FRIGID ZONE **MEDICINE**
Review • DOI: 10.2478/fzm-2023-0011

Multiple inducible thermogenic mechanisms in the development of cold acclimatization

Huanyu Lu, Wenjing Luo*

Abstract

Extreme cold environment can threaten human health and life through increasing the risk of myocardial infarction, stroke, frostbite, and hypothermia. Insufficient heat production to maintain core body temperature is a major cause of cold injury. To cope with cold stress, human and other mammals have developed the capacity of cold acclimatization to adapt to such a harsh environment. Adaptive non-shivering thermogenesis is a ubiquitous form of cold acclimatization. This review article systematically summarizes the role of three inducible thermogenic forms, including food intake, circadian rhythms, and cold exposure in mediating non-shivering thermogenesis under cold exposure and presents the potential interventions for minimizing the adverse health consequences of cold temperature.

Keywords

cold exposure; proteomic profile; hypothalamus; pituitary

Received 26 June 2022, accepted 20 December 2022

Department of Occupational and Environmental Health, the Ministry of Education Key Lab of Hazard Assessment and Control in Special Operational Environment, Shaanxi Key Laboratory, School of Public Health, Fourth Military Medical University, Xi'an 710000, China

**Corresponding author Wenjing Luo, E-mail: luowenj@fmmu.edu.cn*

1 Introduction

The risk and possibility of cold exposure depends largely on geographical location, climate, season, and housing conditions. Acute cold stress induces sympathetic vasoconstrictor response and adipose lipid mobilization with markedly increased systolic and diastolic blood pressure, blood cholesterol and fatty acids, and blood viscosity in a matter of hours, which may increase the risk of atherosclerotic plaque rupture, myocardial infarction and stroke[1,2]. Indeed, acute cold stress also occurs with reduced skin temperature and increases the risk of frostbite and eventually affects the sustainment of internal body temperature (core temperature) leading to hypothermia. As well recognized, extreme cold temperature threatens human health[1]. Thus, it is important to develop public-health interventions to minimize the adverse health consequences of cold temperature.

Moreover, in frigid zones, long-term cold exposure can induce cold acclimatization which helps human and other mammals better survive and adapt to the extreme environment. In response to cold stress, the activation of thermogenic regulatory mechanism can improve heat production to maintain the normal body temperature. But inappropriate thermogenesis (shivering thermogenesis), thermogenic deficiency, and excessive heat dissipation may seriously increase the risk of cold exposure injury. Indeed, adaptive non-shivering thermogenesis is critical for cold acclimatization. In this paper, we systematically summarize the food intake, circadian rhythms, and cold exposure-mediated non-shivering thermogenic pathways during cold acclimatization and highlight the future direction of research in the field of Frigid Zone Medicine.

2 Food-induced thermogenesis

Food-induced thermogenesis (FIT) is one of the three components of daily energy expenditure. Compared to the basal metabolic rate and activity-induced thermogenesis, FIT plays a critical role in the development of cold acclimatization.

2.1 Fatty acid and its derivatives

In cold environment, increasing energy substance intake from food can boost up metabolic function. With the same quantity of energy substance intake, fatty acids generate more ATP and heat as well than carbohydrate and amino acids[3-5]. Furthermore, fatty acids are not only the fundamental building blocks of lipid droplets in the form of triacylglycerols in adipose tissues, which assist the body in attenuating heat dissipation[6-7] but also the physiological lipokine that regulates muscle glucose intake, adipose lipolysis and thermogenesis, thereby maintaining the

high efficiency of heat production.

For example, carnitine is a nutrient enriched in meat, fish, poultry, and milk. Carnitine conjugates to long-chain fatty acids and facilitates the transportation of substances into mitochondria for oxidation and energy production. More importantly, carnitine is concentrated in tissues, like skeletal muscle, which utilize fatty acids as a dietary fuel. Upon cold stress, carnitine helps raising the efficiency of fatty acids disposition and thermogenesis in muscle and brown adipose tissue (BAT). As reported[8], cold exposure stimulates long-chain acylcarnitines (LCACs) production and absorption by BAT for heat production. And carnitine supplements significantly improve thermogenic efficiency and enhance cold tolerability[8].

Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, are produced by fermenting dietary fiber through gut microbiota, including anaerobic bacteroides, bifidobacterium and lactobacillus. As reported[9], microbiota depletion significantly reduces the short-chain fatty acid (SCFA) levels, impairs thermogenesis of brown adipose tissue, and enhances cold sensitivity. SCFA supplement, especially butyrate, increased the thermogenic capacity of microbiota depleted mice and reversed the cold tolerant deficit[9]. Mechanistically, butyrate acts on the gut-brain neural circuit to improve energy metabolism and enhance thermogenic effect by activating BAT[10]. Furthermore, some studies support that SCFAs (propionic acid and butyric acid) control adipose lipolysis and thermogenesis, depending on the activation of G protein coupled receptors (GPR120, GPR43)[11].

Polyunsaturated fatty acid (PUFA) and its derivatives are not only the fundamental substrates for the synthesis of cell membrane phospholipids, but also function as key lipokines regulating cellular signaling pathway, cell proliferation, energy consumption, and thermogenesis in liver, muscle, adipose, *etc*.[12-13]. Dietary PUFAs have been widely investigated for their roles in the prevention and treatment of cardiovascular disease[14]. Moreover, both *in vivo* and vitro studies showed that n-3 PUFAs supplement can induce the expression of brown adipose thermogenic genes uncoupling protein 1, UCP1 and improve cold tolerance[15-16]. In recent studies[17-18], Lynes, *et al.* presented that PUFAs-derived lipid 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) is increased in the circulation of humans and mice exposed to cold. And 12,13-diHOME increased fatty acid (FA) uptake into brown adipocytes by promoting the translocation of the FA transporters FATP1 and CD36 to the cell membrane. 12,13-diHOME treatment stimulates BAT thermogenic activity and enhances cold tolerance[17-18].

2.2 Carbohydrate and its derived TCA intermediates

In addition to fatty acids, carbohydrate serves as the major precursor for the *de novo* lipogenesis[19-20] and by-products of various metabolites, especially the metabolic intermediates of the tricarboxylic acid (TCA) cycle . On the one hand, carbohydrate metabolism provides the fuel for various physiological functions through the rapid generation of ATP. On the other hand, carbohydrate metabolic by-products are critical for the *de novo* synthesis of lipid droplet and glycogen, which efficiently increases body energy storage to maintain cold-induced heat production.

Additionally, the metabolic intermediates of carbohydrate by-products generated through the TCA cycle have been proved to play multiple roles in regulating thermogenic effect. Succinate is significantly accumulated in thermogenic adipose tissue upon activation following exposure to cold. And Succinate oxidation by succinate dehydrogenase (SDH) is required for the activation of adipose thermogenesis. Mills, *et al.* revealed that SDH mediated-succinate oxidation initiates reactive oxygen species (ROS) production and thereby drives UCP1-dependent thermogenic respiration. Moreover, succinate supplement drives UCP1-dependent BAT thermogenesis *in vivo*, and improves cold tolerance[21]. Furthermore, Wang *et al.* reported that succinate supplementation increased endurance exercise ability, oxygen consumption, and mitochondrial biogenesis in skeletal muscles *via* the SUNCR1 signaling pathway[22].

Alpha-ketoglutaric acid (AKG), an intermediate of the TCA cycle, is a metabolic signature of resistance exercise performance. AKG treatment has been shown to induce muscle hypertrophy, brown adipose tissue (BAT) thermogenesis, and white adipose tissue (WAT) lipolysis *in vivo* and has a high potential to enhance cold tolerance. Mechanistically, AKG stimulates the adrenal release of adrenaline through 2-oxoglutarate receptor 1 (OXGR1) expressed in adrenal glands, which induces thermogenesis and other beneficial metabolic effects[23]. More importantly, Shahmirzadi, *et al.* reported that AKG promotes a longer, healthier life associated with a decrease in the levels of systemic inflammatory cytokines[24].

These findings indicate that succinate and alpha-ketoglutaric acid are systemically derived thermogenic and beneficial metabolic nutrients.

2.3 Amino acid and its derived branched-chain fatty acids

In contrast to carbohydrates and fatty acids, amino acids play a main role in the synthesis of proteins which provide constituent materials for body strengthening L-Arginine[25-26], an essential amino acid, has been reported to enhance the development of

brown adipose tissue and induce the browning of white adipose tissue, which improves cold tolerability[27]. Furthermore, arginine/creatine metabolism is a thermogenic signature of beige adipose tissue, and creatine, an arginine catabolite, enhances respiration in beige-fat mitochondria and increases whole-body energy expenditure[28]. Thus, l-arginine treatment could be of great interest in thermogenic metabolism and thermal homeostasis under cold stress.

Branched-chain amino acid (BCAA; valine, leucine, and isoleucine) supplementation has been shown to be beneficial to energy expenditure. Upon cold exposure, BAT actively utilizes BCAA in the mitochondria for thermogenesis and promotes systemic BCAA clearance. Mechanistically, active BCAA catabolism in BAT is mediated by SLC25A44, which transports BCAAs into the mitochondria[29]. Thus, BAT serves as a key metabolic filter that controls BCAA clearance *via* SLC25A44, thereby contributing to the thermogenic effect.

Furthermore, catabolism of branched chain amino acids contributes significantly to the synthesis of monomethyl branched-chain fatty acids (mmBCFAs) in adipose tissue. Brown fat exhibits the highest BCAA catabolism and mmBCFAs synthesis fluxes, which sustains its thermogenic activity. Increase in circulating mmBCFAs is also associated with beneficial metabolic status[30]. Branched fatty acid esters of hydroxy fatty acids (FAHFAs), a kind of BCFAs, have been identified to regulate insulin sensitivity, adipose thermogenesis, and inflammatory response through the GPR120 signaling pathway[31-33]. Thus, FAHFAs are endogenous BCFAs with the potential to enhance cold acclimation.

Generally, food-induced thermogenesis is not only dependent on sufficient substrate energy source, but also on the regulatory roles of non-substrates through food-intake. Thus, increasing diet quality, quantity, and variety can enhance body thermogenesis and improve cold acclimatization.

3 Circadian-mediated thermogenesis

Circadian coordination of food availability, physical activity, and energy expenditure is crucial for metabolic adaptation to cold environmental challenges. The homeostatic repertoire of body temperature in response to cold environments is orchestrated by circadian rhythm of neural circuits, endocrine hormones, and metabolic organ activity[34-37].

Circadian rhythms of body temperature, oxygen consumption, and minimal thermal conductance critically regulate the nervous system[38,39]. The preoptic area (POA) where GABAergic interneurons in the median preoptic nucleus (MnPO), the distinct populations of warm-sensitive (W-S) neurons in the medial preoptic (MPO) subnucleus, and the rostral raphe pallidus (rRPa) in the rostral ventromedial medulla, form the circadian thermoregulatory circuits to control the activation of cutaneous vasoconstriction and thermogenesis[40-47].

Endocrine systems, aside from the nervous system, serve as effective signals to transmit the rhythm to peripheral organs. Plasma hormone levels of catecholamines, testosterone, cortisol, and triiodothyronine (T3) and thyroxine (T4) vary daily and are tightly regulated by endocrine circadian systems, including the hypothalamic-pituitary-thyroid (HPT) axis[48,49]. Cortisol, a steroid hormone, is widely known as a stress hormone. Cortisol plays a critical role in regulating metabolic activity, including liver gluconeogenesis, ketogenesis, adipose lipolysis, and thermogenesis to protect against acute cold stress[50-53]. Furthermore, thyroid hormone (TH) has been shown to promote mitochondrial biogenesis and the expression of UCP in skeletal muscle and brown adipose tissue to increase body metabolic activity[54-58].

Peripheral metabolic organs function as the terminal thermogenic effector in response to the circadian rhythms[59-61]. Circadian rhythm of BAT activity plays a critical effect on circadian body temperature and circadian cold sensitivity. As reported[62], the circadian transcriptional repressor Rev-erbα represses BAT thermogenic programming. Upon acute cold stress, cold-mediated reduction of Rev-erbα expression occurs in parallel with the induction of the thermogenic regulators UCP1 and Peroxisome proliferators-activated receptor-γ coactivator-αl (PGC-1α). At thermoneutrality, the circadian oscillations of the expression profile of Rev-erbα gene in BAT mediate the circadian patterning of cold tolerance[34,62]. During chronic cold exposure, the expression of metabolic genes for fatty acid oxidation (FAO) and *de novo* lipogenesis (DNL) acquires high-amplitude circadian rhythms in association with high thermogenic capacity of BAT. Rev-erbα also plays a rhythmic regulatory role in brown fat *de novo* lipogenesis, which is necessary for maintenance of body temperature during long-term cold exposure[63]. Generally, circadian genes control the thermogenic activity of the peripheral metabolic organs and regulate body temperature changes in response to cold stress.

In conclusion, the circadian rhythmicity is systematically controlled by central and peripheral pacemakers and influenced by exogenous factors like food intake, exercise and light/dark-sleeping cycle.

3.1 Daily food-intake patterns affect circadian rhythm

Emerging research supports that the timing of food intake, eating behavior, and food preference are associated with of the function of the circadian system in humans. The timing of food intake

is an increasing interest because of its influence on metabolic health[64-65]. As reported, nighttime eating leads to misalignment between central and peripheral endogenous circadian rhythms and impaired glucose tolerance, whereas daytime eating prevents internal circadian misalignment and metabolic disorder[66]. Thus, appropriate circadian alignment of eating can benefit circadian and metabolism health. Recent study has also shown that the effect of feeding restriction on metabolism of peripheral tissues can lead to uncoupling of peripheral oscillators from the central pacemaker in the suprachiasmatic nucleus (SCN). Specifically, temporal feeding restriction significantly changes the phase of circadian gene expression in peripheral cells but has no effect on the phase of cyclic gene expression in the SCN. Thus, sudden large changes in feeding time, similar to abrupt changes in the photoperiod, reset the phase of rhythmic gene expression and may affect circadian-mediated metabolic activities[67]. Furthermore, binge eating (BE) behavior can disturb the peripheral circadian oscillators and may have adverse metabolic effects[68]. Generally, daily food intake patterns may control circadian-mediated thermogenesis to regulate cold acclimatization.

3.2 Exercise timing affects circadian rhythm

Physical exercise has been well proved to improve physiological and psychological parameters and general quality of life in literally all age groups. Clearly, exercise has circadian rhythm phase-shifting properties[69]. Maximum performance for strength and endurance training normally occurs in the afternoon and evening hours as the circadian rhythm is controlled by rhythmic changes in blood flow through the distal limbs which reaches its maximum in the late evening and its minimum in the morning[70].

Furthermore, the effect of exercise on hormonal pathways often alter the central and peripheral endogenous circadian rhythms. As reported[71], cortisol is a frequently studied exercise hormone that influences the circadian rhythm. An acute high intensity exercise significantly elevates cortisol concentrations. However, after exercise cortisol concentration falls rapidly and can lead to a decrease in basal cortisol levels during sleep. Snice the basal cortisol concentration is rhythmically changed, which peaks in the early morning and falls in the afternoon, exercise training should be performed in the afternoon, which has the greatest influence on the increase in cortisol while its level is low[71-72].

Generally, the circadian phase-shifting effect of exercise timing is potentially a unique therapeutic approach for improving circadian misalignment and cold acclimation.

3.3 Sleeping affects circadian rhythm

Sleep has a variety of physiological function, including reduction of oxidative stress, removal of metabolic waste products, enhancement of immune function, and stabilization of synaptic homeostasis and memory consolidation[73]. These processes are vital for the maintenance of cognitive, endocrine, and immune functions, especially under stress conditions.

Sleeping behavior is closely related to the circadian health. As well known, sleep deprivation activates the sympatho-adreno-medullary (SAM) axis *via* the sympathetic nervous system and stimulates catecholamines release. Chronically increases in cortisol and adrenaline drive a wide-spread stress responses which reduce insulin release, increase heart rate and blood pressure, suppress immune response, limit tissue repair, and disturb cognitive function. Thus, chronic sleep-restriction renders poor health conditions and circadian misalignment[74]. Furthermore, insufficient sleep probably contributes to the metabolic alterations observed during circadian misalignment. As reported, sleeping during biological daytime contributes to alterations of 24-h rhythms of metabolic status and energy expenditure rate. And working during biological night is also associated with increased rates of metabolism-related diseases[75-77]. These results highlight the importance of optimal and sufficient sleep in the maintenance of circadian and metabolic health, which may promote acclimation to the cold conditions.

In conclusion, circadian-mediated thermogenesis is critical for acclimatization to cold environment. Perturbation of circadian rhythms can induce metabolic disorders and lead to detrimental effects on cold tolerability. Therefore, regular eating, training, and sleeping behaviors are closely correlated with the endogenous circadian rhythms, enabling organisms to prepare for cold environmental challenge.

4 Cold-induced non-shivering thermogenesis

Cold temperature is a ubiquitous environmental stress promoting body thermogenesis and energy expenditure[78]. Adipose-mediated non-shivering thermogenesis, but not muscle mediated shivering thermogenesis, is critical for the adaption of human and other mammals to cold environment[79]. Adipose tissues are broadly classified as white adipose tissue (WAT), brown adipose tissue (BAT), and beige adipose tissue. WAT functions as an energy storage depot with classical large lipid droplets. In contrast, brown and beige adipose tissues form an energy dissipation depot, which metabolizes stored chemical energy to produce heat through a process called adaptive thermogenesis. BAT is abundant in small mammals and in newborns as a primary source of thermogenesis to survive cold temperatures. However, in adult humans, BAT is essentially absent or thermogenic deficient, but it can be activated upon cold stress. Furthermore, during cold acclimation,

multiple organs secrete factors, known as batokines, to promote adipose microenvironment neurite outgrowth, angiogenesis and immune cell interactions, so as to enhance the effect of adipose thermogenesis on body energy dissipation, glucose sensitivity, and cold tolerance[80-84]. Thus, adipose tissue plays a key role in controlling the cold-induced thermogenesis in the development of cold acclimatization.

4.1 The sympathetic nerve-induced adipose thermogenesis

In response to cold stress, the sympathetic nervous system releases norepinephrine to mediate the thermogenic function of brown adipocytes. Norepinephrine and β-adrenergic receptor (βAR) efficiently induce lipolysis and lipography of adipose lipid droplets to promote mitochondrial oxidation and heat production[85-86]. In addition, the βAR-mediated cAMP-PKA-Creb signaling pathway transcriptionally up-regulates the expression of Ucp1, Pgc1a and deiodinase, iodothyronine, type II (DIO2), which are essential for cold-induced adipose mitochondrial uncoupling-mediated heat production, mitochondrial biogenesis, and catalyzed T4 to T3 conversion[87-89]. Sympathetic nervous system controls lipid dynamics and transcriptional programs in thermogenic adipose, especially upon cold stress.

4.2 The vasculature remodeling-mediated adipose thermogenesis

Adipose tissues, particularly BAT, are densely vascularized. The intra-adipose vasculature markedly increases in response to chronic cold stress. These changes are important for continuous supply and delivery of oxygen, nutrients and hormones to adipose tissues for maintaining high thermogenic capacity[90-91]. Furthermore, both WAT and BAT produce various proangiogenic factors that induce vascularization and its remodeling. For example, cold exposure results in elevated expression of proangiogenic factors, such as VEGF and suppresses the expression of thrombospondin, an endogenous angiogenesis inhibitor[92-94]. Blockage of cold-induced angiogenesis significantly impairs non-shivering thermogenesis capacity during cold acclimation.

4.3 The immune response-mediated adipose thermogenesis

The immune response mediated by adipose tissue regulates the thermogenic capacity during cold acclimation. As reported, adipose relies on eosinophils, type 2 innate lymphoid cells (ILC2s), and alternatively activated macrophages for the maintenance adaptive thermogenesis]. In response to environmental cold, adipose-secreted adiponectin and eosinophil-derived IL-4 induce the alternatively activated macrophages in adipose tissue, producing catecholamines to regulate beige fat biogenesis[95,98-99]. Type 2 innate lymphoid cells (ILC2s) in adipose tissue secrete IL-5 and IL-13 to orchestrate type 2 innate and adaptive immune responses[100-102], which is required for long-term cold exposure acclimatization.

4.4 The muscle and liver derived cytokine-mediated adipose thermogenesis

Importantly, in response to cold stimuli, skeletal muscle shivering-derived myokines, such as irisin and metrnl, improve metabolic activity[103-107]. Irisin upregulates adipocytes uncoupling protein-1 expression and promotes WAT browning transformation, which enhance the effect of thermogenesis. Differing from the direct role of irisin in cellular thermogenesis, metrnl stimulates an eosinophil-dependent increase in IL-4 expression and promotes alternative activation of adipose tissue macrophages, which are required for the increased adipose thermogenic effect. Furthermore, liver-derived FGF21 also promotes efficiently brown adipose activity and browning of WAT in adaptive thermogenesis to defend against cold stress[8,103,108-111]. FGF21 can also increase body temperature by reducing heat loss to defend against cold stress, independent of energy expenditure and UCP1.

Taken together, multi-organ, multi-cell interactive regulatory pathways are requisite for sustaining adipose adaptive non-shivering thermogenesis. Recent investigations have fueled the interest in adult BAT, since cold-induced BAT thermogenic activity is an effective means to prevent metabolic, inflammatory and cancer diseases.

4.5 The benefits of cold exposure

Cold exposure improves glycolipids metabolism and insulin resistance of obese and type 2 diabetes mellitus (T2DM) in humans and rodents, mainly *via* activating BAT to accelerate the consumption of glucose and lipids and reduce the insulin secretion requirement[103,110,112]. Recent study presents that the beneficial effects of cold exposure on improving inflammatory status depend on BAT. Cold stimulation promotes BAT production of maresin 2 (MaR2), a bioactive lipid that reduces inflammatory response partially by targeting macrophages[113]. Furthermore, cold exposure can also decrease the expression of the major histocompatibility complex class II (MHCII) in monocytes and suppress T cell priming and pathogenicity in mouse models to protect from autoimmune-mediated diseases[114]. Besides, cold exposure has also been recently reported to markedly inhibit the growth of various types of solid tumours, including clinically untreatable cancers such as pancreatic cancers. Mechanistically, cold-induced BAT activation

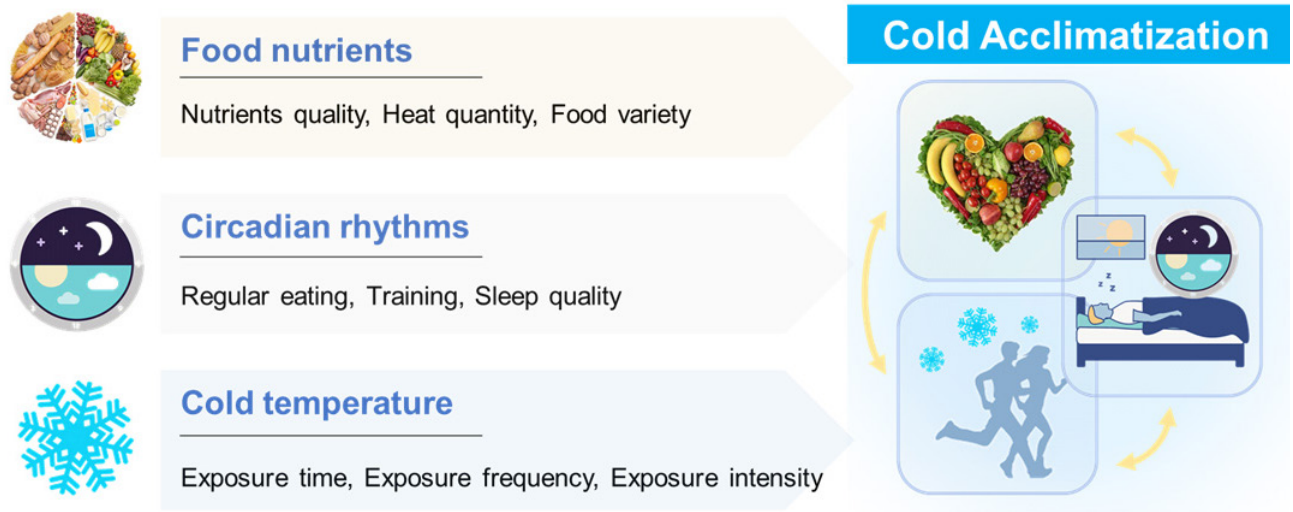

Fig. 1 The health interventions to promote cold acclimatization

substantially decreases blood glucose and impedes the glycolysis-based metabolism in cancer cells[115].

Therefore, long-term or short-term repeated moderate cold exposures are beneficial to cold acclimatization and may be considered a therapeutic strategy for inflammatory and metabolic diseases and cancers

5 Conclusion

In summary, food intake, circadian rhythms, and cold exposure are the major inducible thermogenic mechanisms in the development of cold acclimatization. Thus, scientific interventions will help us adapt to cold environment. The validated interventions include (1) diets of greater quality, quantity, and variety, (2) well-balanced rhythms of food intake, regular exercise, and high-quality sleep, and (3) long-term or short-term repeated moderate cold exposures (Fig. 1).

Acknowledgements

This work was supported by the National Natural Science Foundation of China (NO.82001989; NO.82030055).

Conflicts of interests

The authors declare no financial or commercial conflicts of interest.

References

[1] Lei J, Chen R, Yin P, *et al.* Association between cold spells and mortality risk and burden: a nationwide study in China. Environ Health Perspect, 2022; 130(2): 27006.
[2] Mugele H, Marume K, Amin S B, *et al.* Control of blood pressure in the cold: differentiation of skin and skeletal muscle vascular resistance. Exp Physiol, 2022; 108(1): 38-49.
[3] Huang S G. Binding of fatty acids to the uncoupling protein from brown adipose tissue mitochondria. Arch Biochem Biophys, 2002; 412(1): 142-146.
[4] Schonfeld P, Wojtczak L. Brown adipose tissue mitochondria oxidizing fatty acids generate high levels of reactive oxygen species irrespective of the uncoupling protein-1 activity state. Biochim Biophys Acta, 2012; 1817(3): 410-418.
[5] De Meis L, Ketzer L A, Camacho-Pereira J, *et al.* Brown adipose tissue mitochondria: modulation by GDP and fatty acids depends on the respiratory substrates. Biosci Rep, 2012; 32(1): 53-59.
[6] Argentato P P, de Cassia Cesar H, Estadella D, *et al.* Programming mediated by fatty acids affects uncoupling protein 1 (UCP-1) in brown adipose tissue. Br J Nutr, 2018; 120(6): 619-627.
[7] Paulus A, Drude N, van Marken Lichtenbelt W, *et al.* Brown adipose tissue uptake of triglyceride-rich lipoprotein-derived fatty acids in diabetic or obese mice under different temperature conditions. EJNMMI Res, 2020; 10(1): 127.
[8] Simcox J, Geoghegan G, Maschek J A, *et al.* Global analysis of plasma lipids identifies liver-derived acylcarnitines as a fuel source for brown fat thermogenesis. Cell Metab, 2017; 26(3): 509-522.
[9] Li B, Li L, Li M, *et al.* Microbiota depletion impairs thermogenesis of brown adipose tissue and browning of white adipose tissue. Cell Rep,

2019; 26(10): 2720-2737.
[10] Li Z, Yi C X, Katiraei S, *et al.* Butyrate reduces appetite and activates brown adipose tissue *via* the gut-brain neural circuit. Gut, 2018; 67(7): 1269-1279.
[11] Huang W, Man Y, Gao C, *et al.* Short-Chain fatty acids ameliorate diabetic nephropathy *via* GPR43-Mediated inhibition of oxidative stress and NF-kappaB signaling. Oxid Med Cell Longev, 2020; 2020: 4074832.
[12] Leiria L O, Wang C H, Lynes M D, *et al.* 12-Lipoxygenase Regulates Cold Adaptation and Glucose Metabolism by Producing the Omega-3 Lipid 12-HEPE from Brown Fat. Cell Metab, 2019; 30(4): 768-783.
[13] Nagatake T, Shibata Y, Morimoto S, *et al.* 12-Hydroxyeicosapentaenoic acid inhibits foam cell formation and ameliorates high-fat diet-induced pathology of atherosclerosis in mice. Sci Rep, 2021; 11(1): 10426.
[14] Kharazmi-Khorassani J, Ghafarian Zirak R, Ghazizadeh H, *et al.* The role of serum monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) in cardiovascular disease risk. Acta Biomed, 2021; 92(2): e2021049.
[15] Fleckenstein-Elsen M, Dinnies D, Jelenik T, *et al.* Eicosapentaenoic acid and arachidonic acid differentially regulate adipogenesis, acquisition of a brite phenotype and mitochondrial function in primary human adipocytes. Mol Nutr Food Res, 2016; 60(9): 2065-2075.
[16] Kim J, Okla M, Erickson A, *et al.* Eicosapentaenoic acid potentiates brown thermogenesis through FFAR4-dependent up-regulation of miR-30b and miR-378. J Biol Chem, 2016; 291(39): 20551-20562.
[17] Lynes M D, Leiria L O, Lundh M, *et al.* The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. Nat Med, 2017; 23(5): 631-637.
[18] Pinckard K M, Shettigar V K, Wright K R, *et al.* A novel endocrine role for the BAT-released lipokine 12,13-diHOME to mediate cardiac function. Circulation, 2021; 143(2): 145-159.
[19] Song Z, Xiaoli A M, Yang F. Regulation and Metabolic Significance of *De Novo* Lipogenesis in Adipose Tissues. Nutrients, 2018; 10(10): 1383.
[20] Martinez Calejman C, Trefely S, Entwisle S W, *et al.* mTORC2-AKT signaling to ATP-citrate lyase drives brown adipogenesis and *de novo* lipogenesis. Nat Commun, 2020; 11(1): 575.
[21] Mills E L, Pierce K A, Jedrychowski M P, *et al.* Accumulation of succinate controls activation of adipose tissue thermogenesis. Nature, 2018; 560(7716): 102-106.
[22] Wang T, Xu Y Q, Yuan Y X, *et al.* Succinate induces skeletal muscle fiber remodeling *via* SUNCR1 signaling. EMBO Rep, 2019; 20(9): e47892.
[23] Yuan Y, Xu P, Jiang Q, *et al.* Exercise-induced alpha-ketoglutaric acid stimulates muscle hypertrophy and fat loss through OXGR1-dependent adrenal activation. EMBO J, 2020; 39(7): e103304.
[24] Asadi Shahmirzadi A, Edgar D, Liao C Y, *et al.* Alpha-Ketoglutarate, an endogenous metabolite, extends lifespan and compresses morbidity in aging mice. Cell Metab, 2020; 32(3): 447-456.
[25] Lopez-Soriano F J, Fernandez-Lopez J A, Mampel T, *et al.* Amino acid and glucose uptake by rat brown adipose tissue. Effect of cold-exposure and acclimation. Biochem J, 1988; 252(3): 843-849.
[26] Tome D. Efficiency of free amino acids in supporting muscle protein synthesis. J Nutr, 2022; 152(1): 3-4.
[27] Wu Z, Satterfield M C, Bazer F W, *et al.* Regulation of brown adipose tissue development and white fat reduction by L-arginine. Curr Opin Clin Nutr Metab Care, 2012; 15(6): 529-38.
[28] Kazak L, Chouchani E T, Jedrychowski M P, *et al.* A creatine-driven substrate cycle enhances energy expenditure and thermogenesis in beige fat. Cell, 2015; 163(3): 643-655.
[29] Yoneshiro T, Wang Q, Tajima K, *et al.* BCAA catabolism in brown fat controls energy homeostasis through SLC25A44. Nature, 2019; 572(7771): 614-619.
[30] Wallace M, Green C R, Roberts L S, *et al.* Enzyme promiscuity drives branched-chain fatty acid synthesis in adipose tissues. Nat Chem Biol, 2018; 14(11): 1021-1031.
[31] Balas L, Feillet-Coudray C, Durand T. Branched Fatty Acyl Esters of Hydroxyl Fatty Acids (FAHFAs), appealing beneficial endogenous fat against obesity and Type-2 diabetes. Chemistry, 2018; 24(38): 9463-9476.
[32] Benlebna M, Balas L, Pessemesse L, *et al.* FAHFAs regulate the proliferation of C2C12 myoblasts and induce a shift toward a more oxidative phenotype in mouse skeletal muscle. Int J Mol Sci, 2020; 21(23): 9046.
[33] Kellerer T, Kleigrewe K, Brandl B, *et al.* Fatty Acid Esters of Hydroxy Fatty Acids (FAHFAs) are associated with diet, bmi, and age. Front Nutr, 2021; 8: 691401.
[34] Chappuis S, Ripperger J A, Schnell A, *et al.* Role of the circadian clock gene Per2 in adaptation to cold temperature. Mol Metab, 2013; 2(3): 184-193.
[35] Moraes M N, de Assis L V M, Henriques F D S, *et al.* Cold-sensing TRPM8 channel participates in circadian control of the brown adipose tissue. Biochim Biophys Acta Mol Mol Metab, 2013; 2(3): 184-193.
[36] Fischl H, McManus D, Oldenkamp R, *et al.* Cold-induced chromatin compaction and nuclear retention of clock mRNAs resets the circadian rhythm. EMBO J, 2020; 39(22): e105604.
[37] Zhang Z, Cheng L, Ma J, *et al.* Chronic cold exposure leads to daytime preference in the circadian expression of hepatic metabolic genes. Front Physiol, 2022; 13: 865627.
[38] Barber A F, Sehgal A. Cold temperatures fire up circadian neurons. Cell Metab, 2018; 27(5): 951-953.
[39] Ishii M. Circadian variations in response to cold. Kurume Med J, 1981; 28(3): 211-221.
[40] De Jonghe B C, Hayes M R, Banno R, *et al.* Deficiency of PTP1B in POMC neurons leads to alterations in energy balance and homeostatic response to cold exposure. Am J Physiol Endocrinol Metab, 201; 300(6): E1002-1011.
[41] Xi D, Gandhi N, Lai M, *et al.* Ablation of Sim1 neurons causes obesity through hyperphagia and reduced energy expenditure. PLoS One, 2012; 7(4): e36453.
[42] Takahashi Y, Zhang W, Sameshima K, *et al.* Orexin neurons are indispensable for prostaglandin E2-induced fever and defence against environmental cooling in mice. J Physiol, 2013; 591(22): 5623-5643.
[43] Jeong J H, Lee D K, Blouet C, *et al.* Cholinergic neurons in the dorsomedial hypothalamus regulate mouse brown adipose tissue metabolism. Mol Metab, 2015; 4(6): 483-492.
[44] Wu C S, Bongmba O Y N, Yue J, *et al.* Suppression of GHS-R in AgRP neurons mitigates diet-induced obesity by activating thermogenesis. Int J Mol Sci, 2017; 18(4): 832.
[45] Francois M, Qualls-Creekmore E, Berthoud H R. Genetics-based manipulation of adipose tissue sympathetic innervation. Physiol Behav, 2018; 190: 21-27.
[46] Yang W Z, Du X, Zhang W, *et al.* Parabrachial neuron types categorically encode thermoregulation variables during heat defense. Sci Adv, 2020; 6(36): eabb9414.
[47] Gizowski C, Bourque C W. Sodium regulates clock time and output

via an excitatory GABAergic pathway. Nature, 2020; 583(7816): 421-424.
[48] Touitou Y, Haus E. Alterations with aging of the endocrine and neuroendocrine circadian system in humans. Chronobiol Int, 2000; 17(3): 369-390.
[49] Sato M, Murakami M, Node K, *et al.* The role of the endocrine system in feeding-induced tissue-specific circadian entrainment. Cell Rep, 2014; 8(2): 393-401.
[50] Hernandez-Morante J J, Gomez-Santos C, Milagro F, *et al.* Expression of cortisol metabolism-related genes shows circadian rhythmic patterns in human adipose tissue. I nt J Obes (Lond), 2009; 33(4): 473-480.
[51] Stimson R H, Andersson J, Andrew R, *et al.*Cortisol release from adipose tissue by 11beta-hydroxysteroid dehydrogenase type 1 in humans. Diabetes, 2009; 58(1): 46-53.
[52] Richards E M, McElhaney E, Zeringue K, *et al.* Transcriptomic evidence that cortisol alters perinatal epicardial adipose tissue maturation. Am J Physiol Endocrinol Metab, 2019; 317(4): E573-E585.
[53] Vella C A, Nelson O L, Jansen H T, *et al.* Regulation of metabolism during hibernation in brown bears (Ursus arctos): Involvement of cortisol, PGC-1alpha and AMPK in adipose tissue and skeletal muscle. Comp Biochem Physiol A Mol Integr Physiol, 2020; 240: 110591.
[54] Lechan R M, Fekete C. The TRH neuron: a hypothalamic integrator of energy metabolism. Prog Brain Res, 2006; 153: 209-235.
[55] Martinez de Mena R, Scanlan T S, Obregon M J. The T3 receptor beta1 isoform regulates UCP1 and D2 deiodinase in rat brown adipocytes. Endocrinology, 2010; 151(10): 5074-5083.
[56] Guilherme A, Yenilmez B, Bedard A H, *et al.* Control of adipocyte thermogenesis and lipogenesis through beta3-Adrenergic and thyroid hormone signal integration. Cell Rep, 2020; 31(5): 107598.
[57] Yau W W, Yen P M. Thermogenesis in adipose tissue activated by thyroid hormone. Int J Mol Sci, 2020; 21(8): 3020.
[58] Zhou J, Tripathi M, Ho J P, *et al.* Thyroid hormone decreases hepatic steatosis, inflammation, and fibrosis in a dietary mouse model of NASH. Thyroid, 2022; 32(6): 725-738.
[59] Froy O, Garaulet M. The circadian clock in white and brown adipose tissue: mechanistic, endocrine, and clinical aspects. Endocr Rev, 2018; 39(3): 261-273.
[60] Straat M E, Hogenboom R, Boon M R, *et al.* Circadian control of brown adipose tissue. Biochim Biophys Acta Mol Cell Biol Lipids, 2021; 1866(8): 158961.
[61] Heyde I, Begemann K, Oster H. Contributions of white and brown adipose tissues to the circadian regulation of energy metabolism. Endocrinology, 2021; 162(3): bqab009.
[62] Gerhart-Hines Z, Feng D, Emmett M J, *et al.* The nuclear receptor Rev-erbalpha controls circadian thermogenic plasticity. Nature, 2013; 503(7476): 410-413.
[63] Adlanmerini M, Carpenter B J, Remsberg J R, *et al.* Circadian lipid synthesis in brown fat maintains murine body temperature during chronic cold. Proc Natl Acad Sci U S A, 2019; 116(37): 18691-18699.
[64] Dashti H S, Scheer F, Saxena R, *et al.* Timing of food intake: identifying contributing factors to design effective interventions. Adv Nutr, 2019; 10(4): 606-620.
[65] Romo-Nava F, Guerdjikova A I, Mori N N, *et al.* A matter of time: A systematic scoping review on a potential role of the circadian system in binge eating behavior. Front Nutr, 2022; 9: 978412.
[66] Chellappa S L, Qian J, Vujovic N, *et al.* Daytime eating prevents internal circadian misalignment and glucose intolerance in night work. Sci Adv, 2021; 7(49): eabg9910.
[67] Damiola F, Le Minh N, Preitner N, *et al.* Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. Genes Dev, 2000; 14(23): 2950-2961.
[68] Stunkard A J, Allison K C. Two forms of disordered eating in obesity: binge eating and night eating. Int J Obes Relat Metab Disord, 2003; 27(1): 1-12.
[69] Youngstedt S D, Elliott J A, Kripke D F. Human circadian phase-response curves for exercise. J Physiol, 2019; 597(8): 2253-2268.
[70] Lewis P, Korf H W, Kuffer L, *et al.* Exercise time cues (zeitgebers) for human circadian systems can foster health and improve performance: a systematic review. BMJ Open Sport Exerc Med, 2018; 4(1): e000443.
[71] Kraemer W J, Ratamess N A, Hymer W C, *et al.* Growth hormone(s), testosterone, insulin-like growth factors, and cortisol: roles and integration for cellular development and growth with exercise. Front Endocrinol (Lausanne), 2020; 11: 33.
[72] Haupt S, Eckstein M L, Wolf A, *et al.* Eat, train, sleep-retreat? hormonal interactions of intermittent fasting, exercise and circadian rhythm. Biomolecules, 2021; 11(4): 516.
[73] Chaput J P, McHill A W, Cox R C, *et al.* The role of insufficient sleep and circadian misalignment in obesity. Nat Rev Endocrinol, 2022: 1–16.
[74] Buckley T M, Schatzberg A F. On the interactions of the hypothalamic-pituitary-adrenal (HPA) axis and sleep: normal HPA axis activity and circadian rhythm, exemplary sleep disorders. J Clin Endocrinol Metab, 2005; 90(5): 3106-3114.
[75] Knutson K L, Spiegel K, Penev P, *et al.* The metabolic consequences of sleep deprivation. Sleep Med Rev, 2007; 11(3): 163-178.
[76] Mullington J M, Haack M, Toth M, *et al.* Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Prog Cardiovasc Dis, 2009; 51(4): 294-302.
[77] Laposky A D, Bass J, Kohsaka A, *et al.* Sleep and circadian rhythms: key components in the regulation of energy metabolism. FEBS Lett, 2008; 582(1): 142-151.
[78] Kovanicova Z, Kurdiova T, Balaz M, *et al.* Cold exposure distinctively modulates parathyroid and thyroid hormones in cold-acclimatized and non-acclimatized humans. Endocrinology, 2020; 161(7): bqaa051.
[79] Li Q, Sun R, Huang C, *et al.* Cold adaptive thermogenesis in small mammals from different geographical zones of China. Comp Biochem Physiol A Mol Integr Physiol, 2001; 129(4): 949-961.
[80] Lu H, Ye Z, Zhai Y, *et al.* QKI regulates adipose tissue metabolism by acting as a brake on thermogenesis and promoting obesity. EMBO Rep, 2020; 21(1): e47929.
[81] Lu H, Tang S, Xue C, *et al.* Mitochondrial-Derived peptide MOTS-c increases adipose thermogenic activation to promote cold adaptation. Int J Mol Sci, 2019; 20(10): 2456.
[82] Wang T Y, Liu C, Wang A, *et al.* Intermittent cold exposure improves glucose homeostasis associated with brown and white adipose tissues in mice. Life Sci, 2015; 139: 153-159.
[83] Nishimura T, Katsumura T, Motoi M, *et al.* Experimental evidence reveals the UCP1 genotype changes the oxygen consumption attributed to non-shivering thermogenesis in humans. Sci Rep, 2017; 7(1): 5570.
[84] Larson C J. Translational pharmacology and physiology of brown adipose tissue in human disease and treatment. Handb Exp Pharmacol,

2019; 251: 381-424.
[85] Gonzalez-Hurtado E, Lee J, Choi J, *et al.* Fatty acid oxidation is required for active and quiescent brown adipose tissue maintenance and thermogenic programing. Mol Metab, 2018; 7: 45-56.
[86] Shi M, Huang X Y, Ren X Y, *et al*. AIDA directly connects sympathetic innervation to adaptive thermogenesis by UCP1. Nat Cell Biol, 2021; 23(3): 268-277.
[87] Bianco A C, McAninch E A. The role of thyroid hormone and brown adipose tissue in energy homoeostasis. Lancet Diabetes Endocrinol, 2013; 1(3): 250-258.
[88] Razzoli M, Emmett M J, Lazar M A, *et al*. Beta-Adrenergic receptors control brown adipose UCP-1 tone and cold response without affecting its circadian rhythmicity. FASEB J, 2018; 32(10): 5640-5646.
[89] Lu W H, Chang Y M, Huang Y S. Alternative polyadenylation and differential regulation of Ucp1: implications for brown adipose tissue thermogenesis across species. FASEB J, 2018; 32(10): 5640-5646.
[90] Lim S, Honek J, Xue Y, *et al.* Cold-induced activation of brown adipose tissue and adipose angiogenesis in mice. Nat Protoc, 2012; 7(3): 606-615.
[91] Honek J, Lim S, Fischer C, *et al*. Brown adipose tissue, thermogenesis, angiogenesis: pathophysiological aspects. Horm Mol Biol Clin Investig, 2014; 19(1): 5-11.
[92] Seki T, Hosaka K, Fischer C, *et al.* Ablation of endothelial VEGFR1 improves metabolic dysfunction by inducing adipose tissue browning. J Exp Med, 2018; 215(2): 611-626.
[93] Seki T, Hosaka K, Lim S, *et al.* Endothelial PDGF-CC regulates angiogenesis-dependent thermogenesis in beige fat. Nat Commun, 2016; 7: 12152.
[94] Xue Y, Petrovic N, Cao R, *et al*. Hypoxia-independent angiogenesis in adipose tissues during cold acclimation. Cell Metab, 2009; 9(1): 99-109.
[95] Nguyen K D, Qiu Y, Cui X, *et al*. Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis. Nature, 2011; 480(7375): 104-108.
[96] Fischer K, Ruiz H H, Jhun K, *et al.* Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermogenesis. Nat Med, 2017; 23(5): 623-630.
[97] Henriques F, Bedard A H, Guilherme A, *et al.* Single-Cell RNA profiling reveals adipocyte to macrophage signaling sufficient to enhance thermogenesis. Nat Med, 2017; 23(5): 623-630.
[98] Hui X, Gu P, Zhang J, *et al.* Adiponectin enhances cold-induced browning of subcutaneous adipose tissue *via* promoting M2 macrophage proliferation. Cell Metab, 2015; 22(2): 279-90.
[99] Wei Q, Lee J H, Wang H, *et al*. Adiponectin is required for maintaining normal body temperature in a cold environment. BMC Physiol, 2017; 17(1): 8.
[100] Mathis D. IL-33, Imprimatur of adipocyte thermogenesis. Cell, 2016; 166(4): 794-795.
[101] Odegaard J I, Lee M W, Sogawa Y, *et al.* Perinatal licensing of thermogenesis by IL-33 and ST2. Cell, 2016; 166(4): 841-854.
[102] Lee M W, Odegaard J I, Mukundan L, *et al.* Activated type 2 innate lymphoid cells regulate beige fat biogenesis. Cell, 2015; 160(1-2): 74-87.
[103] Lee P, Linderman J D, Smith S, *et al.* Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. Cell Metab, 2014; 19(2): 302-309.
[104] Vliora M, Grillo E, Corsini M, *et al.* Irisin regulates thermogenesis and lipolysis in 3T3-L1 adipocytes. Biochim Biophys Acta Gen Subj, 2022; 1866(4): 130085.
[105] Zheng S L, Li Z Y, Song J, *et al.* Metrnl: a secreted protein with new emerging functions. Acta Pharmacol Sin, 2016; 37(5): 571-579.
[106] Jung T W, Lee S H, Kim H C, *et al.* Metrnl attenuates lipid-induced inflammation and insulin resistance *via* AMPK or PPARdelta-dependent pathways in skeletal muscle of mice. Exp Mol Med, 2018; 50(9): 1-11.
[107] Lee J O, Byun W S, Kang M J, *et al.* The myokine meteorin-like (metrnl) improves glucose tolerance in both skeletal muscle cells and mice by targeting AMPKalpha2. FEBS J, 2020; 287(10): 2087-2104.
[108] Chartoumpekis D V, Habeos I G, Ziros P G, *et al.* Brown adipose tissue responds to cold and adrenergic stimulation by induction of FGF21. Mol Med, 2011; 17(7-8): 736-740.
[109] Lee P, Brychta R J, Linderman J, *et al*. Mild cold exposure modulates fibroblast growth factor 21 (FGF21) diurnal rhythm in humans: relationship between FGF21 levels, lipolysis, and cold-induced thermogenesis. J Clin Endocrinol Metab, 2013; 98(1): E98-102.
[110] Peres Valgas da Silva C, Hernandez-Saavedra D, White J D, *et al.* Cold and exercise: therapeutic tools to activate brown adipose tissue and combat obesity. Biology (Basel), 2019; 8(1): 9.
[111] Ameka M, Markan K R, Morgan D A, *et al.* Liver derived FGF21 maintains core body temperature during acute cold exposure. Sci Rep, 2019; 9(1): 630.
[112] Ivanova Y M, Blondin D P. Examining the benefits of cold exposure as a therapeutic strategy for obesity and type 2 diabetes. J Appl Physiol, 2021; 130(5): 1448-1459.
[113] Sugimoto S, Mena H A, Sansbury B E, *et al*. Brown adipose tissue-derived MaR2 contributes to cold-induced resolution of inflammation. Nat Metab, 2022; 4(6): 775-790.
[114] Spiljar M, Steinbach K, Rigo D, *et al.* Cold exposure protects from neuroinflammation through immunologic reprogramming. Cell Metab, 2021; 33(11): 2231-2246.
[115] Seki T, Yang Y, Sun X, *et al*. Brown-fat-mediated tumour suppression by cold-altered global metabolism. Nature, 2022; 608(7922): 421-428.