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RESEARCH HIGHLIGHT

Live cold to grow old? Thermogenesis to fight cancer

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A drop in ambient temperature induces systemic changes in glucose metabolism that enable thermogenesis. A recent article by Seki and colleagues explored the potential of cold exposure and brown fat activation to stop tumor growth.

Core temperature is remarkably consistent across our species, falling between 36 °C and 38 °C. The body's biochemical reactions have been optimized for this physiologic range. Too high a temperature runs the risk of denaturing enzymes and too low a temperature may impair the rate of the reaction causing metabolism to run too slow. To ensure stability, humans and other mammals have developed complex, multi-organ, neuroendocrine systems to precisely regulate body temperature.[1] The outputs of this regulation include vasoconstriction to minimize convective heat loss within the skin, and non-shivering thermogenesis (NST), which generates heat from stored energy.

NST produces heat in the brown adipose tissue (BAT) by short-circuiting the proton gradient within the mitochondria. The stored power reserves are quickly oxidized and dissipated into heat, and a new influx of energy arrives in the form of nutrients like glucose and lactate.[2] In humans and rodents, glucose uptake into the BAT is controlled by catecholamines, and increases by ~5-fold during cold exposure as compared to thermoneutral conditions.[3,4] The glucose is primarily oxidized to restore the proton motive force and continue heat generation.[3] The amount of energy consumed by the BAT can be quite dramatic in small mammals like mice where nearly 50% of the total daily energy expenditure is directed toward NST when housed at room temperature.[5] In adult humans, the contribution of NST to total energy expenditure is unclear but presumed to be low at room temperature because of clothing and heated environments; however, several research groups have proposed the activation of NST in humans as a treatment for obesity and diabetes. This approach would divert circulating nutrients into the BAT, increase energy expenditure via mitochondrial uncoupling, and prevent/reverse the storage of macromolecules in the adipose tissue.

Like the BAT, tumors are also avid consumers of glucose.[6] Despite the vast heterogeneity across tumor types, glucose usage is a common feature that supports the anabolic, catabolic, and redox requirements for hyperproliferating cells. For this reason, many investigators have attempted to block glucose uptake in cancer using transporter inhibitors; however, this approach is limited by systemic toxicity. An alternative approach is to target the signaling pathways that control glucose uptake like the phosphatidylinositol 3-kinase (PI3K) pathway. This work has produced alpelisib, a PI3K inhibitor that blocks growth factor signaling and reduces tumor glucose uptake, which is now approved for patients with hormone receptor positive, PI3K-mutated, metastatic breast cancer.[7] However, many believe that there is a much broader potential for "starving tumors" of glucose.

Seki and colleagues have now tested a new strategy to restrict tumor glucose uptake. In an elegant experiment, they utilized exposure to cold temperatures to activate BAT in tumor-bearing mice.[8] This approach effectively creates a diversion of circulating glucose away from the tumor and into the BAT. The resulting metabolic state restricts the growth of several murine tumor models arising from different tissues. The mice also experienced an improvement in systemic glycemic control and, presumably, a reduction in systemic insulin levels, which may also impair tumor growth. Removing the BAT from the mice and feeding them a diet high in glucose restored cancer progression despite cold treatment, verifying that the effect is reliant on activation of BAT through NST.

The authors provide preliminary data to support the translational relevance of their findings. In a pilot trial in healthy human volunteers, the authors found that exposure to mildly cold temperatures (16 °C for 2–6 h per day) for 14 days led to an increase in glucose uptake into BAT as indicated by fluorodeoxyglucose (FDG)-positron emission tomography (PET), a useful clinical measure of glucose avidity in tumors and healthy tissues. In a single 18-year-old cancer patient with Hodgkin's lymphoma, 7 days of mild cold exposure (22 °C) increased glucose uptake into the BAT, while exposure to warm temperatures (28 °C) for 4 days increased glucose uptake into the tumor. This data reinforces the dramatic effect that environment can have on tumor and systemic metabolism. It is well known that glucose uptake is dramatically perturbed by room temperature, anesthesia, and duration of fasting; however, these factors are rarely controlled in clinical FDG-PET imaging.[9]

The data adds to the enthusiasm for targeting BAT as a therapeutic strategy in humans.[1] About 7% of patients with cancer show active BAT on standard-of-care FDG-PET imaging, and its amount positively correlates with markers of metabolic health.[10] Existing clinical studies using β-adrenergic agonists have provided proof-of-principle data that the activation of BAT using small molecules is a viable strategy.[11] Moreover, advancements in BAT imaging with more specific PET ligands may lead to improvements in drug delivery to this tissue.

Open questions remain regarding the magnitude of glucose uptake that can be generated by the BAT. While the data support BAT as a major glucose disposal site in mice,[2] studies in humans suggest that the total contribution of BAT to glucose uptake during cold exposure could be as little as <1% compared to ~50% through skeletal muscle.[12] Furthermore, the diversion of glucose into the BAT could deprive other tissues of energy and exacerbate weight loss in the setting of cancer. This weight loss could promote or exacerbate

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the progressive wasting of skeletal muscle and white adipose tissue that occurs in cachexia, which is prevalent in many cancers and independently associated with survival.

Nevertheless, the exciting data by Seki and colleagues opens the door to novel approaches in the battle against cancer and supports the applicability of BAT-mediated strategies in human diseases. We are looking forward to future studies that refine methods to target BAT and explore their potential in clinical populations. It will be particularly exciting to see whether mild cold exposure can complement traditional anti-cancer treatments like surgery, radiation, chemotherapy, and targeted therapy. This approach would build on other complementary treatments such as diet or exercise, which also improve glucose tolerance, lower circulating growth factors, and increase catecholamine signaling.

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ADDITIONAL INFORMATION

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