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# Depletion of JunB increases adipocyte thermogenic capacity and ameliorates diet-induced insulin resistance

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ABSTRACT

Adipose tissue is a crucial metabolic organ in the human body. It stores and exerts distinct physiological functions in different body regions. Fat not only serves as a cushion and insulator but also stores energy and conveys endocrine signals within the body. There is a growing recognition that adipose tissue is an organ that is misunderstood and underestimated in contribution to human health and disease progression by regulating its size and functionality. In mammals, the adipose tissue reservoir consists of three functionally distinct types of fat: white adipose tissue (WAT), brown adipose tissue (BAT), and beige or inducible brown adipose tissue (iWAT), which exhibits thermogenic capabilities intermediate between the other two. Fat in different depots exhibits considerable differences in origin, characteristics, and functions. They vary not only in adipocyte lineage, properties, thermogenesis, and endocrine functions but also in their immunological functions. In a recent study published in Nature Metabolism, Zhang et al. investigated the role of JunB in the thermogenic capacity of adipocytes and its significance in obesity and metabolic disorders. The study revealed that JunB expression in BAT coexists with both low and high thermogenic adipocytes, indicating a fundamental feature of heterogeneity and plasticity within BAT. In summary, this article demonstrates that research targeting JunB holds promise for improving diet-induced obesity and insulin resistance, offering new avenues for treating metabolic disorders.

WAT functions as the primary energy storage site in the body. It synthesizes triglycerides for long-term storage and releases free fatty acids to provide energy when needed [1]. In comparison to BAT, WAT is primarily consists of large adipocytes with a single lipid droplet and fewer mitochondria [2]. Depending on their anatomical location in the body, WAT can be categorized into two types: visceral WAT (VAT) and subcutaneous WAT (SAT) [3]. Lineage studies in mice have shown that VAT and SAT have different origins, but their developmental origins in humans are not yet fully elucidated [4]. VAT encompasses adipose depots such as the omentum, mesentery, retroperitoneum, gonadal, and pericardial WAT. The accumulation of VAT and the resulting inflammation increase the risk of metabolic syndrome, insulin resistance, and cardiovascular diseases [5–7].

It is well-known that newborns possess active BAT to maintain normal body temperature, which regresses with age. However, functional BAT expressing significant levels of uncoupling protein 1 (UCP1) can be found in healthy adults in areas such as the supraclavicular region and other upper trunk sites [8,9]. Various factors such as cold exposure, feeding, low BMI, sympathetic nervous system (SNS) activity, cancer, and burn injury, positively correlate with BAT content in adults [10]. Unlike WAT, BAT contains multiple small lipid droplets and abundant mitochondria [11]. Within these mitochondria, UCP1 located on the inner mitochondrial membrane can be activated under stimuli such as cold exposure, generating heat and promoting systemic energy metabolism [12–14]. For instance, cold exposure activates BAT via the sympathetic nervous system, leading to increased glucose uptake, accelerated plasma triglyceride clearance, and suppression of triglyceride concentrations, thereby reducing the risk of obesity and cardiovascular diseases [15]. Consequently, BAT plays a pivotal role in thermoregulation and energy metabolism through non-shivering thermogenesis [10]. However, despite the anti-obesity effects of BAT activation induced by cold stimuli, its activation declines significantly with age [16]. Thus, there are currently no reports of BAT being utilized as a pharmacological target for therapeutic intervention.

Increasing evidence suggests the existence of distinct subpopulations of brown adipocytes with different characteristics within BAT, demonstrating high heterogeneity in terms of thermogenesis, insulin sensitivity, and secretory functions. For instance, both high and low thermogenic fat cells coexist within BAT [17,18]. Nevertheless, little is known about the molecular mechanisms regulating thermogenic adipocyte heterogeneity and its significance in obesity and metabolic disorders.

Beige adipose tissue represents a phenotypic transition of WAT into a BAT-like phenotype [19]. The induction of WAT browning is primarily stimulated by cold exposure or dietary factors and transmitted through the release of norepinephrine (NE) from sympathetic nerve terminals [20]. Similar to BAT, beige adipose tissue contains multilocular lipid droplets and exhibits abundant mitochondria, thus possessing the capability to generate heat and promote systemic energy metabolism upon stimulation.

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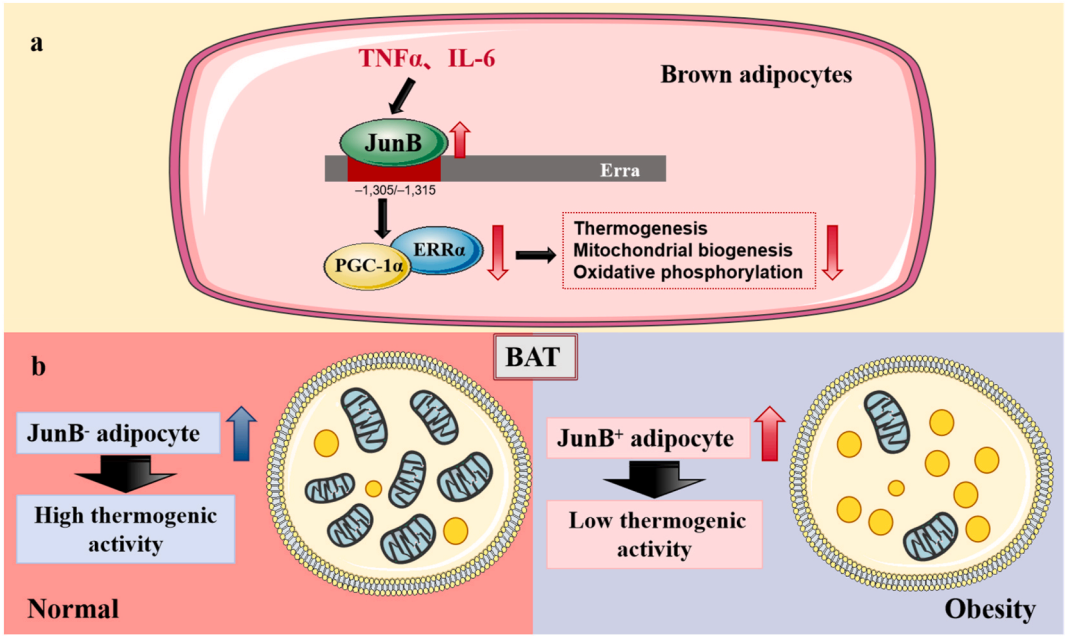


**Fig. 1.** Mechanisms of JunB in thermogenic capacity of brown adipose tissue. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

In a recent study published in *Nature Metabolism*, Zhang *et al.* identified an atypical subset of brown adipocytes that express the AP1 transcription factor JunB, which increases in abundance during obesity and is induced by inflammation. These JunB-expressing adipocytes can be found throughout various depots of BAT, exhibiting significantly lower lipid droplets and thermogenic capacity compared to high thermogenic adipocytes. Acting as a transcriptional regulatory factor, JunB integrates inflammatory and metabolic signals, modulating the interconversion and energy metabolism of low and high thermogenic adipocytes by binding to the ERRα promoter and inhibiting the PGC-1α-ERRα pathway [21]. Specific knockout of JunB in thermogenic adipocytes or the ablation of JunB expression in adipocytes improves energy metabolism, ameliorating energy balance and preventing/treating obesity and insulin resistance.

In conclusion, this study unveils an atypical subset of thermogenic adipocytes that responds to obesity and inflammation by expressing JunB. The abnormal induction of JunB affects the heterogeneity of thermogenic adipocytes and compromises BAT function by generating more low thermogenic cells. As an AP1 transcription factor, JunB regulates the interconversion of low and high thermogenic adipocytes through the PGC-1α-ERRα pathway, thereby altering adipose thermogenic capacity and heterogeneity by integrating inflammatory and metabolic signals (see Fig. 1). These findings provide insights into the biological characteristics of brown adipocytes and lay a solid foundation for the development of therapeutic interventions targeting obesity, inflammation, and related diseases. Further research is warranted to better understand the biological functions and mechanisms of JunB and other AP1 members in various types of adipose tissue.

## CRediT authorship contribution statement

**Qian Zhou:** Conceptualization, Writing – original draft, Writing – review & editing. **Suzhen Chen:** Conceptualization, Supervision, Validation, Writing – review & editing. **Junli Liu:** Conceptualization, Supervision, Validation, Writing – review & editing.

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