FRIGID ZONE **MEDICINE**
Editorial • DOI: 10.2478/fzm-2023-0026

# Acute cold exposure triggers thermogenic memory in brown adipose tissue

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Received 27 November 2023, accepted 27 November 2023

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## 1 Introduction

Infants are born with a substantial amount of brown adipose tissue (BAT), primarily clustered around their upper back, shoulders, and upper chest[1]. As age progresses, the primary BAT gradually diminishes, and concomitantly, de novo lipogenesis (DNL) continues to occur in subcutaneous adipose tissue throughout the body. The abundance of BAT in young children enhances their thermogenic capacity, making weight gain challenging and increasing resistance to cold temperatures. In adults, exposure to cold may enhance BAT. When cold receptors on the skin are activated, a signal is transmitted to the nervous system, leading to an increase in sympathetic nerve tone and the secretion of norepinephrine by the hypothalamus[2]. These two factors cooperate to induce the differentiation of white adipocytes into brown adipocytes and upregulate the expression of uncoupling protein 1 (UCP1), thereby boosting thermogenic capacity. The cold environment triggers apoptosis in white adipocytes, resulting in a gradual decline in the population of brown adipocytes, while simultaneously increasing their numbers.

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Adipose tissue functions as a dynamic metabolic organ, exerting a profound influence on energy homeostasis throughout the body. It plays a pivotal role in the regulation of various processes, encompassing food intake, glucose metabolism, insulin sensitivity, thermogenesis, and immune response. In the mammalian body, two distinct types of adipocytes have long been recognized- white and brown adipocytes. White adipocytes are characterized by a singular large lipid droplet and limited mitochondrial content, whereas brown adipocytes display numerous small multilocular lipid droplets and abundant mitochondria with densely packed cristae structures, indicating their heightened metabolic potential[3]. Cold stimulation robustly activates the thermogenic capacity of brown adipocytes, facilitating energy substrate uptake (such as lipids and glucose) and cellular metabolism, particularly energy metabolism in mitochondria[4]. After decades of rigorous research, the non-shivering thermogenesis pathway has been comprehensively elucidated, with a focus on mitochondrial metabolism. Specifically, UCP1 activity has the capacity to uncouple electron transfer in the mitochondrial respiratory chain, thereby inhibiting ATP generation. The activation of this pathway depends on the transcriptional co-regulator protein PR domain-containing 16 (PRDM16) that forms complexes with various proteins, including euchromatic histone lysine methyltransferase 1 (EHMT1)[5]. However, it is noteworthy that critical physiological processes, like temperature regulation and energy balance, are intricately governed by multiple mechanisms. It is now widely accepted that non-shivering thermogenesis does not solely depend on UCP1, as exemplified by an alternative mechanism for the maintenance of body temperature in pigs lacking functional UCP1 genes[6].

Recent investigations have unveiled that both brief and prolonged exposure to cold temperatures can activate the thermogenic function of BAT. Mammals frequently encounter episodes of intermittent cold exposure in their natural habitats, and studies conducted under such conditions offer a more accurate understanding of BAT's heat generation process throughout biological evolution. Notably, cold stimulation or β3-adrenergic treatment can trigger the initial thermogenic response and facilitate the transformation of white adipocytes into beige adipocytes[7]. After a subsequent increase in temperature, these beige adipocytes undergo chromatin remodeling, transitioning back to a white state. However, they retain an epigenetic memory that facilitates the reactivation of the thermogenesis process upon subsequent exposure to cold—a phenomenon referred to as secondary thermogenesis. Patrick *et al.* documented that BAT serves as a heat-generating memory store, enabling it to promptly initiate a thermogenic response following cold exposure, with the capacity to retain thermogenic memory for at least 16 days. These findings underscore the crucial role of heterogeneous brown adipocyte populations in 'thermogenic memory', which could hold therapeutic potential for harnessing short-term thermogenesis to counteract obesity[8].

## 2 Secondary thermogenesis under acute cold exposure

The mice were initially acclimated to a thermoneutral environment (30°C) before undergoing an 8-hour cold challenge, after which they were returned to thermal neutrality for four days. Subsequently, they were subjected to another 8-hour cold exposure. Remarkably, upon re-exposure to cold after four days of returning to thermal neutrality, the mice demonstrated significantly enhanced cold tolerance. This heightened secondary thermogenic response was accompanied by an increase in whole-body energy expenditure compared to the primary cold challenge. The researchers conducted acute cold exposure treatments on mice with BAT and UCP1 knockout individually, followed by a subsequent cold exposure treatment four days after thermal neutralization. The results revealed that both BAT-excised mice and UCP1 knockout mice exhibited reduced cold tolerance during the initial cold exposure, in comparison to Wild type (WT) mice. However, no significant difference was observed in the secondary thermogenic response. These findings imply that the augmentation of secondary thermogenic response under acute cold conditions depends on the presence of BAT and UCP1. Building on this observation, the researchers shifted their focus towards investigating BAT to elucidate its impact on secondary thermogenic molecular, cellular, and metabolic processes following brief cold exposures.

## 3 Transcriptional changes of genes in primary thermogenic reactions

The RNA-Seq analysis of BAT in mice subjected to acute cold exposure and thermally neutral treatment revealed four patterns of differential gene expression: (1) rapid upregulation following cold exposure; (2) rapid downregulation after cold exposure; (3) delayed upregulation after cold exposure; and (4) sustained upregulation for several weeks post-cold exposure. The initial thermogenic response triggered by acute cold exposure induces a delayed lipid biosynthesis program and tissue-specific upregulation in BAT. The alterations in transcriptional programs within BAT are correlated with the duration of metabolic benefits elicited by the initial thermogenic response. Specific knockout of Scap in BAT results in a significant downregulation of Srebp1c gene expression, thereby inhibiting downstream lipogenic genes[9]. Scap loss in BAT attenuated the transcriptional stimulation of fatty acid synthase (Fasn) and Scd1 on day 4 after the initial cold exposure, while Ucp1 expression remained unaffected. However, simultaneous deletion of both Scap and Fasn genes failed to fully explain the observed effects on BAT lipidogenesis during initial and secondary cold exposures. To get deeper insights, researchers utilized a pharmacological inhibitor targeting Fasn activity, selectively impeding DNL between initial and secondary cold exposures. The findings indicated that this drug treatment compromises the thermogenic response during secondary heat production, highlighting the role of brown adipocyte lipidogenesis in sustaining metabolic benefits even beyond cold stimuli elimination.

## 4 Bat responses to primary thermogenic challenge

Single-cell nuclear sequencing was conducted on the BAT of mice with or without exposure to cold, leading to the identification of five distinct subgroups: A1, $Slc7a10^{+}/Cyp2e1^{+}$ adipocytes; A2, intermediate adipocytes; A3, $Ucp1^{lo}$ adipocytes; A4, $Ucp1^{hi}$ adipocytes; and A5, lipogenic brown adipocytes. In parallel, an analysis of the transcriptome dataset of human BAT unveiled a specific subset of lipid-producing brown adipocytes identified by Fasn expression, distinct from the $Ucp1^{hi}$ subset. This discovery not only corroborates the presence of a unique population of lipogenic cells in BAT but also designates Fasn as a reliable marker gene for this particular subset, demonstrating its evolutionary conservation in both mice and humans. This finding further confirms the presence of a unique population of lipogenic cells in BAT and highlights Fasn as a marker gene for this specific subset, which is highly conserved in both mice and humans. Furthermore, it has been observed that the DNL pathway is enhanced specifically in BAT subsequent to initial cold exposure, leading to an elevation of acylcarnitine levels. This augmentation in acylcarnitine further stimulates downstream fatty acid catabolism and enhances mitochondrial thermogenesis capacity, ultimately ameliorating the secondary thermogenic response.

The findings of this study underscore the enduring nature of thermogenic memories within BAT, with a remarkable persistence for at least 16 days. The researchers revealed that even brief exposure to cold temperatures induces a sustained transcriptional and metabolic adaptation in BAT. Notably, the initial thermogenic response not only elicits a protracted activation of lipid biosynthesis programs but also initiates a delayed yet substantial enhancement of lipid production even after the termination of cold exposure. Moreover, the study sheds light on an intriguing mechanism wherein a specific subset of A5 lipoblasts emerges as key players in driving the metabolic advantages linked to primary thermogenesis. This subset's remarkable ability to generate acylcarnitine is identified as a pivotal contributor to the observed benefits. Encouragingly, supplementation with acylcarnitine has been demonstrated to amplify secondary thermogenesis, further accentuating its potential as a therapeutic intervention. In summary, this research stresses the pivotal role of diverse populations of brown adipocytes in preserving "thermogenic memory." The implications of these findings may extend to the realm of combating obesity and metabolic diseases, suggesting that harnessing short-term thermogenesis could be a promising avenue for therapeutic exploration.

## Acknowledgement

This study was funded by the National Natural Science Foundation of China (82270396).

## Author contributions

Zhao T drafted the manuscript. Liu X edited and reviewed the manuscript.

## Ethics approval

Not applicable.

## Conflict of interest

The authors declare no competing interest.

## Data availability statement

Not applicable.

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