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Adipose-specific *CLSTN3B* gene associates with human obesity

Under genetic and environmental cues, adipose tissue retains a dynamically active organ that plays a critical role in the regulation of energy homeostasis [1]. The abnormal expansion of adipose tissue has been implicated in the pathogenesis of several metabolic disorders, including obesity, type 2 diabetes, and cardiovascular disease [2]. Despite significant efforts, the specific genes associated with adipose function and their impact on whole-body metabolic remain largely elusive.

Calsyntenin 3β (CLSTN3β), a novel adipocyte-specific product of *Clstn3* gene locus. Plays a critical role in promoting brown adipose thermogenesis in mice via enhancing sympathetic innervation [3]. Later research showed that CLSTN3β regulates the formation and function of lipid droplets, facilitating fatty acid oxidation in mouse thermogenic adipocytes [4]. However, the presence of *CLSTN3B* gene in human adipose tissue remains unclear. Bai et al. previously reported a discordant expression pattern on *Clstn3/CLSTN3* locus between mice and humans [5]. In their recent publication in *Life Metabolism* titled "Transcript profile of *CLSTN3B* gene in human white adipose tissue is associated with obesity and mitochondrial gene program", the authors revealed an association between the *CLSTN3B* transcript profile in human white adipose tissue and individual metabolic status and mitochondrial gene program [6].

The diversity of human white adipose tissue composition depends on the anatomical location [7]. Subcutaneous adipose tissue (SAT) comprises the majority of human body fat, while the smaller amount of visceral adipose tissue (VAT) is considered more pernicious and associated with metabolic disorders [8]. Despite the relatively low abundance of mitochondria in white adipocytes, emerging evidence suggests their crucial role in maintaining white adipocyte function [9]. Comparative studies have demonstrated higher expression of thermogenic genes in human visceral adipocytes compared to subcutaneous adipocytes [10]. Hence, a comprehensive understanding of the mitochondrial regulation in human adipose tissue is imperative to develop targeted and effective strategies for understanding adipose biology and promoting overall health.

In this novel study, the authors conducted an investigation on the association between the transcript profile of CLSTN3B and metabolic status in adipose tissue. They observed a significant reduction in the relative abundance of *CLSTN3B* transcript in abdominal SAT and VAT samples from a total of 210 participants with BMI increased. Moreover, they found that the transcript levels of *CLSTN3B* were significantly correlated with various metabolic parameters, including adipose mass and function measures, as well as whole-body insulin resistance. To further explore the potential role of *CLSTN3B* in human adipose tissue, co-expression analysis was performed on VAT, which revealed that the positively correlated genes were enriched in mitochondrial gene programs, indicating that *CLSTN3B* may participate in maintaining mitochondrial activities. Lastly, the authors demonstrated that the protein-coding variant rs7296261 of *CLSTN3B* gene was linked with a high BMI and exacerbated insulin resistance among participants, providing further insight into the underlying mechanisms of the association between CLSTN3B and metabolic disorders.

Taken together, the findings from this study reveal a negative association between the transcript profile of *CLSTN3B* gene in human adipose tissue and obesity. Moreover, the study highlights the potential role of *CLSTN3B* in modulating mitochondrial homeostasis. These findings suggest that targeted upregulation of the *CLSTN3B* gene in adipose tissue may hold therapeutic potentials for the treatment of obesity and related metabolic disorders.

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CRediT authorship contribution statement

Wenfei Li: Writing – original draft, Writing – review & editing. **Quanxin Jiang:** Writing – original draft, Writing – review & editing. **Suzhen Chen:** Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Junli Liu:** Conceptualization, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

No conflict of interest to disclose.

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