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Journal Club

Glycogen as a Regulator of White Fat Browning

A new study on the relationship between glycogen metabolism and thermogenesis

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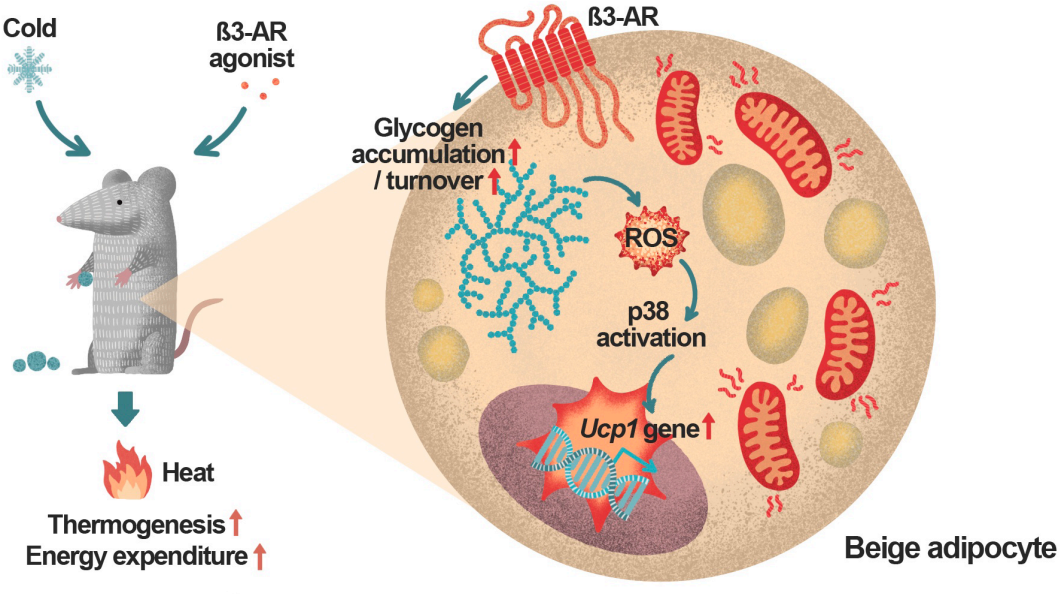

A proposed model of glycogen metabolism when regulating thermogenesis. The β3-adrenergic receptor is activated in mice during continuous cold stimulation or β3-adrenergic agonist treatment. As a result, glycogen accumulation and degradation are increased in beige adipocytes, and ROS production is induced. Increased ROS activates p38. Eventually, UCP1 expression is increased through this process. Thus, thermogenesis and energy expenditure of mice are enhanced.

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Glycogen is the storage form of glucose, and the production and degradation of glycogen molecules are catalyzed by glycogen synthase and glycogen phosphorylase, respectively. Protein targeting to glycogen (PTG) is another regulatory protein that plays a role in glycogen metabolism. PTG is also a scaffolding protein that forms a complex with phosphorylase kinase, phosphorylase a, and glycogen synthase (Printen et al., 1997).

Although glycogen accumulation in adipocytes is lower than in the liver or skeletal muscle, glycogen metabolism still occurs in these cells (Markan et al., 2010). Previous studies have shown that glycogen accumulation is increased in brown adipose tissue (BAT) after refeeding or during acclimatization due to cold stimulation (Carmean et al., 2013; Jakus et al., 2008). However, the role of glycogen in adipose tissues and the relevant molecular mechanisms need to be investigated in detail.

A recent study by Keinan et al. (2021) demonstrated a novel function of glycogen as a regulator that links glucose metabolism and thermogenesis in adipocytes.

Furthermore, Keinan et al. (2021) investigated the effect of β3-adrenergic signals on adipose glycogen levels, considering that previous studies demonstrated the regulatory effect of feeding and fasting signals in BAT on glycogen metabolism (Carmean et al., 2013). Results obtained from this study confirmed that mice treated with β3-adrenergic agonist CL-316,243 exhibited increased mRNA levels of glycogen metabolic genes, such as glycogen synthase, PTG, and glycogen phosphorylase. An increase in glycogen content in the inguinal white adipose tissue (iWAT) was observed. Additionally, to determine whether increased gene expression and glycogen levels in beige adipocytes play a thermogenic role, the researchers used PTG-knockout (KO) mice with a targeted deletion of *Ppp1r3c*. Findings showed that following the CL-316,243 treatment, glycogen accumulation was reduced in the PTG-KO mice compared with the control. Interestingly, UCP1 expression and energy expenditure were decreased in the iWAT of PTG-KO mice. Moreover, Keinan et al. (2021) used adipocyte-specific PTG-KO (PTG-AKO) mice to rule out metabolic changes caused by the systemic knockout of PTG. Normal chow diet- and high-fat diet (HFD)-fed PTG-AKO mice exhibited reduced UCP1 expression and energy expenditure compared with the control. Thus, glycogen metabolism is crucial for thermogenesis in lean and obese mouse models. Furthermore, the human cohort data indicated that an increased expression of adipose glycogen metabolism correlates with improved metabolic parameters, such as reduced body weight and enhanced insulin sensitivity.

Additionally, the researchers experimented at the cellular level using primary adipocytes isolated from iWAT to elucidate the molecular mechanism associated with the role of glycogen metabolism in thermogenesis. Interestingly, CL-316,243 treatment increases glycogen content, enhances Ucp1 expression, and activates p38 in wild-type but not in PTG-KO adipocytes. Therefore, this study showed that glycogen regulates Ucp1 expression by activating p38. A previous study revealed that reactive oxygen species (ROS) production activates p38, thus elucidating how glycogen activates p38 (McCubrey et al., 2006). CL-316,243 treatment increased ROS levels in adipocytes. However, this phenomenon was not observed in PTG-KO adipocytes or adipocytes treated with glycogen phosphorylase inhibitors. As a result, glycogen production and turnover promote ROS formation, thus activating p38.

To further determine the effect of glycogen metabolism under prolonged cold exposure in mice, the researchers generated beige and brown adipocyte-specific PTG-knockout mice (PTG-BKO). UCP1 expression and energy expenditure of cold-exposed PTG-BKO mice were decreased compared with the control. These findings were similar to the results of the CL-316,243 treated adipocytes.

This study revealed the new function of glycogen in adipocytes, which has still not received much attention. There is abounding literature on glycogen functions in the liver and skeletal muscle. Notably, the researchers found that glycogen can regulate various signaling pathways, extending beyond the general knowledge that glycogen is a simple energy storage source. Interestingly, the role of glycogen in BAT has also been reported recently. A study showed that glycogen degraded by glycophagy during brown adipocyte development plays a role in lipid droplet formation (Mayeuf-Louchart et al., 2019). Another remarkable study showed that mice lacking lipid droplets in brown adipocytes use stored glycogen, glucose, and fatty acids as fuel for thermogenesis under cold stress (Chitraju et al., 2020). However, unlike this study, they mainly focused on the function of glycogen as a substrate or energy source for other biological processes. However, the role of glycogen metabolism in cellular signaling has not been explored.

Additionally, glycogen metabolism regulates Ucp1 expression only in iWAT but not in BAT in PTG-BKO mice under long-term cold stimulation. However, the reason for the different phenotypes appearing in BAT and iWAT is unknown. Since the detailed molecular mechanism has not been clarified about whether glycogen accumulation and metabolic-related gene expression are increased by activating the β3-adrenergic receptor (AR) signaling system, further research in this area is recommended. Although this study did not elucidate in detail how the increased glycogen dynamics enhanced ROS production, it is speculated that ROS may be increased because glucose-1-phosphate, which is generated during glycogen metabolism, could become a substrate for glycolysis.

Nevertheless, this study investegated the novel relationship between glycogen metabolism and thermogenesis. The effect of increased energy expenditure was also revealed. Therefore, since glycogen metabolism can regulate the browning of white adipose tissues, regulation of glycogen in iWAT could be an important treatment option for obesity in the future.

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CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

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