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Molecular mediators of cold adaptation in mammalian cells

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Hypothermia is defined as a drop in temperature below the homeostatic range of cells and tissues. This elicits a response in mammalian cells geared towards cellular and metabolic adaptation. Hibernating mammals provide natural models of cold tolerance and adaptation. Mammalian cells across species share signaling mechanisms for adaptation to hypothermic stimuli. Key molecular mediators of hypothermic signaling, including: (i) cold-sensing ion channels such as TRPM8 and TRPA1, which link temperature changes to calcium signaling and thermoregulatory responses; (ii) β-adrenergic signaling and uncoupling protein 1 (UCP1)-mediated non-shivering thermogenesis in brown adipose tissue; (iii) cold-induced epigenetic modifications such as histone acetylation, DNA methylation, and enhancer activation that imprint transcriptional memory of cold exposure; and (iv) RNA-binding proteins CIRBP and RBM3, which are rapidly induced during mild-to-moderate hypothermia and confer neuroprotection, enhance differentiation, and modulate metabolism. Together, these findings outline a molecular framework by which mammalian cells sense, respond, and adapt to cold, with implications for neuroprotection, metabolic health, and therapeutic hypothermia.

Mammals are endotherms and they can maintain a steady internal body temperature. The optimal operation of enzymes, cellular functions, and metabolic activities depend on the ability to maintain this relatively constant temperature. Hypothermia develops when the core body temperature falls below the typical range, typically below 35 °C[1]. Here we outline the major molecules and pathways that sense and mediate hypothermic adaptation within mammalian cells, particularly focused on cellular metabolic remodeling.

Hypothermia in humans has been classified into mild (35 °C–32 °C), moderate (32 °C–28 °C), and severe (<28 °C)[1]. By utilizing specific molecular responses to tolerate lower temperatures, cells can adjust to changing environmental conditions. Hypothermia has been shown to have both positive and negative effects in a context dependent manner. Decline in core body temperature leads to progressive impairment of vital functions, such as consciousness, and respiratory rate[2,3]. During accidental hypothermia the likelihood of cardiac arrest increases significantly below 32 °C and becomes markedly higher at temperatures below 28 °C[2,3]. Hypothermia causes dysfunction in clotting mechanisms, contributing to coagulopathy[4,5]. Hypothermia therapy is a well-established neuroprotective strategy used in various conditions such as cardiac arrest, traumatic brain injury (TBI), and stroke[6]. Hypothermia therapy is widely used during organ preservation and cardiopulmonary bypass in surgery[7,8]. Hypothermic adaptation and cold exposure have also been shown to have beneficial effects on organisms. For example, in a study performed in mice, the core body temperature was reduced by 0.3°–0.5 °C by the overexpression of UCP2 in hypocretin neurons of mice. This decrease in temperature leads to improved energy efficiency and longer median lifespans. Females experienced a 20% increase in lifespan, while males experienced a 12% increase[9]. Benefits of cold exposure are also observed in humans. For example, there was an improvement in glucose homeostasis and cardiometabolic risk markers in overweight or obese adults after 10 days of cold acclimation. It improved blood pressure, lipid metabolism, and glucose tolerance. There was a 10 mmHg drop in resting systolic blood pressure and a 7 mmHg drop in resting diastolic blood pressure[10].

Overall, hypothermia has been demonstrated to exert both beneficial and deleterious effects, which are highly dependent on the specific context. Therefore, precise assessment of hypothermia across different temperature ranges and underlying mechanisms is essential for its beneficial use. Here we discuss key molecular mediators of hypothermia in mammalian cells, providing mechanical insights into how cells respond to this physiological stimulus.

Insights from hibernating mammals

Mammals that hibernate and go into torpor during the colder months can serve as a model for studying hypothermic adaptation. Hibernation involves coordination between hypothermic adaptation and metabolic plasticity.

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Hibernation comprises of prolonged hypometabolic, hypothermic phases known as torpor. In almost all hibernating mammals, torpor is consistently interrupted by shorter rewarming phases with increased metabolism known as interbout arousal (IBA)[11]. In the hypothermic adaptation context, we have primarily focussed only on the torpor-state. Animals such as brown bears (*Ursus arctos*) and thirteen-lined ground squirrels (*Ictidomys tridecemlineatus*) significantly lower their body temperature during the winter season and undergo a period of hibernation[12,13]. Body temperature in brown bears drops to 33.5 °C during hibernation[12] while thirteen-lined ground squirrels and arctic ground squirrels (*Urocitellus parryii*) can decrease their body temperature to as low as 5 °C and −2 °C respectively[13,14]. The body undergoes physiological changes in these situations, enabling the animal to endure challenging environmental conditions.

Cold sensing ion channels are specialized proteins that detect and respond to cold temperatures. Cold sensing Ion channels play an essential role in responding to lower temperatures but their role in hibernation is poorly understood. A study performed in thirteen-lined ground squirrels and Syrian hamsters reported changes in the amino acid sequences of the transmembrane domain of TRPM8 (transient receptor potential cation channel subfamily M member 8) in somatosensory neurons. This led to their reduced sensitivity to cold[15]. Inserting the transmembrane domain from TRPM8 of the cold-sensitive rats into that of the squirrel and hamster was able to restored their cold sensitivity. This suggests that the cold-sensing ion channel TRPM8 in hibernating mammals may have evolved differently as compared to non-hibernating mammals.

Other proteins have been implicated in hypothermic adaptation associated with hibernation. For example, Uncoupling protein 1 (UCP1) levels were reported to be higher in neurons of torpid thirteen-lined ground squirrels. The mitochondria isolated from these tissues also show a high level of palmitate-induced uncoupling[16]. Transcript levels of (UCP2) in WAT (1.6-fold) and Uncoupling protein 3 (UCP3) in skeletal muscle (3-fold) were upregulated during hibernation in arctic ground squirrels[14]. Uncoupling proteins (UCPs) are key regulators of energy metabolism and thermogenesis. Their upregulation in various tissues during hibernation highlights their essential role in adaptive heat production and metabolic control under low-temperature conditions. HDAC1 (Histone Deacetylase 1) and HDAC4 (Histone Deacetylase 4) protein levels increased in skeletal muscle and Brown Adipose tissue (BAT) of thirteen-lined ground squirrels during torpor[17,18]. This indicates potential epigenetic regulation linked to hibernation. Protein levels of Cold-inducible RNA-binding protein (CIRBP), a cold shock protein, were reported to be upregulated in skeletal muscle, liver, and brown adipose tissue of thirteen-lined ground squirrels during the torpor[19,20]. Transcript levels of RNA-binding motif protein 3 (RBM3), an RNA-binding protein responsive to cold stress also showed upregulation in liver, heart, and brain tissues during torpor of hibernation in golden-mantled squirrel (*Callospermophilus lateralis*) and black bears (*Ursus americanus*)[21–23]. RNA-binding proteins (RBPs) are involved in key RNA processing events and thereby regulation of protein synthesis[24]. The upregulation of CIRBP and RBM3 across multiple tissues highlights their role in mediating cellular adaptation during hibernation.

During hibernation, a major rewiring of metabolism occurs with shifting of energy utilization from carbohydrates to fatty acids[25]. Glucose levels in the serum of thirteen-lined ground squirrels drop from 8.5 mM (summer active state) to 3.3 mM (torpor in winter)[26]. bHB (d-β-hydroxybutyrate) levels in the plasma of thirteen-lined ground squirrels, a fat-derived ketone increases from 0.26 mM (summer active state) to 2.3 mM (during torpor in winter)[13]. bHB other than being a source of acetyl-CoA is also linked to epigenetic gene regulation[27]. The gene expression profiles of heart and skeletal muscle tissue from thirteen-lined ground squirrels showed upregulation of genes related to fatty acid metabolism and oxidative metabolism during the torpor stage of hibernation[28]. In conjunction with this, the Peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) transcript expression was upregulated during the torpor stage of hibernation in the skeletal muscle of these animals[28]. This suggests that mitochondrial activity may be enhanced during hibernation to facilitate fatty acid mobilization.

The IGF (Insulin-like growth factor) signaling pathway, plays a crucial role in regulating growth, development, metabolism, and cell survival[29]. IGF signaling also plays a positive role in regulating growth of skeletal muscle and bone[30,31]. Insulin-like growth factor-1 (IGF1) and Insulin-like growth factor-2 (IGF2) transcript levels were upregulated during the torpor stage of hibernation in the skeletal muscle of thirteen-lined ground squirrels[28]. Co-localization of IGF-1 and its receptor was also reported to be increased during pre-hibernation and re-entry into torpor in Daurian ground squirrels (*Spermophilus dauricus*)[32]. Conversely, in another study performed in hibernating Scandinavian brown bears (*Ursus arctos arctos*), it was reported that the plasma circulating levels of IGF-1 and IGF-2 decreased. But in spite of this, the IGF/IGFBP (Insulin-like growth factor binding protein) in fact increased in the target tissues due to reduced levels of Acid labile subunit (ALS)[33], to increase tissue-availability of these growth factors. Hibernating mammals despite long period of inactivity do not show significant loss of skeletal muscle mass[34,35]. This increase in IGF signaling may contribute to the conservation of muscle and bone mass during extended periods of inactivity in hibernating mammals.

Hibernating bears and small rodents like squirrels exhibit distinct physiological profiles. Bears undergo mild to moderate hypothermia, while squirrels enter torpor with near-freezing body temperatures[12–14].These differences suggest species-specific adaptations and potentially divergent molecular responses. However, some core signaling cascades involved in metabolism and neuroprotection are conserved across both groups. The comprehensive molecular mechanism and signaling cascades underlying hibernation need further analysis. Overall, cold-sensing ion channels, UCPs, epigenetic modifications and RNA-binding proteins have emerged as key molecular mediators of hypothermic adaptation in hibernating mammals. We discuss the molecular mechanisms of these mediators in mammals in the following sections.

Ion Channels

TRPM8: an ion channel for cold sensation and thermoregulation

TRPM8 is a principal ion channel responsible for cold- sensation in peripheral sensory neurons. TRPM8 stands out as the only well-established mammalian ion channel that is directly activated by cold via an intrinsic structural mechanism. It is triggered by hypothermia in the range of 8–28 °C, as well as in response to chemicals such as menthol or icilin[36,37]. TRPM8 is a homotetrameric cation channel belonging to the TRPM (melastatin) subfamily, with each subunit comprising six transmembrane segments and extensive intracellular N- and C-termini[38]. Cryo-electron imaging of TRPM8 demonstrates an overall structure akin to other TRP channels, featuring a pore-forming S5–S6 region and a cytosolic "TRP domain" helix crucial for gating[38]. The temperature-dependent gating of TRPM8 is associated with conformational alterations in the S6 helix: a decrease in temperature facilitates a transition from disordered to ordered (coil-to-helix) in the S6 segment, which aids in the opening of the channel pore[39]. When the channel opens, hydrophobic gate residues, such as Phe979 in mouse TRPM8, retract from the ion conduction pathway, facilitating cation flow[39]. TRPM8 gating necessitates the membrane phospholipid PIP_2 as a cofactor with cold. Removal of PIP_2 results in channel desensitization, indicating that PIP_2 binding stabilizes the open state[40]. Activation of TRPM8 by cold stimuli or menthol depolarizes sensory neurons and triggers messages to the central nervous system[41,42]. Afferents expressing TRPM8 can elicit autonomic responses for thermoregulation. TRPM8 activation stimulates sympathetic outflow to brown adipose tissue (BAT), enhancing thermogenesis and heat generation[41,42]. In murine models, pharmacological activation of TRPM8 (e.g., by menthol) enhances brown adipose tissue activity and elevates core body temperature[41,43]. In contrast, the absence of TRPM8 hinders thermoregulatory mechanisms against cold, since TRPM8-knockout mice demonstrate a significant decrease in core body temperature when exposed to cold[44]. TRPM8-null mice exposed to repeated mild

freezing exhibit late-onset obesity accompanied by metabolic dysfunction, likely due to the absence of TRPM8-mediated thermogenic signaling, leading to hyperphagia and diminished fat burning in response to cold stress[44]. Chronic activation of TRPM8 has been demonstrated to replicate the effects of cold exposure and provide metabolic advantages. For instance, dietary menthol (a TRPM8 agonist) consistently increases UCP1 levels in brown adipose tissue and promotes the "browning" of white adipose tissue, thereby safeguarding mice from diet-induced obesity and enhancing glucose tolerance without diminishing food consumption[43]. A newly identified truncated splice variant of TRPM8, named as "eTRPM8," in skin keratinocytes, suggests diverse functions for this channel in metabolism. This truncated variant targets the endoplasmic reticulum and, upon cooling, liberates Ca^{2+} into mitochondria at ER–mitochondria contact sites, thereby augmenting mitochondrial Ca^{2+} and activating Ca^{2+}-dependent metabolic enzymes to increase ATP production. These findings underscore that TRPM8 functions not only as a peripheral cool sensor but also directly links temperature signals to cellular metabolism. In the liver, TRPM8-linked pathways help maintain glucose and energy homeostasis by tuning insulin clearance via hepatic innervation and upregulating mitochondrial oxidative function[45,46]. Therefore, under non-hypothermic physiological conditions, TRPM8 acts as a metabolic regulator in non-neural tissues. It promotes fat burning and heat production in adipose depots while fine-tuning glucose metabolism and energy production in the liver. These coordinated actions of TRPM8 in fat and liver contribute to overall metabolic balance, influencing body weight, insulin sensitivity, and energy expenditure in mice and humans[47].

TRPA1: activation by cold via oxidative stress and cellular stress responses

TRPA1 is an ion channel associated with cold sensation, albeit its function in thermal perception maybe be more indirect. In contrast to TRPM8, TRPA1 does not function as a conventional sensor for mild cooling; rather, research indicates that excessive cold may activate TRPA1 indirectly via intracellular oxidative stress related mechanisms[48]. Each TRPA1 subunit possesses an N-terminal ankyrin repeat domain (ARD) featuring several reactive cysteine residues capable of covalent modification by oxidative agents. Cold-induced generation of reactive oxygen species (ROS), such as those from mitochondria during cold shock, can oxidize cysteine residues, resulting in conformational alterations that facilitate the opening of the TRPA1 channel pore[48,49]. Consequently, ROS may serve as a mediator connecting a decrease in temperature with TRPA1 activation in sensory neurons. TRPA1 is a tetrameric channel characterized by a long N-terminus, comprising around 17 ankyrin repeat domains (ARD) per subunit, and a transmembrane domain akin to other TRP channels[50].The long ARD repeats are believed to affect ligand gating and interact with regulatory proteins. However, it is not essential for TRPA1's cold sensitivity, as truncated TRPA1 devoid of the ARD continues to respond to cold. This suggests that the molecular mechanism for cold-gating is located within the core transmembrane/pore domains[51]. Upon activation of TRPA1, the resultant Ca^{2+} influx depolarizes nociceptors and induces the release of neuropeptides, including calcitonin gene-related peptide (CGRP), from nerve terminals, resulting in neurogenic inflammation and pain signaling[52]. Prolonged activation or overactivation of TRPA1 by reactive oxygen species and extended exposure to cold might result in intracellular Ca^{2+} excess and mitochondrial malfunction. Elevated Ca^{2+} levels can trigger the opening of the mitochondrial permeability transition pore (mPTP), resulting in the loss of mitochondrial membrane potential and can lead to apoptotic cell death[53]. In contrast, hibernating mammals seem to prevent cold-induced cellular damage. In response to severe cold exposure, hibernators enhance antioxidant defenses and undergo mitochondrial modifications that presumably inhibit mPTP opening and subsequent apoptosis, allowing their tissues to endure intense hypothermia with minimal damage[54]. These data emphasize TRPA1's dual function as a detector of harmful cold and oxidative signals and as a facilitator of cold-induced stress responses, while illustrating adaptive methods in nature that mitigate TRPA1-mediated cytotoxicity during extended cold exposure.

In addition to TRPM8 and TRPA1, other ion channels have been shown to contribute to cold response, albeit in a modulatory or context-dependent manner. An example is the two-pore domain potassium channel TREK-1 ($K_2P2.1$). TREK-1 is a background K^+ channel characterized by significant temperature sensitivity; its activity escalates with increased temperature and is suppressed by cooling below approximately 20-s24 °C[55]. Consequently, at typical warm temperatures, TREK-1 facilitates the establishment of a hyperpolarized resting membrane potential; nevertheless, cooling induces the closure of TREK-1 channels, thereby diminishing K^+ outflow and increasing neuronal excitability. TREK-1 functions as a cold-inhibited "brake" on neuronal activity. TREK-1 mutant mice exhibit increased cold sensitivity and pain behaviors, indicating that TREK-1 typically mitigates cold responses by hyperpolarizing neurons under normothermic settings[56]. Significantly, the ablation of TREK-1, particularly in conjunction with the ablation of the associated channel TRAAK, elevates the ratio of cold-responsive sensory neurons and amplifies behavioral sensitivity to cold, despite TREK-1 not functioning as a direct cold sensor like TRPM8[56]. TREK-1's cold-induced closure likely enhances the depolarizing effects of other cold-activated pathways. TRPC5, a member of the TRP canonical family, is another channel involved in cold transduction. TRPC5 is present in a specific group of peripheral sensory neurons and is triggered by moderate cooling, with a threshold of approximately 25–30 °C, in heterologous systems[57]. In vitro, reducing the temperature from physiological levels to approximately 25 °C can directly activate TRPC5 currents (in the absence of TRPM8), demonstrating that TRPC5 possesses inherent cold sensitivity within the mild-cool range[57]. The role of TRPC5 in vivo seems to be context-dependent. Mice deficient in TRPC5 exhibit normal acute cold response under baseline conditions, indicating that TRPM8 and other mechanisms mostly govern standard cold detection; In a physiological environment, TRPC5, in conjunction with TRPA1, may facilitate vasomotor responses to cold, including cold-induced vasoconstriction, but this domain is still under examination. Overall, channels such as TREK-1 and TRPC5 do not function as primary cold receptors universally; rather, they modulate the excitability of cold-sensing circuits or fulfill specialized roles under specific circumstances (e.g., TREK-1 influencing the thermal sensitivity of nociceptors, TRPC5 participating in cold pain or localized cold responses).

Uncoupling Proteins

During hypothermia, the body generates heat by shivering and non-shivering thermogenesis (NST). BAT is primarily responsible for NST enabling mammals to maintain core body temperature in cold environments. Therefore, it plays a critical role in energy homeostasis[58]. NST in BAT is maintained by UCP1[59]. There are five homologs of UCP in mammals: UCP1, UCP2, UCP3, UCP4 and UCP5. UCP1 is abundant in BAT. It is located in the inner mitochondrial membrane and is associated with the maintenance of thermogenesis. It disrupts the proton gradient generated by the electron transport chain (ETC), releasing energy as heat. Other UCP homologs (UCP2, UCP3, UCP4 and UCP5/BMCP1) share sequence similarity with UCP1 and may contribute to NST in other tissues[60]. However, conflicting data indicate that UCP3 may not be functionally relevant for NST, as UCP3 knockout mice do not display cold sensitivity or hypothermia[60]. Ucp2 and Ucp3 mRNA expression correlate with increased mitochondrial proton leak under certain conditions such as cold exposure and thyroid hormone treatment[61]. UCP5 (BMCP1) and UCP4 are upregulated in response to cold exposure, suggesting a role in localised thermoregulation in the brain and liver where it facilitate proton leak across the mitochondrial inner membrane to generate heat[61]. UCP1 activation during hypothermia is mediated by the β-adrenergic signaling pathway. During hypothermia, the SNS gets stimulated and activated[62]. Norepinephrine (NE) is released from the sympathetic nerve endings. It binds to β-adrenergic receptors, which trigger a signaling cascade that elevates cAMP levels and

activates protein kinase A (PKA)[63]. This increases the lipolytic activity at the surface of lipid droplets in BAT, which release fatty acids. These fatty acids increase the UCP1 activity[63–66].Therefore, the β-adrenergic receptor emerges as an important mediator of BAT-driven heat production. This is also evident from the study which reported the β1 receptor knockout mice (KO) failed to maintain core temperature during cold exposure (4 °C). Also, β1KO mice fail to increase energy expenditure on a high-fat diet leading to increased adiposity, glucose intolerance, hypercholesterolemia and hypertriglyceridemia[62]. UCP1's cysteine residues undergo oxidative modifications during cold-induced thermogenesis (4 °C for 3days). The sulfenylation of Cys253 regulates UCP1's proton-conductance activity[67]. This pathway underlies the thermogenic efficiency of BAT and its importance in protecting against hypothermia. The mitochondrial calcium uniporter (MCU) complex also plays an important role in enhancing thermogenesis in BAT by regulating calcium uptake, which drives aerobic metabolism. MCU consists of several subunits including EMRE and mitochondrial calcium uptake 1 (MICU1) which modulate its activity. MCU recruits UCP1 via EMRE to form a thermoporter complex which enhances calcium influx. This also increases the TCA cycle and UCP1-mediated uncoupled respiration. Deletion of MCU or EMRE in BAT reduces their thermogenic capacity[68]. This suggests that the thermoporter significantly enhances thermogenesis under cold exposure (4 °C). O-GlcNAc modification mediated by O-GlcNAc transferase (Ogt) is crucial for cold-induced thermogenesis in brown adipose tissue (BAT) under cold exposure (4 °C for 3 h). Ogt knockout (Ogt-KO) mice exhibit an increased number of large lipid droplets in BAT. The absence of O-GlcNAc modification also leads to decreased levels of Ucp1 and mitochondrial DNA–encoded proteins. These findings correlate with their inability to maintain body temperature in cold conditions[69]. Studies have also revealed the importance of transcriptional regulators such as PR Domain containing 16 (PRDM16) in governing adipose tissue browning. PRDM16 regulates thermogenesis by increasing the gene expression of UCP1 by forming a complex with transcription factors including Peroxisome Proliferator Activated Receptor γ (PPARγ), PGC-1α and CCAAT/enhancer-binding protein β(CEBP-β). The thermogenic role of PRBM16 is inhibited by Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1). Pin1 is a prolyl isomerase that interacts with PRDM16 via the ubiquitin-proteasome pathway to promote its degradation and suppress thermogenesis[70,71]. Pin1 interacts with PRDM16 via its WW domain and it binds to the N-terminal PR domain containing Ser/Thr-Pro sites of PRDM16. Therefore, Pin1 expression inhibits NST[70,71]. While UCP1 is central to BAT function, alternative thermogenic pathways can compensate for its absence. UCP1 knockout (KO) mice can promote alternative thermogenic mechanisms like cycles driven by calcium and creatine. However, these pathways take time to adapt and are not as efficient as UCP1-dependent thermogenesis[64,72]. For example, these UCP1-deficient animals require ~60% more caloric intake to rewarm from torpor than wild-type controls, demonstrating the efficiency of UCP1-mediated heat generation[72]. These findings highlight the regulation of thermogenesis during cold exposure with UCP1 acting as a central effector in BAT-mediated non-shivering thermogenesis (Fig. 1). In contrast, pigs rely mainly on shivering thermogenesis. Pigs lack functional BAT and carry a loss-of-function mutation in Ucp1 gene[73]. This genetic defect explains the poor thermoregulation and high cold susceptibility of piglets, which depend instead on shivering and behavioral strategies[73]. In hibernating animals like the thirteen-lined ground squirrel, the expression of UCP1 mRNA and protein is increased in the brain during hibernation[16]. This helps in local thermogenesis for synaptic integrity, metabolic transitions and rapid arousal from torpor[16]. In Arctic ground squirrels, Ucp2 in white adipose tissue increased ~2.5-fold and Ucp3 in skeletal muscle increased ~2.4-fold under hibernating conditions. This suggests that WAT and skeletal muscle also aid cold defense in these animals[14].

Though we have emphasized a UCP1-dependent mechanism of thermogenesis in this review, recent studies have reported that in adipose tissue UCP1-independent mechanism of thermogenesis also exists[74]. For example, the body can generate heat by futile calcium cycling. Heat is generated during calcium (Ca^{2+}) cycling when Ca^{2+} is actively transported into the lumen of the endoplasmic reticulum or sarcoplasmic reticulum by ATP-dependent Ca^{2+} pumps like SERCA1 in skeletal muscle and SERCA2b in adipose tissue. At the same time, Ca^{2+} is continuously released into the cytosol through channels such as inositol trisphosphate receptors (IP3Rs) and ryanodine receptors (RYRs)[74]. In a study using an isothermal titration calorimetry (ITC) platform coupled with bioinformatic screening and structural modelling, C4orf3 has been identified as a small ER-anchored peptide that binds to SERCA2b. Unlike typical SERCA inhibitors, C4orf3 uncouples ATP hydrolysis from Ca^{2+} transport, leading to lower transport efficiency and increased heat dissipation, essentially making the SERCA2-C4orf3 complex a "molecular resistor". C4orf3 knockout (CRISPRi-C4orf3) mice showed reduced SERCA2-dependent thermogenesis in inguinal WAT, increased Ca^{2+} transport efficiency and lower heat production[74]. These findings indicate an essential backup mechanism for thermogenesis when UCP1 is deficient or absent.

Epigenetic modifications

Cold-induced adaptive processes are governed at the molecular level through extensive epigenetic modifications. Histone deacetylase (HDAC3) is an epigenetic modulator of gene expression[75]. BAT-specific KO of HDAC3 in mice results in a decrease in core body-temperature within hours of being subjected to hypothermia (4 °C)[76]. In these BAT-specific KO mice HDAC3 forms a complex with PGC-1α and ERRα. HDAC3 enhances the function of PGC-1α through lysine deacetylation[77]. In NIH3T3 cells, HDAC3 also increases the transcriptional activity of ERRα in the presence of PGC-1α at the enhancer region of Ucp1 gene[76]. Short-term exposure to mild cold temperature (STEMCT) of 15 °C for 24 h restores the level of Ucp1 in HDAC3 KO mice[64]. STEMCT led to an increase in bZIP transcription factor C/EBPb in BAT, which was persistently increased for 7 days, revealing a memory for the hypothermia. This suggests an HDAC3-independent enhancer activation for Ucp1 expression[64]. The effect of STEMCT was persistent due to the constant expression of C/EBPb[64]. C/EBPb and PGC-1α self-regulate their expression by binding to their own gene loci while also targeting the Ucp1 and OXPHOS-related genes to enhance their expression[64]. These findings indicate that STEMCT-driven BAT activation triggers a thermogenic mechanism independent of HDAC3 and a memory response to hypothermia.

In mice exposed to 8 °C for 2 weeks, there was increased methylation (H3.2K9me2/3) and acetylation (H4K16ac) of histones H3.2 and H4 respectively. These modifications were associated with increased expression of thermogenic and oxidative phosphorylation genes. In these mice the promoters of thermogenic genes Ucp1 *and* Ppargc1a showed hypomethylation correlating with their transcriptional upregulation[78]. However, longer cold exposure (−1 °C to 4 °C for 30 days) in mice induced global DNA hypermethylation and elevated histone deacetylase 1 (HDAC1) expression in hippocampal CA1 neurons[79]. Cold exposure also enhanced expression of mitochondrial proteins (VDAC1, cytochrome C), increased the number of IRS2 and leptin receptor-positive cells, indicating improved central insulin and leptin sensitivity. These changes were epigenetically regulated via methylation and histone deacetylation of irs2, ob-r, vdac1, and cytc promoters[79]. In rats exposed to 4 °C for 8 days, BAT showed increased phosphorylation of IR, IRS-1/2, Akt/ERK and glucose uptake. This indicates an increase in insulin signaling[80]. But skeletal muscle and WAT displayed reduced IR/IRS phosphorylation and Akt activation, indicating insulin resistance[80]. Histone demethylase JMJD1A also play an important role in mediating cold-induced thermogenesis via a dual mechanism[81]. BAT of mice exposed to 4 °C for 6 h triggered increased PKA-mediated phosphorylation of JMJD1A at Ser265. This enabled chromatin looping and activation of *Ucp1* independent of its demethylase activity[81]. But the beige adipocytes in subcutaneous WAT of mice exposed to 4 °C for 7 days require both phosphorylation and demethylation of H3K9me2 for sustained thermogenic gene expression. Jmjd1a-S265A knock-in mice confirm that loss of phosphorylation or demethylase function impairs thermogenesis, beigeing and insulin sensitivity[81]. Thus, JMJD1A acts as a phospho-switch regulating

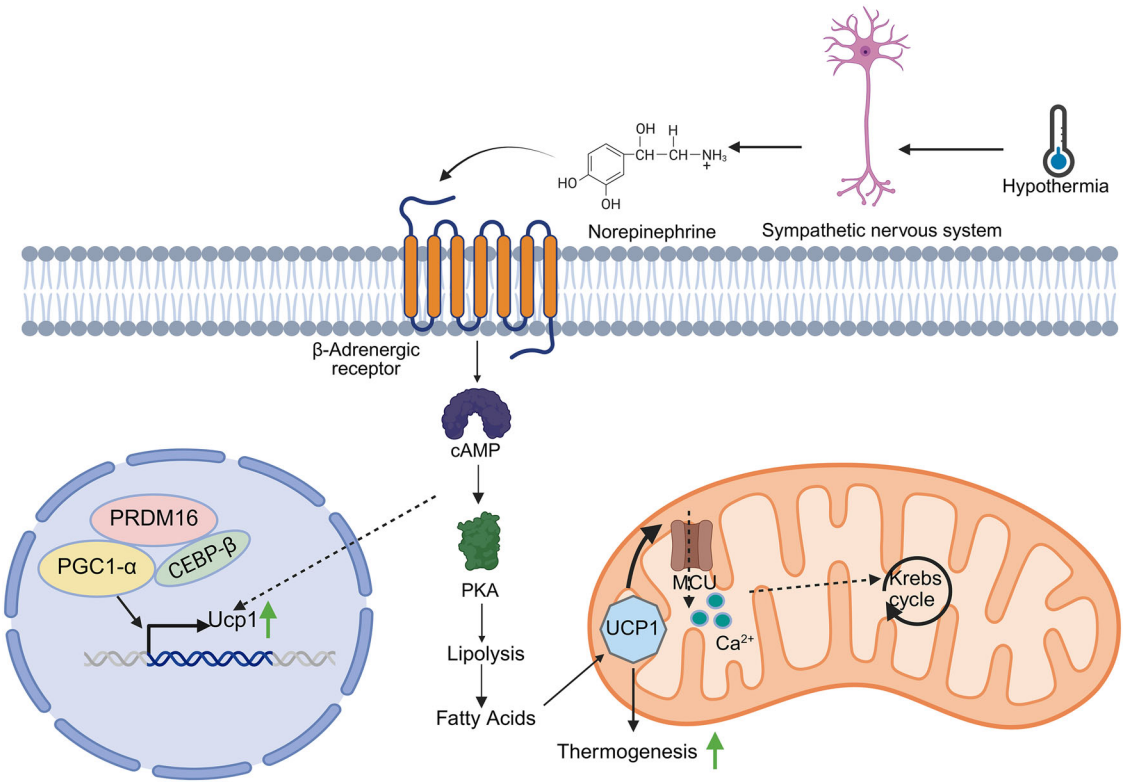

Fig. 1 | β-adrenergic receptor and UCP1 axis. β-adrenergic receptors mediated regulation of non-shivering thermogenesis (NST) via uncoupling protein 1 (UCP1) in brown adipose tissue.

acute and long-term cold adaptation and offers a potential therapeutic target for metabolic diseases[81]. A recent study on humans demonstrated that cold environmental exposure before conception (especially during the fertilization period) increases long-term BAT activity, systemic metabolism and cold-induced thermogenesis in human offspring[82]. This highlights the relevance of cold-induced epigenetic programming not only in thermoregulation and metabolic plasticity but also in shaping offspring physiology via heritable epigenetic marks.

RNA-binding proteins

RNA-binding proteins (RBPs) are known to be involved in RNA processing events like post-transcriptional modifications and mRNA stability thereby governing the protein synthesis[24,83]. RNA-binding motif protein 3 (RBM3) and cold-inducible RNA-binding protein (CIRBP) are two well-studied cold shock proteins that are upregulated in response to hypothermia (35 °C-25 °C)[84]. Their molecular signaling and functions during hypothermia are discussed below:

CIRBP

CIRBP is a cold-shock protein composed of two distinct domains: The N-terminal domain is an RNA-binding domain and the C-terminus is a Glycine-rich domain[19]. Three mRNA splice variants of Cirbp (long: 800 bp; middle: 700 bp; short: 500 bp) are constitutively expressed in the brain, heart, liver and kidney of euthermic mice. However, the short-form variant, which encodes the full-length functional CIRBP, is dominantly expressed upon hypothermic induction (28 °C). In isolated leukocytes from mice, the splicing shift is driven by a significant decrease in temperature (28 °C for 30 and 60 min)[85]. NIH3T3 mouse fibroblast cell were exposed to 33 °C for 2 h which led to temperature-dependent accumulation of Cirbp mRNA by alternative splicing[86]. Molecular interactors of CIRBP could provide insights into the pathways involved in hypothermic adaptations. In HEK293T cells stably expressing telomerase reverse transcriptase (TERT) shows that CIRBP is present in the TERT complex. CIRBP is essential for maintaining the TERT complex at both 37 °C and 32 °C[87]. CIRBP interacts directly with telomerase RNA components (TERC) and stabilizes TERT mRNA, maintaining the activity of telomerase at 32 °C in HEK293T cells[87]. Rat model showed that hypothermia-induced CIRBP contributes to cerebral recovery by directly interacting with IP3R and VDAC1 in mitochondrial-associated endoplasmic reticulum membrane (MAM) during cardiac arrest[88]. CIRBP inhibits their expression, regulates Ca^{2+} transport, and influences energy metabolism[88]. CIRBP was identified as a key component of the IP3R-Grp75-VDAC1 macro complex at ER-mitochondria contact sites. In NIH3T3 fibroblast mouse cells, CIRBP bound to mRNAs associated with circadian processes such as Sirtuin1, CLOCK and PEROID3[89]. Knockdown of CIRBP using siRNA leads to a reduced circadian gene expression[89]. Therefore, CIRBP can control numerous cellular processes, including apoptosis, circadian rhythm and calcium homeostasis in cells.

CIRBP has been also studied in therapeutic hypothermia. Therapeutic hypothermia is commonly used in cardiac surgery to protect the heart from ischemic damage; however, patients with chronic hypoxia (CH) exhibit impaired cold-induced cardio-protection. Cardiopulmonary bypass model of rat showed that chronic hypothermia induced the hypermethylation of the *Cirbp* promoter[90]. This resulted in reduction of CIRBP expression and increase in myocardial injury. Also, CIRBP overexpression enhances cardio-protection by modulating the cardiac ubiquinone biosynthesis pathway, essential for ATP production and oxidative stress mitigation[90]. Elevated levels of CIRBP were found in MEB5 neural stem cells at 32 °C in 24 and 48 h and knockdown of CIRBP using siRNA significantly increased apoptosis in neural stem cells[91,92]. This suggests that CIRBP helps in neuroprotection. Deep Hypothermic Circulatory Arrest (DHCA) enables complex cardiovascular surgeries by temporarily halting blood circulation. Deep hypothermia reduces metabolic demand, protecting the brain during periods of interrupted blood flow. This technique allows safe intervention on major vessels that cannot be bypassed without risking hemorrhage or ischemic injury[93]. In rats, DHCA during cardiac pulmonary bypass (CBP) was achieved by 30 min of cooling till rectal temperatures were at 18 °C and

1 h of rewarming[94]. CIRBP knockout rats showed loss of intestinal epithelial barrier and decreased ATP and creatine levels during deep hypothermic circulatory arrest[94]. Therefore, CIRBP maintains intestinal barrier function during deep hypothermic circulatory arrest by preserving epithelial structure and energy metabolism[94].

Intracellular CIRBP plays cytoprotective roles by stabilizing transcripts involved in cell survival and metabolism but elevated extracellular CIRBP (in plasma) can have deleterious effects. During haemorrhage and polymicrobial sepis, CIRBP is secreted into the circulation, where it functions as a damage-associated molecular pattern (DAMP). Extracellular CIRBP activates TLR4/MD2 signaling, driving the release of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)[95]. In acute pancreatitis, increased CIRBP levels cause endothelial permeability, which consequently leads to multi-organ dysfunction[96]. The mechanisms governing the regulation of extracellular CIRBP functioning as a damage-associated molecular pattern (DAMP) during therapeutic hypothermia remain poorly understood.

RBM3

RBM3 is another well-studied cold shock protein[23]. The temperature-sensing mechanism of RBM3 involves nonsense-mediated decay (NMD) associated with the alternative splicing of Rbm3 mRNA. When exposed to hypothermia, a poison exon (E3a) at exon 3 undergoes splicing, preventing NMD-mediated Rbm3 mRNA degradation[97]. In iPSC-derived neurons, HNRNP1, an alternative splicing factor, has been found to facilitate the splicing of the poison exon by binding to G-rich motifs in mRNA of RBM3. HNRNPH1 acts as a positive regulator of Rbm3 by promoting alternative splicing of the poison exon from Rbm3 mRNA under hypothermia (32 °C for 72 h)[98].

In human neuroblastoma cell line (SH-SY5Y), Focal Adhesion Kinase (FAK) activates Src-kinase and NF-kb activated RBM3 transcription during hypothermia (32 °C for 24 h). Inhibition of FAK or Src resulted in reduced neuroprotective effects, suggesting that the FAK-Src cascade is an important upstream signaling mediator of RBM3[99]. In primary neurons derived from mouse hippocampus, Trkβ-pCREB signaling increased levels of Rbm3 mRNA and protein during hypothermia (32 °C for 24 h). Activation of the Trkβ receptor triggers the PLC-γ pathway, leading to CREB phosphorylation (pCREB) and increased RBM3 expression[100]. Several signaling proteins downstream of RBM3 have been discovered in the context of hypothermia. In a mouse model of prion disease, RTN3 has been identified as one of the effectors. Under hypothermia (32 °C for 24 h), RTN3 mediates RBM3's neuroprotective effects by improving synapse formation, preventing a decrease in the number of neurons, and rescuing neurodegenerative disease-related cognitive decline[101]. In skeletal muscle of mice, levels of RBM3 increased within two to four hours of acute cold exposure (4 °C)[102]. This further revealed that RBM3 activated AKT by phosphorylation at Serine 473 and Threonine 308, finally leading to an increase in glycolysis via the phosphorylation of the glycolytic enzyme PFKFB2 at Serine 483. This suggests that RBM3 promotes glucose metabolism in skeletal muscles during acute cold exposure[102]. In mouse skeletal muscle myoblasts, hypothermia enhanced the differentiation of myoblasts into myotubes. Also, levels of RBM3 significantly increased after 48 h and 72 h at 32 °C. Knockdown and over-expression studies confirmed that RBM3 helped to enhance differentiation and promote mitochondrial metabolism under hypothermia[103]. SOX11 is essential for neural progenitor cell proliferation, migration, and differentiation, and its deletion impairs neurogenesis in the hippocampus. Exposure of progenitor cells to 35 °C increased RBM3 expression, which stabilized SOX11 mRNA, enhancing neuronal differentiation[104]. RBM3 plays a protective regulatory role in neurogenesis during maternal cold stress. It mediates these effects by increasing the stability and expression of the Yap1 gene (Yes-associated protein 1), which is important for brain development. The knockdown or knockout of RBM3 under maternal cold stress conditions leads to more severe impairments in embryonic brain development[105]. RBM3 protects against ER stress-induced apoptosis by inhibiting the PERK-eIF2α-CHOP pathway during hypothermia (32 °C for 24 h)[106]. Polysome profiling in N2a cells revealed that RBM3 interacts with the 60S ribosomal subunit. Due to this interaction, there was an increase in total protein synthesis[107].

Studies have extensively reported RBM3's role in neurons due to its neuroprotective function in hypothermia and neurodegenerative diseases[108–110]. In mouse models of Alzheimer's and prion diseases, overexpression of RBM3 contributes to the protection of synapse and regeneration[108]. Overexpression of RBM3 in primary neuronal stem cells revealed that RBM3 interacts with IGF2 mRNA binding protein 2(IGFBP2). This increases the levels of Insulin Growth Factor 2 (IGF2) and supports neuronal stem cell proliferation[111]. Ischemic stroke, caused by insufficient blood flow to the brain, results in irreversible brain damage[112]. Hypothermia (31 °C or less) correlates with a positive functional outcome in animal models of acute ischemic stroke (IS)[113]. In IS patients, RBM3 correlated with good stroke outcome at 3 months[114]. In rats, therapeutic hypothermia(32 °C for 4 h) decreased cerebral tissue loss and protected cerebellar volume under hypoxic ischemic encephalopathy (HIE)[115]. Here, levels of RBM3 and RTN3 were also increased, which resulted in neuroprotection[115]. Overexpression of RBM3 in C17.2 mouse neural stem cells increased cell viability and proliferation under hypoxia (2.5% oxygen)[116]. The role of RBM3 in cold adaptation suggests its therapeutic potential for hypothermia-based treatments in neurodegeneration and stem cell-based therapies.

Future Perspectives

An integrative understanding of hypothermic signaling and metabolism has been outlined in this review (Fig. 2). However, several questions remain unanswered about the biochemical and biophysical mechanisms underlying sensing and adaptation to hypothermia. For example, ion channels like TRPM8 are activated at temperatures below 30 °C but the mechanisms that trigger the hypothermic response during mild hypothermia (32 °C–35 °C) remain unanswered. A direct mechanism for sensing temperatures might be the change in tertiary structures of multiple enzymes within the cell. Temperature changes are known to reprogram the sub-cellular localization and function of multiple proteins[117]. Changes in proteome-wide behaviour under hypothermia will illuminate new cold-sensing paradigms in mammalian cells. The same approaches should be extended towards other macromolecules including RNA to understand their conformational changes and resulting behaviours under hypothermia. The best characterized cold-responsive proteins in mammalian cells are RBM3 and CIRBP. A Global RNA and protein interactome of these RNA binding proteins under hypothermia is required to understand their signaling mechanism. Three Cirbp mRNA variants exist, yet the functions and expression patterns of the resulting isoforms are unknown. CIRBP is phosphorylated at its RGG domain aiding to its nuclear localization. But its comprehensive PTM profiling under hypothermia is lacking[118,119].The regulation of RBM3 expression and its subcellular localization under hypothermia remains poorly understood.

In prokaryotes, proteins containing cold shock domains (CSD) are known to play an important role in hypothermic sensing and adaptation[120,121]. Though these CSD-containing proteins have been discovered with mammalian proteins, their role in hypothermic adaptation is not apparent so far. It is fascinating that certain mammals can tolerate extreme cold temperatures close to 0 °C. For example, thirteen-lined ground squirrels can decrease their body temperature to as low as 5 °C[13]. The mechanisms by which these vertebrates respond to extreme cold temperatures may provide important insights into unknown aspects of hypothermic signaling. Membrane lipid composition and fluidity are also critical factors that influence hypothermic signalling[122]. Overall a comprehensive understanding of proteome-wide structural alterations and membrane lipid compositions will enable understanding of hypothermic signaling and adaptation.

Current studies have demonstrated the roles of histone deacetylases (HDAC3, HDAC1), demethylases (JMJD1A) and transcription factors (PGC-1α, C/EBPβ, ERRα) in regulating Ucp1 and other thermogenic genes across brown and beige adipose depots[64,79–81]. Despite these advances there are several important gaps in these studies. The molecular basis for long-

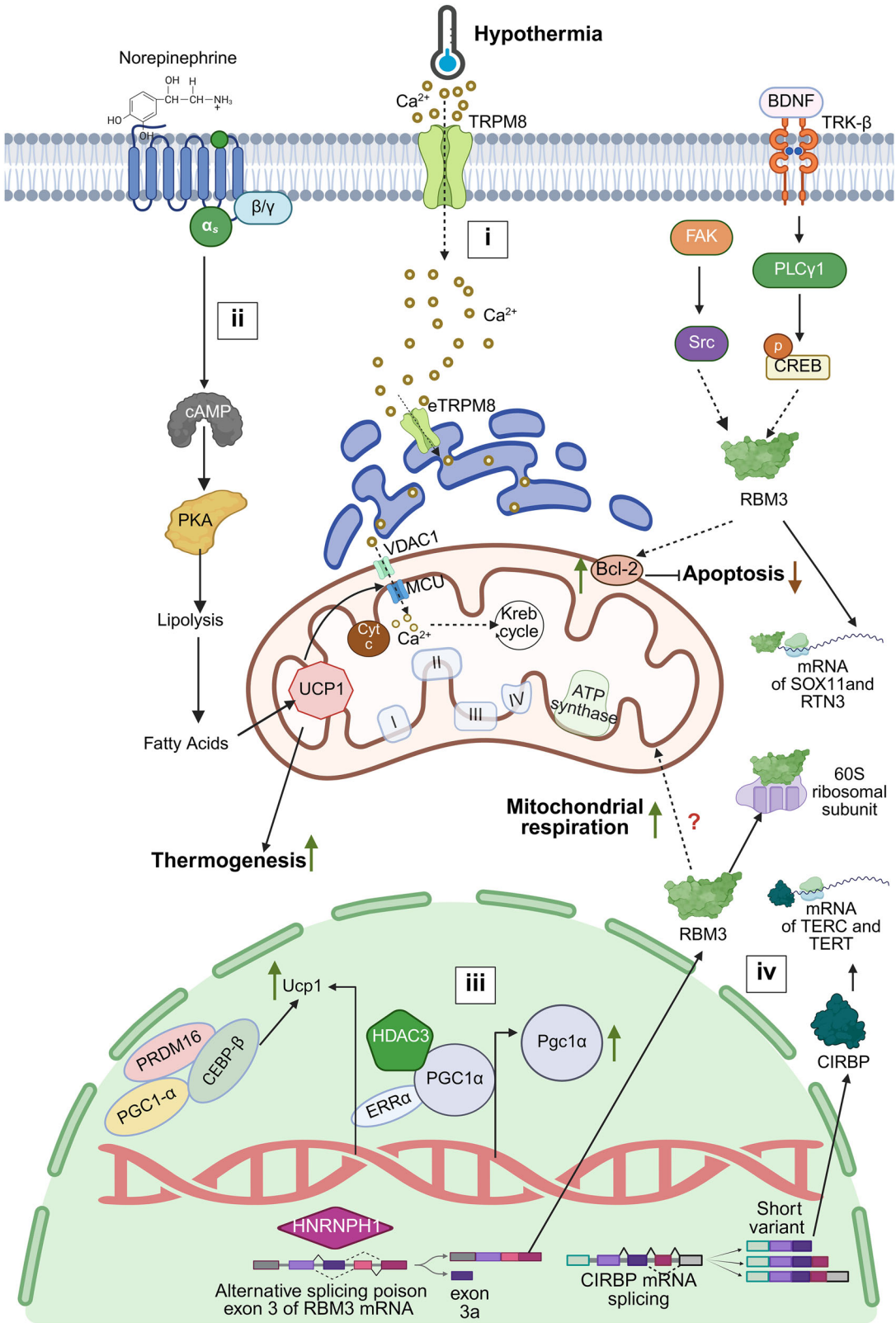

Fig. 2 | Molecular mediators of hypothermic signaling. Molecular mediators of hypothermic signaling includes (i). TRPM8 ion channel (ii). β-Adrenergic receptor induced regulation of UCP1 (iii). Epigenetic modifications (iv). RNA-binding proteins (RBM3 and CIRBP).

term epigenetic memory in BAT and WAT requires further research. While C/EBPβ appears central to sustained Ucp1 expression post short term cold exposure, how this transcription factor maintains chromatin accessibility or recruits co-activators over time is not understood[64]. Similarly, although the role of JMJD1A demethylase activity in chronic beigeing has been defined, the upstream signaling dynamics that regulate its dual function (phosphorylation and demethylation) under varying cold intensities or durations remain to be fully elucidated)[81]. The recent observation that pre-fertilization

cold exposure in humans enhances BAT activity and energy expenditure in offspring introduces the concept of intergenerational epigenetic inheritance[82]. However, the molecular mechanisms governing this trans-generational programming remain unknown[82]. Whether cold exposure induces stable epigenetic modifications in the germline such as DNA methylation, small RNAs or histone mark alterations in sperm or oocytes and how these changes are retained post-fertilization is an important open question.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

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Author contributions

P.D. contributed to uncoupling proteins, epigenetic modifications, future perspective sections and Fig. 1. H.L. contributed to introduction and insights from hibernating mammals sections. P.S. contributed to RNA-binding proteins section and Fig. 2. A.R. contributed to Ion channels and future perspective sections and participated in the conceptualization of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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