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Perspective

A mechanistic view of the use of cold temperature in the treatment of cancer

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SUMMARY

In their latest article, Seki and colleagues investigate the potential role of cold as a therapeutical option to treat various cancer types, including even clinically untreatable cancers such as pancreatic cancers. The authors suggest that cold exposure may have a tumor-suppressive effect mediated by the activation of brown adipose tissue (BAT), in charge of dissipating heat through non-shivering thermogenesis. In this regard, circulating blood glucose is decreased, restricting the tumor glucose uptake, which is redistributed, favoring BAT uptake to fuel thermogenesis.[1]

To prove this idea, authors exposed immunocompetent C57BL/6 mice implanted with colorectal cancer to 4°C and observed that tumor growth was inhibited up to 80%, while overall survival was markedly prolonged when compared to its littermates housed at 30°C. Excitingly, similar results were observed in multiple mouse models of fibrosarcoma, breast cancer, melanoma, pancreatic ductal adenocarcinoma, and secondary liver cancer,[1] fairly raising the question of how cold temperature could prevent tumor development?

Seki and colleagues observed that upon cold exposure, circulating blood glucose decreases, restricting the tumor's glucose uptake, thus depriving cancer cells of their primary source of energy, glucose. Glucose deprivation, observed by decreased expression levels of glucose transporters present in the membrane of cancer cells, suppresses the glycolytic pathway, essentially required for energy production used for tumor growth and proliferation.[1] Upon cold exposure, the body redistributes blood to maintain vital organ normothermia. Similarly, authors proposed that glucose is redistributed towards the brown adipose tissue (BAT) to prioritize thermogenesis required to regulate and maintain core body temperature, vital for the survival of the organism.

Mechanistically, cold exposure favors the activation of the sympathetic nervous system (SNS), favoring non-shivering thermogenesis mediated by the uncoupling protein 1 (UCP1), thus generating heat[2] (Figure 1). In response to cold, the SNS releases norepinephrine that binds to β-adrenergic receptors inducing white adipose tissue (WAT) lipolysis and UCP1 activation[2].UCP1 allows protons from the inner mitochondrial membrane to cross into the matrix carrying high kinetic energy levels, resulting in oxygen consumption and heat dissipation required for thermogenesis[2] (Figure 1). Interestingly, authors showed that UCP1 increases in tumor-bearing mice, while surgical removal of BAT or genetic depletion of UCP1 abolishes the cold-induced anticancer effects. In addition, BAT removal enhanced blood glucose levels, hypoxia, angiogenesis, and tumor hyperproliferation, supporting that BAT activation is essential for cold-induced tumor suppression and protection.[1]

At a deeper molecular level, the BAT-specific apoptosis-inducing mitochondrion-associated factor 2 (Aifm2) translocates into the mitochondria, where it oxidizes NADH to maintain high cytosolic NAD^+ levels, promoting glycolysis and the electron transport chain activity required to fuel heat generation for thermogenesis.[3] Importantly, Aifm2 has been shown to be induced, not only upon cold exposure but also upon fasting and β-adrenergic stimuli promoting NAD^+ synthesis.[3,4] Considering that UCP1 is essential to confer cold antitumorigenic effects and that UCP1 fuels both ATP and NAD^+, it is tempting to speculate that cold exposure could also naturally boost NAD^+ levels and hence could represent a central mechanism connecting cold to its antitumorigenic properties, in addition to its vital role in regulating energy metabolism and thermoregulation.[3,4] Not far from this idea, several lines of research support that boosting NAD^+ levels by nicotinamide riboside presents multiple beneficial properties to improve health quality and prevent and aid aging and other age-related diseases, such as arthritis, neurodegeneration, neuropathies (Alzheimer,

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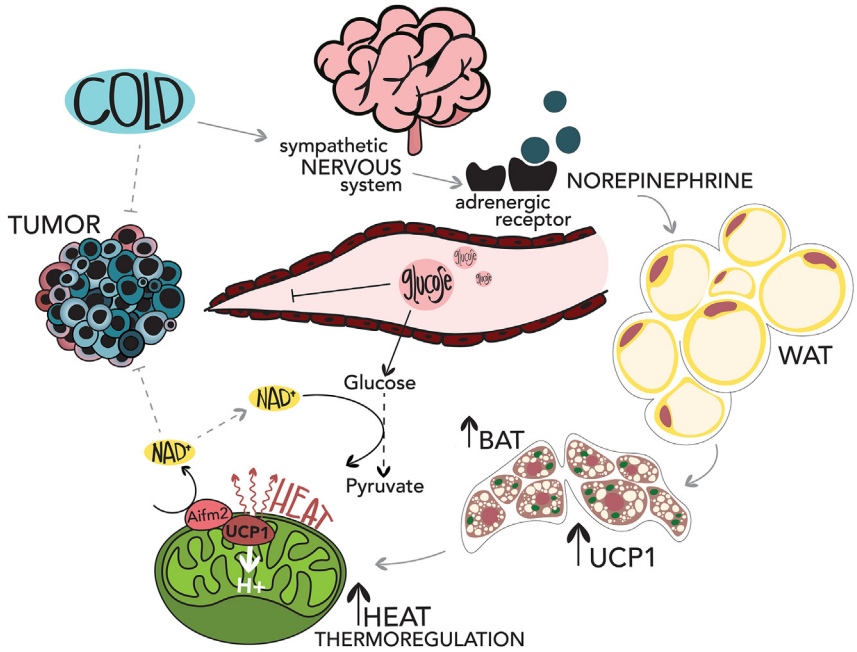

Figure 1. Effect of cold in thermoregulation and NAD$^+$ synthesis

Cold exposure activates SNS, releasing norepinephrine that binds to β-adrenergic receptors inducing WAT lipolysis BAT stimulation, and UCP1 activation favoring, thus, non-shivering thermogenesis that is mediated by UCP1. UCP1 activation generates heat that is used for thermogenesis. Alongside, the apoptosis-inducing mitochondrion-associated factor 2 (Aifm2) translocates into the mitochondria, where it oxidizes NADH to maintain high cytosolic NAD$^+$ levels, promoting glycolysis and the electron transport chain activity required to fuel heat generation for thermogenesis. Redistribution of glucose uptake upon cold exposure, starves tumors from their main source of fuel, while favoring UPC1 heat generation and boosting most likely NAD$^+$ concentrations, a key molecule demonstrated to present antitumorigenic properties.

Parkinson, multiple sclerosis, among others), and cancer, pioneered by our group.[5–8] Thus, it will be of great interest to elucidate if cold modulates NAD$^+$ pools, hence linking the multiple antitumorigenic properties to NAD$^+$, which could activate the DNA repair machinery to support genome integrity, and protection against inflammation, oxidative stress, and reactive oxygen species.[6,9–11] Combining the use of nicotinamide riboside with cold exposure could be an alternative and easily applicable therapeutic strategy for the treatment of cancers.

Moreover, considering that cold has been shown to induce PGC1α favoring UCP1 expression,[12,13] and that PGC-1 is capable of regulating NAD$^+$ synthesis,[5,14] it will be of great interest to explore the role of PGC1α, which in response to cold and other environmental and physiological cues modulates energy metabolism. PGC1α coactivators also regulate the immune response and confer protection against oxidative stress.[13] Thus, PGC1α could play an important role in connecting cold temperature and protection against tumorigenesis.

Lastly, to extrapolate its translation into the clinics, authors performed a pilot experiment where they demonstrated that cold exposure is tolerable by humans, after exposing patients to 16°C for 2–6 h a day for 14 consecutive days, demonstrating that BAT is activated upon cold in adults. To further prove this principle, they exposed an 18-year-old patient with Hodgkin's lymphoma, undergoing chemotherapy, to mild cold (22°C) for 7 days, and observed that cold enhanced BAT activation, favoring BAT glucose uptake while reducing glucose uptake in the tumoral tissue.[1] Yet, even though cold exposure could be an inexpensive, less invasive, and efficient treatment against cancer, it may represent a difficult challenge to translate into the clinics and more studies in humans are required to fully elucidate and demonstrate the beneficial effects of cold temperature for cancer treatment.

Despite the beneficial effects of cold temperature to treat several types of diseases (e.g., cardiac arrest, brain and spinal cord trauma, neonate's hypoxic enteropathies, ischemic injuries, cancer, and aging),[15–17]

populational studies revealed that humans living under extreme cold conditions (−20°C) or in countries with low average annual temperatures have a high cancer incidence.[18] However, considering that the high-risk populations belong mainly to the Western civilization, housing conditions (heating), the way of dressing (e.g., thermic cloth), and a lifestyle known to be a risk factor for cancer incidence (e.g., lack of exercise and ingestion of toxic-diets) could have influenced the data analysis and interpretation. Thus, more precise studies, contemplating and taking into consideration various environmental factors (e.g., housing conditions, lifestyle, diet, and genetic background), should be conducted to better determine the role of cold exposure on human cancer risks.

It is noteworthy that the temperature at which mice are housed has a significant impact on their energy expenditure rates, thermoregulation, and immune function.[19–21] Housing mice at thermoneutrality (30°C) can reduce the energy demands for thermoregulation, enhancing antitumor immunity. However, most laboratory mice experience mild cold stress due to regulated housing conditions (22°C–24°C), which increases energy expenditure rates and negatively affects immune function, favoring tumor growth and metastasis, as previously shown.[22] Seki et al. did not observe any differences in tumor growth between mice housed at 30°C and 22°C. The antitumorigenic properties were only observed in mice housed at 4°C, where BAT activation occurs,[1] suggesting that extreme cold temperatures are required to activate BAT and provide antitumorigenic effects. It is worth noting that mice have various mechanisms to enhance cold tolerance and minimize distress,[19–21] leading to decreased energy required for thermoregulation and to support immune activity over time. Therefore, it would be interesting to determine the effects of temperature on cancer progression by long-term housing preclinical mouse models of cancer at 22°C.

In conclusion, Seki et al. reportedly demonstrate that cold temperature activates heat-producing brown fat in mice that consumes glucose from the tumors, thereby inhibiting tumor growth. Importantly, similar metabolic mechanisms were found in one patient with cancer exposed to a lowered room temperature.[1] If cold temperature modulates NAD^+ levels, it is tempting to propose that the simple use of nicotinamide riboside would alternatively be sufficient and easier to circumvent cold exposure for the treatment of cancers previously demonstrated.[6]

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AUTHOR CONTRIBUTIONS

T.P.G. and N.D. wrote the paper. N.D. directed the project and secured funding.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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