused by an imbalance between energy intake and energy consumption. Increasing energy consumption is considered as a potential therapeutic strategy to treat obesity and its related disorders.

Brown fat is a specialized fat depot characterized by increased energy expenditure and heat production[1]. Its expansion and/or activation can protect against diet-induced obesity. The finding of active brown fat in human adults has aroused a great interest in the study of adipose tissue browning[2]. Beige adipocytes that share some common characteristics with brown adipocytes such as high mitochondria content and uncoupling protein 1 (UCP1) expression can be induced in white adipose tissue (WAT)[3].

The origin of classical brown adipocytes and beige adipocytes are different. Classical brown adipocytes originate from precursor cells in the embryonic mesoderm that express *Myf5* and *Pax7*[4]. However, the origin of beige adipocytes is still controversial. Although a few studies have shown that beige adipocytes are originated from the trans-differentiation of mature white adipocytes[5-6], there is a report showing that most of the beige adipocytes are from *de novo* differentiation of a precursor population[7]. These beige pre-adipocytes are characterized by the expression of Cd137 and transmembrane protein 26 (Tmem26) on the cell surface[8].

WAT browning is stimulated by a complex hormonal interplay and numerous environmental factors. WAT is readily converted to beige adipocytes with prolonged cold exposure or β-adrenergic agonist treatment[3,9]. Exercise has also been reported to increase WAT browning and energy expenditure[10]. At the molecular level, WAT browning is regulated by multiple factors and signaling pathways. Peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α) is a cold-induced interacting partner of PPARγ in brown fat[11]. It is also a master regulator of mitochondrial biogenesis and oxidative metabolism in adipocytes and can induce the expression of UCP1 and other thermogenic components. In addition, fibroblast growth factor 21 (FGF21) acts in an autocrine and paracrine manner to enhance WAT browning[12]. Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β (TGF-β) superfamily. BMP4 and BMP7 induce browning of WAT and increase whole body metabolic rate and insulin sensitivity[13-14]. Blocking of TGF-β/Smad3 signaling protects mice from obesity and diabetes through promoting WAT browning[15]. Apparently, imbalanced TGF-β/BMPs signaling occurs during WAT browning, although the precise mechanisms and central regulators remain unknown.

Response gene to complement 32 (*RGC-32*) is a TGF-β downstream target gene. Our study shows that high-fat diet induces RGC-32 expression in adipose tissue. RGC-32 deficiency increases WAT browning and whole body metabolic rate and thus protects against high-fat diet-induced obesity[16]. RGC-32 appears to be involved in the imbalanced TGF-β/BMPs signaling. However, how RGC-32 interacts with Smad3, BMP4 and BMP7 needs an extensive future investigation.

Although animal studies indicate that increased WAT

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browning prevents diet-induced obesity, whether or not the decline of brown fat activity is causally involved in the development of obesity in humans remains to be determined. Therefore, a further understanding of the morphology, development, and metabolism of the classic brown and beige adipocytes is still very important.

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