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Spotlight

Cold exposure as anti-cancer therapy

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Seki et al. report in *Nature* that increasing glucose catabolism in brown adipose tissue by cold exposure lowers blood glucose and insulin tolerance. This systemic effect on body metabolism decreases glucose catabolism in tumors and arrests tumor progression, offering a novel alternative approach for metabolism-based cancer therapy.

Glucose is one of the major nutrients for mammalian cells, and its consumption is increased in many tumors. Increased glucose catabolism in tumors is often thought to be a consequence of the predominant fermentation of glucose into lactate, even in the presence of normal oxygen levels, which is referred to as the Warburg effect. Fermentation is much less efficient in producing ATP than glucose oxidation through mitochondria, and thus significantly increased turnover of glucose catabolism through fermentation would be required to produce sufficient ATP for fast-proliferating tumor cells. Although dysfunctionality of mitochondria was initially proposed as a cause of this process, it has been well-established by now that in many tumors, increased glucose catabolism into lactate is coupled to increased catabolism through the Krebs cycle and the mitochondrial respiratory chain (Liberti and Locasale, 2016). Various explanations have been proposed for the fascinating Warburg effect, including tumor-cell-intrinsic demands in sustaining their requirements in energy and macromolecule synthesis, maintaining redox homeostasis and signaling, and supporting the interaction between tumor cells and their microenvironment (Liberti and Locasale, 2016). Increased glucose catabolism both through glycolysis and mitochondria-based reactions is also intertwined with increased catabolism of other nutrients, including amino and fatty acids, and the way in which glucose is catabolized together with other nutrients is tumor-type specific (Martinez-Reyes and Chandel, 2021). Regardless, though, of its specific catabolism in specific tumors, glucose is an essential nutrient source supporting multiple pathways required for proliferation and survival of tumor cells and cells composing the tumor microenvironment. Hence, the idea of inhibiting glucose availability and glucose catabolism as anti-cancer treatment via pharmacological inhibition or diets has been extensively explored for decades (Luengo et al., 2017).

In a recent paper published in *Nature*, Seki and co-authors explored if decreasing glucose levels in blood by activating brown adipose tissue (BAT) via cold exposure can be used as an alternative way to interfere with glucose availability for tumors and would be sufficient to affect tumor progression (Seki et al., 2022). Activation of BAT by cold has been explored as an alternative approach to battling obesity and treating type 2 diabetes. Activated BAT consumes glucose and produces heat through the process of non-shivering thermogenesis mediated by uncoupling protein 1 (UCP1), which uncouples glucose oxidation in mitochondria from ATP production. Activation of BAT thermogenesis by cold exposure in humans was shown to improve the peripheral glucose uptake and insulin sensitivity as well as to change the levels of circulating fatty acids (Iwen et al., 2017).

To explore the effect of cold on BAT and tumor metabolism, Seki and colleagues exposed tumor-bearing mice to 4°C for several weeks, while control animals were kept at 30°C. This regime resulted in BAT activation accompanied by the increased expression of UCP1. ^{18}Fluoro 2-deoxy-glucose positron emission tomography (FDG-PET) demonstrated significant increase in glucose uptake in activated BAT with significant decrease in FDG-PET signal in tumors in cold-exposed animals in comparison with mice housed at 30°C. Consistent with the changes in FDG-PET signal, BAT in cold-exposed mice with colorectal (CRC) tumors had increased levels of glucose transporter 4 (Glut4) and glycolytic genes, while tumors had decreased levels of Glut1, Glut4, and Glut7 and glycolytic genes in comparison with control animals. The redistribution in glucose uptake and catabolism between activated BAT and tumors was underlined by decreased levels of blood glucose and improved insulin sensitivity. Accordingly, tumor progression was significantly reduced in xenograft models of human colorectal cancer (CRC) or pancreatic ductal adenocarcinoma (PDAC); in allografts of murine CRC, melanoma, PDAC, fibrosarcoma, and breast cancers; and in the spontaneous MMTV-PYMT model and APC^{min} colorectal models (Figure 1). Consistent with the role of UCP1 in BAT activation, whole-body genetic deletion of UCP1 ablated the increase in glucose uptake in BAT and the decrease in glucose uptake in CRC tumors and also prevented the effect of cold exposure on tumor growth. The requirement for activated BAT for reduced blood glucose levels and decreased tumor progression upon cold exposure was confirmed by BAT ablation. While BAT ablation increased blood glucose levels and abolished tumor suppression under 4°C, it had no effect either on blood glucose levels or on tumor growth under thermoneutral conditions. Importantly, Saki et al. provided some preliminary evidence for the clinical significance of their findings. Exposing healthy humans to a lower temperature of 16°C for a few hours a day for 14 days led to BAT activation and increased BAT glucose uptake as compared to 28°C thermo-neutral conditions. Keeping a Hodgkin lymphoma cancer patient at 22°C for 7 days resulted in higher glucose uptake in BAT and lower glucose uptake in a tumor in comparison with 4 days at

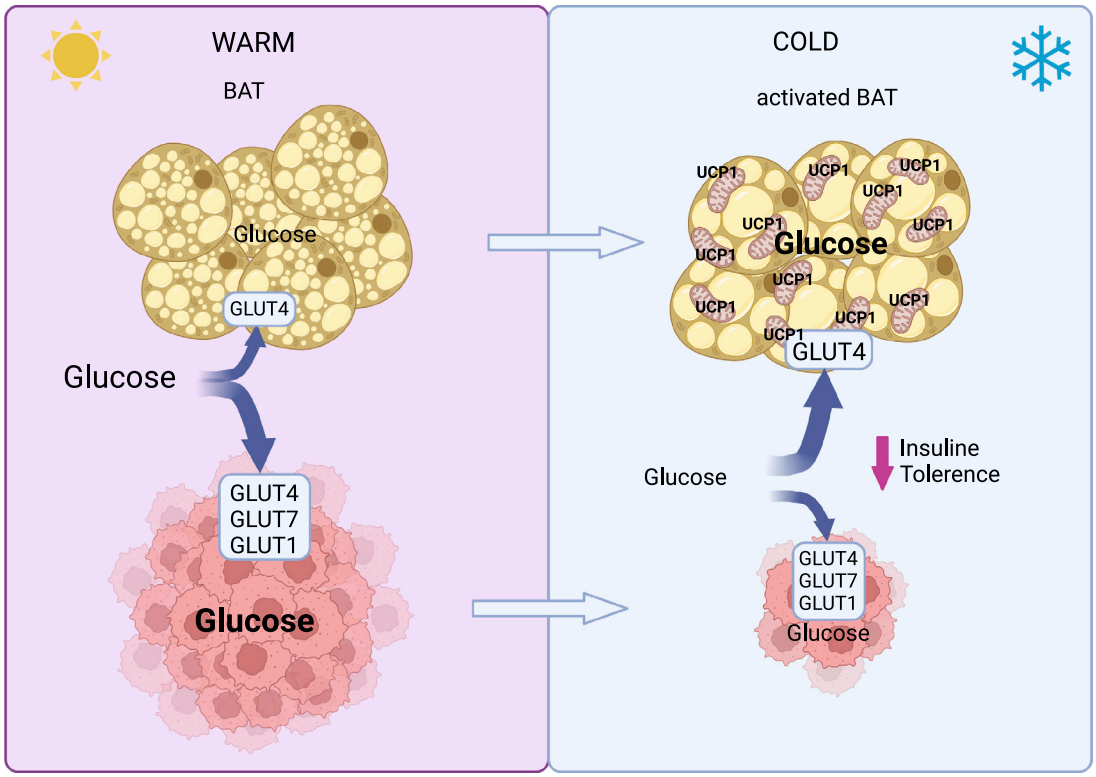

Figure 1. Activation of brown adipose tissue by cold exposure changes systemic glucose metabolism and inhibits tumor growth

Seki et al. demonstrate that subjecting tumor-bearing mice to cold temperatures leads to the uncoupling protein 1 (UCP1)-dependent activation of brown adipose tissue (BAT). Activated BAT has increased glucose uptake and catabolism accompanied by increased expression of glucose transporter 4 (Glut4), which in turn lowers blood glucose and insulin levels. These changes lead to decreased glucose uptake with decreased expression of Glut1, Glut4, and Glut7 and catabolism in tumors, which hampers tumour growth.

28°C. Based on their results, the authors conclude that activating BAT either by cold exposure or pharmacological inhibition may be used as an anti-cancer therapy.

Although the exciting discovery by Seki and co-authors may offer a new simple and cost-efficient therapeutic approach for a metabolism-based cancer therapy, many aspects remain to be thoroughly explored. (1) How much and for how long should the temperature be decreased in human patients to affect body metabolism to a degree sufficient for an anti-tumor effect? (2) How much of this exposure can be tolerated by cancer patients whose health can already be severely compromised? (3) As with other therapies and metabolism-targeting approaches specifically, including diets, the response to BAT activation is likely to vary on a per-patient basis depending on physiology and state of individual patients and interconnected metabolic heterogeneity of tumors, their metabolic flexibility, and plasticity. Indeed, different tumors have different metabolic preferences relying on other nutrient sources than glucose, especially when glucose becomes limited. For example, the uptake and catabolism of branched-chain amino acids (BCAAs) is increased in different tumor types, including PDAC, melanoma, nasopharyngeal carcinoma, and breast cancer, and varies depending on the genetic and environmental context (Sivanand and Vander Heiden, 2020). Activating BAT was shown to increase catabolism of BCAA, resulting in their clearance from the blood stream in mice and humans (Yoneshiro et al., 2019), suggesting that tumors with different requirements for glucose and BCAA would respond differently to BAT activation. As another example, 88% of consumed glucose in activated BAT was shown to be used for lactate production rather than being oxidized (Weir et al., 2018). Lactate can be one of the preferred sources for oxidative metabolism in some tumor cells (Hui et al., 2017), which can blunt the effect of glucose restriction on the progression of these tumors. BAT activation also affects systemic metabolism and, similar to calorie restriction, may elicit its effect through altering lipid metabolism of tumors (Lien et al., 2021). The response of specific tumors to BAT activation in this case may be determined by their capacity to compensate for these metabolic changes as well as by the availability of specific lipids in a diet. These instances underlie the need for thorough evaluation of tumor-intrinsic and -extrinsic factors determining metabolic dependencies and responses of individual tumors in order to identify potential responder groups to BAT activation (as to any metabolism-targeting therapy) and efficient therapeutic regimes.

DECLARATION OF INTERESTS

The author declares no competing interests.

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