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TFEB-dependent Induction of Thermogenesis by Trehalose

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Trehalose is a disaccharide that has been used in neurodegenerative studies due to its ability to induce autophagy—the critical homeostatic process by which organelles, lipids, and proteins are degraded in the cell. We have demonstrated the beneficial effects of trehalose on aspects of the metabolic syndrome, such as non-alcoholic fatty liver disease (NAFLD). Trehalose achieves this by blocking the transport of glucose and fructose via glucose transporter 8 (GLUT8) to trigger a starvation-like response. The metabolic effects of trehalose in the liver and for the whole body are largely unknown. In this project, we showed trehalose's ability to induce hepatic starvation response and trigger downstream TFEB-dependent thermogenesis. Performing *in vivo* mouse experiments, we found that white adipose tissue (WAT) uncoupling protein-1 (UCP1) levels increased with trehalose treatment and thermogenesis simultaneously increased. UCP1 mediates heat and calorie dissipation by decreasing the proton gradient in oxidative phosphorylation, leading to futile cycling. We determined mechanistically that the TFEB, PGC1α, and FGF21 pathway, which are all upregulated in energy-deficient situations (e.g., trehalose treatment), are mediators of WAT (UCP1) levels. *In vivo* experiments with TFEB-deficient mice transfected by adeno-associated virus 8 (AAV8) with TBG promoter, a virus specifically targeting hepatocytes, mitigated heat release and trehalose-induced PGC1α and UCP1 in WAT. Furthermore, ATG16L1, an autophagy protein complex, was dispensable for trehalose-induced thermogenesis. The data serves to demonstrate that trehalose's therapeutic effect on diabetes, obesity, and metabolic syndrome are not necessarily dependent on autophagy; rather there are other mechanisms such as TFEB-dependent induction of thermogenesis involved.