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STATE-OF-THE-ART REVIEW

Importance of temperature on immuno-metabolic regulation and cancer progression

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Keywords

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Cancer immunotherapies emerge as promising strategies for restricting tumour growth. The tumour microenvironment (TME) has a major impact on the anti-tumour immune response and on the efficacy of the immunotherapies. Recent studies have linked changes in the ambient temperature with particular immuno-metabolic reprogramming and anti-cancer immune response in laboratory animals. Here, we describe the energetic balance of the organism during change in temperature, and link this to the immune alterations that could be of relevance for cancer, as well as for other human diseases. We highlight the contribution of the gut microbiota in modifying this interaction. We describe the overall metabolic response and underlying mechanisms of tumourigenesis in mouse models at varying ambient temperatures and shed light on their potential importance in developing therapeutics against cancer.

Introduction

The development of immunotherapies has revolutionized the field of cancer immunology and treatment. However, the majority of cancer patients do not fully benefit from this treatment, partially due to a metabolic reprogramming of the tumour microenvironment (TME), resulting in augmented immunosuppressive activities and limited anti-tumour immune responses [1,2]. Both cancer and immune cells depend on certain metabolic traits for their functions. Various metabolic sensing and utilizing capacities orchestrate the cell viability and behaviour in adaptation to the TME. Notably, the tumour-infiltrating immune cells experience metabolic stresses in the TME that influence their functional activity and efficacy of immune checkpoint blockades. Though the number of new cancer cases has been strikingly increased since 2008 all over the world [3], there is considerable heterogeneity among different types of cancer across countries and parts of the world. These variations can be attributed to genetic differences, environmental factors, lifespan, as well as other cancer inducements, including social behaviours, economic developments and the advancement of the healthcare system [4].

Acclimation to changes in temperature cause alterations of the competitive organismal fitness due to various programs, including activation of thermogenesis [5,6]. In addition, external temperature impacts the organism's basal and dynamic metabolic rates, which

Abbreviations

BAT, brown adipose tissue; DCs, dendritic cells; HSP, heat shock protein; LPS, lipopolysaccharide; MDSCs, myeloid-derived suppressor cells; MHCII, major histocompatibility complex class II; NK cells, natural killer cells; PPARs, peroxisome proliferator-activated receptors; TCA, tricarboxylic acid; TLR4, toll-like receptor 4; TME, tumour microenvironment; UCP1, uncoupling protein-1; WAT, white adipose tissue.

can be linked to body mass and healthspan. However, while the interaction between thermogenic activation and its metabolic regulation has been extensively studied [7], little is known about the effect of ambient temperature on chronic diseases, particularly cancer.

"Cold tumor" is characterized by a paucity of tumour-infiltrating T cells, insufficient to trigger a proper anti-tumour immune response [8,9]. Based on the worldwide incidence and mortality rates of "cold cancers" such as melanoma, colon cancer and lung cancer [10], a higher comprehensive assessment of the cancer burden is trendily shown in areas with lower local temperatures [11,12]. Human and animal studies have demonstrated that cold exposure induces changes in immune responses in both cellular and humoral aspects, indicating suppression of innate immune reactivity under short-term cold exposure [13]. In contrast, prolonged cold exposure enhances lymphocyte proliferation and pro-inflammatory cytokine production [14]. Varying housing temperatures alter how cancer cells grow and metastasize in mice, due to alterations of anti-tumour immune responses that are dependent on cytotoxic T-cell infiltration [15]. Intriguingly, it is emerging that the intestinal microbiome can also regulate the patient response to immune checkpoint blockade therapy through host immune system, supported by evidence that antibiotic treatments can impair the efficacy of the immunotherapies [16,17].

This review focuses on how the whole-body metabolism changes induced by environmental temperature influence the anti-tumour immune response. We also describe the interplay between the gut microbiome and immunometabolism during temperature shifts and cover the known mechanistic insights on regulating tumour progression by the ambient temperature. Finally, we provide insights into the mechanisms that regulate immune response through the temperature-mediated interaction between adipose tissue and the microbiota, which might shed light on therapeutics for metabolic disease and cancer.

Ambient temperature and fat metabolism

Differences in the environmental temperatures influence organism's biophysical requirements, their metabolic activities and the gut microbiota (Fig. 1). Glucose and lipid uptake is essential energy source for the cancer cells, and adipose tissues play a central role in regulating the energy balance during the ambient temperature changes [18,19]. Adipose tissues contain several distinct types of cells [20,21] and are broadly divided into white and brown adipose tissues (WAT and BAT respectively). WATs are generally responsible for storing lipids mainly in the form of triglycerides, while BAT utilizes glucose and fat to generate heat through uncoupling oxidative phosphorylation largely mediated by mitochondrial inner membrane protein uncoupling protein-1 (UCP-1) in a process called non-shivering thermogenesis [22]. Following prolonged cold exposure, brown fat cells also emerge in subaccountants WAT (known as "beige" or "brite" adipocytes) in a process commonly referred to as WAT browning. These multilocular cells have a higher thermogenic capacity than the white adipocytes due to the large number of UCP1-positive mitochondria [23]. Several biological cues can promote WAT browning ranging from cold exposure, endurance exercise and dietary regiments, to sympathetic nervous stimulation via β_3-adrenergic receptor activation, as well as microbiota alterations [24–27]. Cold exposure-induced activation of the β_3-adrenergic receptor signalling promotes uptake of glucose, fatty acid (FA) and triglyceride-rich lipoproteins to the BAT from the internal reservoirs, which are then used as an energy source for the non-shivering thermogenesis [28–31].

The ambient temperatures where metabolic rate is at a minimum are the usual definition of a thermoneutral zone, and it is in the interval of 29 °C in the light phase and up to 33 °C during the dark phase in mice [32]. Housing temperature of 20–22 °C (room temperature, RT), therefore, represents a mild cold environment for mice [33], coupled with proportional allocation of energetic resources to enable thermogenesis. Thermoneutrality leads to "whitening" of the adipose tissues compared to RT-kept mice due to suppression of the sympathetic activity and decreased oxygen consumption rates and thermogenesis [34,35]. In absence of UCP-1, thermoneutrality causes an obesogenic phenotype in mice, most likely due to the lack of a chronically elevated metabolism at this temperature [36]. In humans, even at basal state at warm temperatures, BAT has increased glucose uptake, lactate release and metabolic activity compared to WAT [37]. Interestingly, the "whitened" beige adipocytes following thermoneutrality can regain their thermogenic capacity after cold exposure [38], a process partly mediated by transcriptional and epigenetic regulation under different temperature conditions. Cell-type-specific profiling *in vivo* demonstrated that beige adipocytes undergo whitening-induced chromatin changes [39], enabling preservation of their epigenetic memory from the previous cold challenge. Further research is required to fully understand the cellular machinery leading to the temperature-driven changes in the adipose tissue, as well as the preference of specific

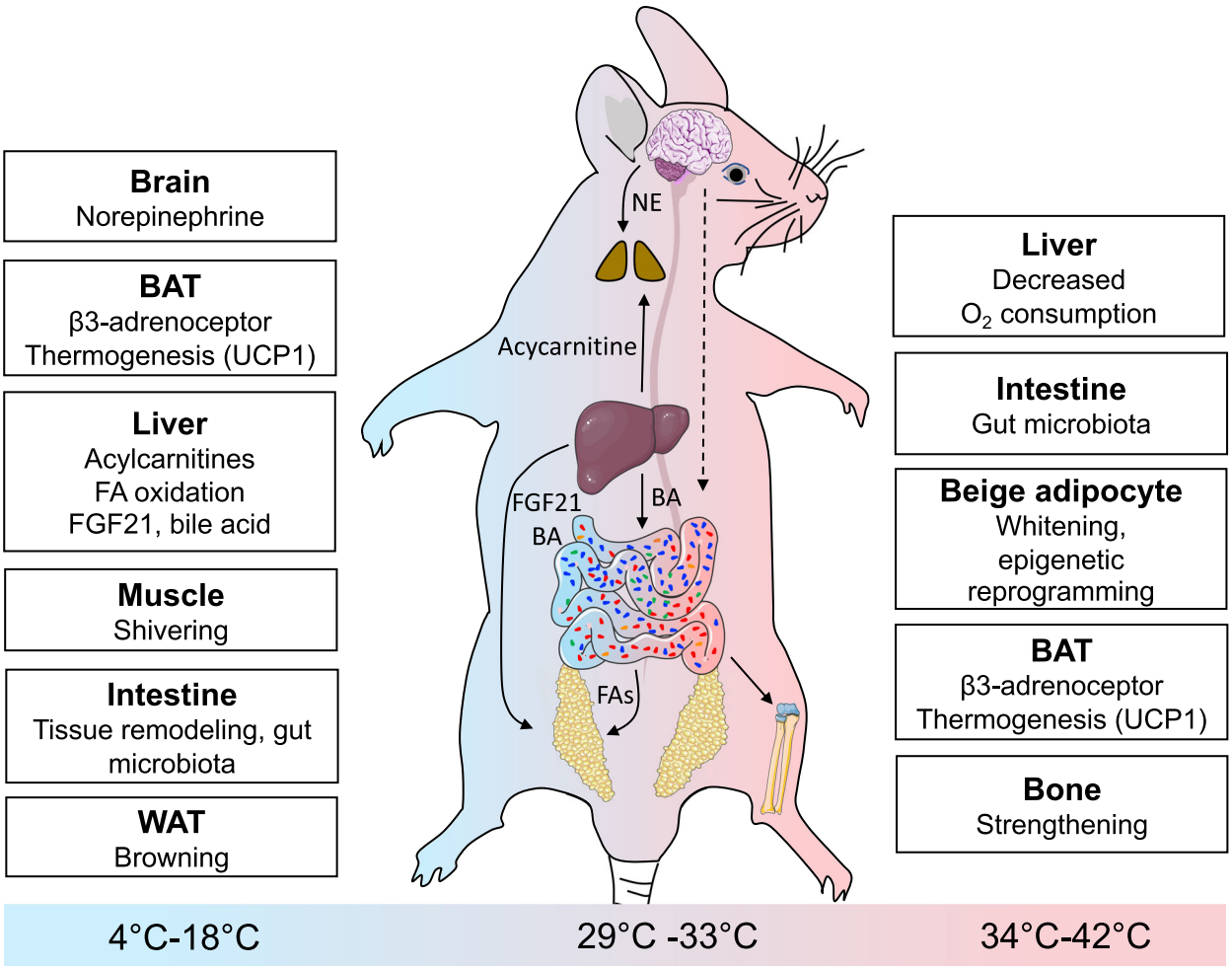

Fig. 1. Temperature change causes metabolic reprogramming in various organs. Organism's biophysical requirements at different ambient temperatures, including their metabolic activities in distinct tissues and gut microbiota. Cold stimuli, sensed by neurons in skin, activate the sympathetic nervous system (SNS) that is responsible for local production of norepinephrine (NE) in BAT. Cold exposure also triggers muscle shivering and thus contributes to BAT thermogenesis. During prolonged cold exposure, browning of WAT is also be involved in thermogenesis through various mechanisms, including stimulation of hepatic FGF21 and bile acid (BA). Increased hepatic acylcarnitine metabolism contributes to lipid oxidation in the liver and other tissues. In addition, cold-induced appetite and metabolic changes lead to gut microbiota shifts in the firmicutes/Bacteroidetes ratio, where firmicutes abundance increases over Bacteroidetes (from 72.6% in RT to 35.2% under cold), and an almost absence of the Verrucomicrobia phylum from both faeces and caecum, affecting various organs. Warm exposure causes opposite changes in the microbiota, with marked beneficial effects on bone remodelling in part through enhanced polyamine production. Resting oxygen consumption is decreased in liver acclimated to warm. Beige adipocytes can undergo epigenomic reprogramming with warming. Cold exposure (4–18 °C); thermoneutral temperature (29–33 °C); warm exposure (≥34 °C).

subcutaneous vs. visceral fat depots to undergo browning with relation to tumour growth.

Ambient temperature and immune responses

The immune cells monitor and respond to the environmental metabolic cues, as well as to various endogenous triggers, resulting in alterations in their function [40]. Human and animal studies have demonstrated that different ambient temperatures can change immune responses in cellular and humoral aspects. The interplay between the immune system and the thermogenic response of the organism can be viewed in the context of the life-history theory [41], which proposes that the prioritization of resources between biological programs depends on the environment. In hostile environments, resources are shifted away from growth and reproduction programs into maintenance programs [41–43]. Interestingly, the competition for resources is also

present between the various maintenance programs, where the metabolic response to cold requires an energetic trade-off with other energy costly programs such as the immune responses. Indeed, cold lowers major histocompatibility complex class II (MHCII) on monocyte and renders them less activated, which in turn suppresses priming of pathogenic T cells during autoimmunity. This results in reduced T-cell cytokine expression and consequently attenuates neuroinflammation [44,45]. These data indicate prioritization of resources towards thermogenesis leading to a constrained immune response, resulting from a decreased energy availability for the mouse immune system [44,45]. While this competition is evidently protective against autoimmunity, it may also explain the increased susceptibility to certain viral infections during cold [46,47], which warrants further investigation. Moreover, thermoneutral housing enhances the infiltration of immune cells in the TME [15]. This is in line with the accumulating body of evidence that repeated cold exposure suppresses immune activities in mice [13], whereas warm provokes greater anti-virus immune responses [46]. Intriguingly, mice at thermoneutral housing accumulate $LyG6^+$ monocytes in bone marrow, but decrease in circulating blood, which causes protective effects against atherosclerosis [48]. While these data strongly support the idea that prioritization of energetic resources constrains the immune response favouring increased thermogenesis, human data are more complex. Evidence suggests both a suppressive and supportive effect of cold environmental temperature on the immune system, which partly depends on the length of the cold exposure. Several studies suggested that while short-term cold stimulation decreases human lymphoproliferative response and Th1 cytokine production [49,50], it also provokes inflammatory responses and immunosuppressive signature genes [51,52]. In line with the data from mice, long-term adaptation to cold exposure induces an anti-inflammatory reaction [14], implying that the shift in the immune response during cold adaptation may be of general importance.

The immune response, in turn, modulates the fat metabolism of both lean and obese mice [53]. Recruitment of anti-inflammatory signals is strongly associated with beige adipogenesis in the fat [54–56]. Low-grade inflammation of the WAT is a hallmark of obesity and is linked to pro-inflammatory (M1-like) macrophage infiltration and activation in the WAT, together with diminished capacity for browning. Earlier reports suggested that after cold exposure, the WAT is infiltrated by an increased number of eosinophils that could drive the macrophage polarization from a pro-inflammatory to an anti-inflammatory state [57,58]. There are several potential mechanisms by which WAT-resident macrophages could exert their browning role [59,60]. M1-like polarized macrophages attach to the adipocytes via binding integrin α4 to vascular cell adhesion molecule 1 (VCAM-1) [61], leading to sustained inhibition of the beiging program. In addition, a subpopulation of macrophages called sympathetic neuron–associated macrophages take up and degrade norepinephrine [62,63] released from the network of sympathetic nerve endings in WAT [64]. The sympathetic neuron–associated macrophages are increased in obesity and ablation of norepinephrine uptake by these cells increases browning. Furthermore, at thermoneutrality, mice show increased infiltration of macrophages in BAT and corresponding pro-inflammatory cytokines, *Ifnγ*, *Tnfα, Il-1β* and *Il*-6 [65]. In humans, T-helper $(CD4^+)$- and T-cytotoxic $(CD8^+)$-cell counts are not significantly changed after 3 weeks of 30- to 60-min cold exposure daily (cold water swimming – 14 °C/18 °C) [14,66]; however, T lymphocytes were increased after 6 weeks of the same intermittent cold. Short-term (20–60 min) cold exposure, on the other hand, led to a decrease in peripheral $CD4^+$ counts [67]. T-cell proliferation may be suppressed partly by the myeloid-derived suppressor cells (MDSCs) under RT conditions compared to thermoneutral temperature, by up-regulating the β_3-adrenergic receptor [57]. As mentioned above, cold exposure reduces T-cell priming via a lower expression of MHCII on monocytes [44]. Also, acute heat stress is reported to increase the number of natural killer cells (NK cells), which are a type of cytotoxic lymphocytes critical to the innate immune response [68], while chronic heat inhibits the activity of splenic NK cells, and increases Th2 to Th1 ratio [69]. The immune response in reaction to hyperthermia (39–43 °C) in both murine and humans includes up-regulation of T-cell priming markers in dendritic cells (DCs), augmented Toll-like receptor 4 $(TLR4)^+$ macrophages and enhanced lymphocyte trafficking to lymphoid [70]. This immunomodulation is concomitant to the augmented heat shock protein (HSP) levels and their interaction with HSP receptors on immune cells after hyperthermia. In human cancer patients, local hyperthermia does not alter cytokine levels; however, whole-body hyperthermia elevates *Il-1*, *Il-6* or *Tnfα* [71], indicating that whole-body hyperthermia could be beneficial in immunotherapies.

Adipose tissue is a highly metabolically active organ that stores and releases lipid metabolites. In a combined lipidomics/RNA-sequencing analysis of inguinal WAT, short-term (3 days) cold exposure resulted in overall changes in lipid compositions: specifically,

enrichment of glycerophospholipids and sphingolipids, as well as transcriptomic changes of the thermogenic machinery, fatty acid metabolism and triacylglycerol and glycerophospholipid synthesis [72]. However, chronic (10 days) cold exposure led to mitochondrial glucose oxidation in mouse BAT and subcutaneous WAT via enrichment in tricarboxylic acid (TCA) cycle intermediates, which is not observed in visceral WAT [73]. Short-term cold exposure also alters the plasma amino acid pool and causes a substantial increase in glutamine and branched-chain amino acids, such as glutamine content, proline, tryptophan and phenylalanine as an energy source for BAT thermogenesis [74,75]. Furthermore, studies point to an involvement of other metabolic mechanisms such as the futile cycle of fatty acids, creatine and calcium for cold-adaptive thermogenesis [76–78]. Thermogenesis-induced lipolysis in adipose tissue may contribute to the recruitment and activation of immune cells in peripheral circulation and essential metabolic organs [79]. In lean individuals, adipose tissue-associated macrophages are small in size and sparsely distributed among adipocytes, but in obesity, they accumulate lipids and are aggregated [80,81]. Additional potential metabolic signals, such as fatty acids, amino acids, hypoxia and adipocyte stress, have been proposed to contribute to the interaction between immune cells and adipocytes at different temperatures [82,83]; however, more efforts are needed to better understand their importance (Table 1).

Ambient temperature and gut microbiome

The human microbiota colonizes various parts of the body, including the airways and skin. The gastrointestinal tract harbours remarkable microbiota abundance and diversity, which mainly comprises strict anaerobic bacteria from the phyla *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria* and *Verrucomicrobia* [84] and a wide diversity of gut virome [85,86] and fungi [87–89]. Beyond the role of the gut microbiota in food digestion and host physiological regulation, accumulating evidence points to its protective immune roles in enhancing anti-tumour immunotherapies in cancer patients [90,91]. Several environmental

Table 1. Metabolic and immunological effects of ambient temperatures in mice and human. BAT, brown adipose tissue; CE, cold exposure; EAE, experimental autoimmune encephalomyelitis; FFA, free fatty acid; HDL, high-density lipoprotein; RT, room temperature; SAT, subcutaneous adipose tissue; TGs, triglycerides.

Temperature range	Metabolic regulation	Immunomodulatory effects	Model	References
CE 10 °C (2 weeks) Control: RT 22 °C	Browning of BAT and SAT	↓MHCII on monocytes ↓IL-17A secreted by $CD4^+$ T cells	EAE (mouse)	[44]
Thermoneutrality, (30 °C, 7 days pre-treatment) Control: RT (22 °C)	↑FFAs and TGs in plasma	↓Macrophage and monocyte recruitment in blood ↑Monocyte in bone marrow	Atherosclerosis (mouse)	[48]
Thermoneutrality (30 °C, 2–4 weeks) Control: RT (22 °C)	Suppression of thermogenetic gene expression in adipose tissue	↓Tyrosine hydroxylase expression in adipose tissue macrophages	Wild-type mouse	[57]
CE (4 °C, acute cold challenge 6 h) Control: RT (22 °C)	↑Thermogenetic gene expression in BAT and lipolysis in SAT	↑Catecholamines secretion in adipose tissue macrophages	Wild-type mouse	[57]
Thermoneutrality (30–31 °C, 2 weeks) Control: RT (22 °C)	Not specified	↑ $CD8^+$ T lymphocytes ↓immunosuppressive MDSCs and regulatory T lymphocytes	Melanoma and colorectal cancer mice model	[15]
Thermoneutrality (30–33 °C, 12 weeks) Control: RT (22 °C)	Obesity via lipid profile alterations (↑cholesterol)	↑Macrophage activation and circulating immune cells	Obesity and atherosclerosis mice model	[157]
Sauna session (96 °C ± 2 °C, 30 min) Control: before session	↑Peripheral blood cortisol levels	↑Leukocyte and monocyte in plasma	Healthy athletes	[158]
Cold water immersion (14 °C, 1 h, 3 times a week, 6 weeks) Control: RT (Not specified)	Increased metabolic rate ↑catecholamines in blood	↑ $CD3^+$, $CD4^+$ and $CD8^+$ cells	Healthy human	[14]
Acute CE (7 °C, 2 h) Control (18–25 °C)	↑HDL	↑IL-1β	Healthy human	[51]

factors, such as nutrients, salts and temperature, affect the microbiota composition, colonization and metabolic activities. Ambient temperature shifts have recently been shown to change multiple biological functions via alteration of the gut microbiome [92,93]. In turn, the intestinal microbiota participates in the whole-body metabolism on multiple levels. On one hand, the cold temperature-adapted microbiota increases absorption of nutrients [94,95], by which influences energy harvest from the diet and storage [96–98], and modulates immune responses. On the other hand, it affects the energy expenditure by regulating the BAT and WAT browning and thermogenesis [99,100]. Long-term cold exposure leads to almost complete depletion of *A. muciniphila*, while increasing the abundance of the family *Lachnospiraceae*, *Clostridiaceae*, *Ruminococcaceae* and the relative production of short-chain fatty acids [99], rendering them less susceptible to high-fat diet-induced obesity [100] (Fig. 1). In addition to the marked increase in food intake, cold exposure also provokes lipoprotein processing in BAT and hepatic conversion of cholesterol to bile acids, which contribute to the microbiota remodelling [101,102]. Thermal stress (> 40 °C) can induce intestinal epithelial damage [103,104] leading to increased intestinal permeability of the bacterially produced lipopolysaccharide (LPS) [105], which provokes local and systemic immune responses, and is associated with increased body mass index, impaired insulin sensitivity and reduced fat browning [106–111].

Exposure to mild warmth (34 °C) induces a change in the gut microbiota composition reflected by an increase of the genera *Turicibacter*, *Akkermansia* and *Parabacteroides*, and a reduction of *Butyricicoccus*, *Peptococcaceae* or *Ruminiclostridium* [112]. Both warmth and warm microbiota transplantation revert the ovariectomy-induced transcriptomics changes of the tibia and increase periosteal bone formation in ovariectomized old female mice, a model of postmenopausal osteoporosis. This effect is, in part, mediated by the increased production of polyamines which can impact the bone remodelling [112], but may also have immune cell functions [113]. Beyond the altered metabolic regulation, heat-stressed induced heat shock proteins are mainly induced by enteric microbiota in response to cellular stress [114]. These proteins serve as intestinal 'gatekeepers' with several critical functions in immune response and gut homeostasis maintenance, including refolding of denatured proteins and eliminating damaged polypeptides from the gut [115,116]. While the above evidence suggests critical contribution of the temperature-adapted microbiota to the host immune regulation, recent studies stressed that on a species level, humans and mice harbour distinct gut microbiota composition [117]. In certain cases, these differences are also evident on a family level. For example, in humans, *Bacteroidetes* phylum is mainly composed of the *Bacteroidaceae* family, and *Firmicutes* phylum of the *Ruminococcaceae* family. In mice instead, *Bacteroidetes* is primarily composed of the S24-7 family, while *Firmicutes* consists of the order *Clostridiales* [118,119]. In light of these reports, different ways can be envisaged to overcome the challenges in using mouse microbiota as a proxy for human; for example, creating mouse models by transplantation of human gut microbiota into germ-free mice [113,118,120], as well as uncovering functional homologues between the species of the mouse and human microbiota [113]. While the work in animal models indicates critical contribution of the microbiota in modulating immunometabolism at different ambient temperatures, the importance of human gut microbiota in this context pends further investigation.

Ambient temperature and cancer

Ambient temperature has been explored more frequently in cancer than other diseases. Several ecological studies indicate lower cancer incidence and mortality rates associated with warmer temperatures [11,12,121]. For example, Repasky et al. [15] found that mice housed at a RT had cancers that grew faster and more aggressively than those accommodated at a thermoneutral temperature (~ 30 °C), due to the higher infiltration of immune cells at the warmer environment. While the molecular explanation for these effects pends additional investigation, hyperthermia, also called thermal therapy, is a well-known alternative strategy for cancer treatment, due to the cancer cell death at a high temperature, up to 45 °C [122,123]. However, this approach is not widely used in cancer patients, due to specific side effects (burns, blisters, diarrhoea and vomiting) and the limitation of therapeutic efficiency.

The ambient temperature may contribute to tumourigenesis through various physiological processes such as metabolic and endocrine changes, as well as alterations in the immune response and the gut microbiome (Fig. 2). Cancer and malignant cells undergo metabolic alterations that acquire energy for their proliferation, survival and migration, primarily through accelerated glycolytic metabolism [124]. However, glucose deprivation in the TME and host macroenvironment can also lead to metabolic reprogramming in cancer cells, such as activation of lipid metabolism, and consequently alter tumour progression and drug

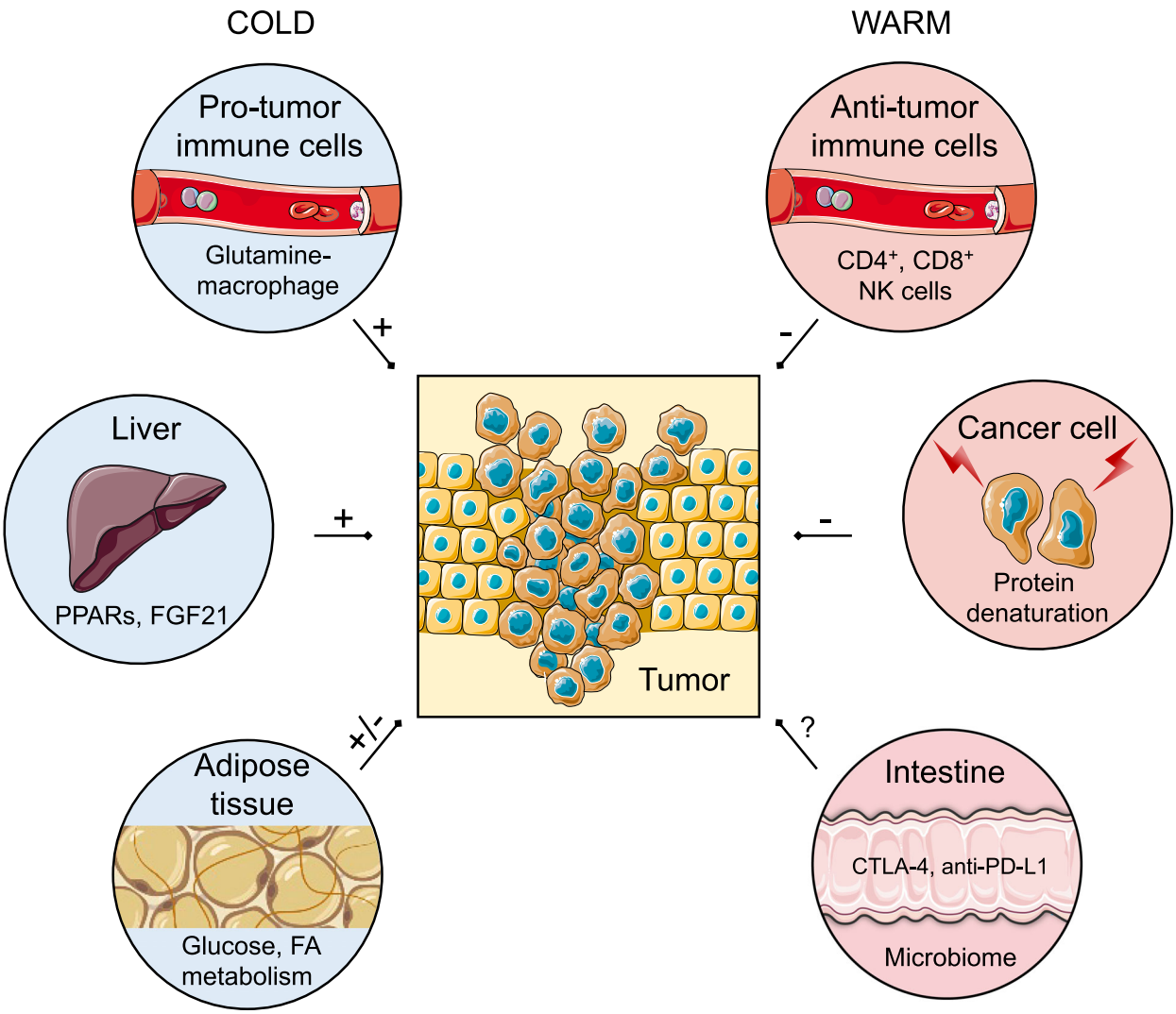

Fig. 2. The effects of cold or warm ambient temperature on the tumour microenvironment during cancer progression. Temperature-induced immune system reprogramming can be a hinder or benefit to anti-tumour immunotherapy. For example, cold exposure increases infiltration of glutamine-secreting macrophages and pro-tumour cytokines to the TME, whereas warmth promotes activated immune cell infiltration to the TME, such as helper T cells, cytotoxic T cells and NK cells. In both liver and adipose tissue, chronic cold-induced hormone and metabolic reprogramming can either trigger tumour growth, such as FGF21 and fatty acid (FA) metabolism; or compete for nutrients with tumour, such as glucose. However, during hyperthermia treatment, cancer cells can be selectively killed via wild protein denaturation and activation of cell apoptosis. Additionally, temperature-induced change in gut microbiota may benefit the efficacy of anti-tumour immunotherapies; for instance, CTLA-4 or anti-PD-L1.

resistance [125,126]. Accumulating evidence reveals a link between BAT and cancer; however, there is conflicting evidence on whether this is a positive or a negative correlation [127–131]. Cancer patients show a greater 18F-fluorodeoxyglucose (18F-FDG) uptake in positron emission tomography/computed tomography (PET/CT) scans, suggesting higher BAT activity compared to healthy controls [128–131]. In contrast, another study reports a better prognosis in cancer patients with atypically strong BAT activity [127]. In animal studies, housing mice at cold induces browning of adipose tissue to support thermogenesis, and increases secretion of cytokines that might promote cancer [132]. Additionally, low ambient temperature has been suggested to enhance tumour progression through glutamine-secreting macrophages [133]. In both liver and adipose tissue, chronic cold stress (> 10 days) triggers the transcriptional activator peroxisome proliferator-activated receptor-gamma coactivator (PGC1α) and the transcription factors peroxisome

proliferator-activated receptors (PPARs) [134,135], both of which play essential roles in regulating tumourigenesis [136,137]. Additionally, cold adaptation-induced increase in metabolic activity has been linked with epigenetic changes that can contribute to a higher risk of cancer [138]. In contrast to these reports, a recent study suggested that cold exposure inhibits growth of various types of solid tumours by impeding the glycolysis-based metabolism in cancer cells. Specifically, circulating glucose is important for cancer glycolysis as energy source for growth, invasion and metastasis. Therefore, the cold-provoked increase of glucose uptake into BAT would render it less available for the tumour disposal [139]. Accordingly, the study reported that providing excess amount of glucose, or deleting UCP1, ablates the cold-induced tumour suppression. The reasons for the inconsistencies between this and the above-mentioned studies warn further investigation, and may partly depend on the exact timing and intensity of the cold exposure, the host microbiota, as well as the diet.

Improving immune surveillance is essential for cancer immunotherapies, which enhance immune-mediated cancer cell clearance. The gut microbiota produces a variety of small molecules and metabolites, which play an indispensable role in human immune response and metabolic health [140]. Accumulating evidence supports the role of gut microbiota in tumour growth, influencing the anti-tumour immunity and efficiency of anti-cancer immune effects of various immune checkpoint inhibitors (ICIs), including cyclophosphamide, CTLA-4 blockade anti-PD-L1 efficacy [90,91,141–143]. Microbial molecules, such as butyrate and pentanoate, enhance the activation of cytotoxic T cells and chimeric antigen receptor (CAR) T cells by increasing their mTOR activity and epigenetic reprogramming [144,145]. It is, therefore, intriguing to understand to which extent the gut microbiota changes due to ambient temperature variations [112] participate in the cancer immunometabolism.

Summary and perspectives

Alterations of the basal physiological metabolism during chronic thermal stress, and the impact it may have on the capacity of the immune response could be of relevance not only in autoimmune [44] or potentially infectious diseases, but also for as anti-tumour response [146]. Exposure to lower temperatures shifts the energetic balance towards thermogenesis on account of the immune response [44], while energy expenditure declines by ~ 50% in thermoneutral mice [146,147]. Different adipose tissues harbour a distinct populations of immune cells [148]. M1-like macrophage-derived pro-inflammatory cytokines, such as IL-1β and TNFα, suppress the expression of UCP1 in BAT and WAT [149,150]. BAT-specific regulatory T cells respond to the activation of BAT under cold stress and directly participate in the modulation of energy homeostasis [151]. The gut microbiota composition regulates fat [99], lipid and glucose metabolism [152,153], thus contributing to the energy homeostasis. Although it has recently become clear that alteration of the gut microbiota causes dysregulation of the immune system [154], the exact nature of this interplay remains to be established.

Mice are widely used for modelling human biology during change in environmental temperature, as they share the similar set of genes implicated in thermogenesis. However, humans and mice differ in physiological thermoregulation in part due to disparate body sizes, as well as due to differences in the living temperature. Humans are often inclined to operate activities within the thermoneutral zone, while most laboratory rodents are housed below their thermoneutral zone and demand increased energy for heat generation [147]. This may create a significant challenge when attempting to translate data from rodents to humans, as the differences of the energy expenditure of mice and humans are reflected on the functioning of the immune system [155,156]. Environmental temperature, therefore, needs to be carefully considered as a factor that may contribute to the responsiveness of the organism to the anti-tumour therapies, and when attempting to translate preclinical data from mice to therapeutics in humans.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors conceptualized and wrote the paper. HW generated the figures and the table, and MT initiated and supervised the work.

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