PHARMACOLOGY

Mystery solved: Trehalose kickstarts autophagy by blocking glucose transport

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Although vertebrates cannot synthesize the natural disaccharide trehalose, exogenous administration of trehalose to mammalian cells may be beneficial for protein misfolding disorders. In this issue, DeBosch *et al.* show that trehalose may also be useful in treating nonalcoholic fatty liver disease and identify inhibition of cellular glucose import through SLC2A (also known as GLUT) transporters as a mechanism by which trehalose stimulates autophagy through the adenosine monophosphate–activated protein kinase (AMPK).

Lysosomal degradation of cellular components through autophagy is crucial not only for normal homeostatic turnover of macromolecules and organelles but also as a powerful defense mechanism that maintains cellular integrity in response to environmental and metabolic stress (*1*). In the past decade, modulation of this catabolic pathway has been at the forefront of therapeutic approaches for diverse pathologies that are either secondary or related to autophagy dysfunction, such as cancer, neurodegenerative proteinopathies, and type 2 diabetes (*2*, *3*). In the liver, the role of autophagy in nonalcoholic fatty liver disease (NAFLD), among other pathologies, is of special interest because of its growing incidence in Western societies as a result of the obesity and metabolic syndrome epidemic. Regulated clearance of intracellular lipid stores in hepatocytes depends on a fully functional autophagy pathway (*4*).

Several small molecules have been identified to enhance autophagy flux in preclinical mouse models. For instance, the dissacharide trehalose provides outstanding protection to a variety of neurodegenerative diseases associated with autophagy induction (*5*, *6*). However, the molecular target of trehalose has remained elusive for more than a decade. Here, DeBosch *et al.* studied the effects of trehalose on hepatic lipid accumulation and discovered that trehalose increases autophagic flux by inducing a starvation-like state, decoupled from food intake. By measuring glucose uptake in the presence of trehalose, DeBosch *et al.* demonstrated that the activity of glucose transporters at the plasma membrane (GLUT1, GLUT2, GLUT3, GLUT4, and GLUT8) is inhibited by trehalose, resulting in the activation of adenosine monophosphate kinase (AMPK) (*7*) and the phosphorylation of the autophagy-inducer kinase ULK1 (Fig. 1).

One of the first preclinical studies with trehalose as a therapeutic agent was conducted in a mouse model of Huntington's disease, a severe proteinopathy characterized by the deposition of aggregates of the mutant huntingtin protein. Oral administration of trehalose, which readily crosses the blood-brain barrier, significantly improved biochemical and behavioral features of the disease, including a decrease in protein aggregation, improvement in motor control, and extension of mouse survival (*8*). These results were initially attributed to trehalose's "chemical chaperone" properties, which might keep aggregation-prone proteins in a more soluble state, maintaining protein homeostasis (proteostasis). However, a subsequent detailed in vitro study found that trehalose induced the clearance of disease-related aggregates by enhancing autophagy through a mechanism that is independent of the autophagy-regulating activity of the kinase mammalian target of rapamycin (mTOR) (*5*). Nutrient deprivation inhibits the mTOR-containing complex mTORC1 to promote autophagy. A similar therapeutic outcome was observed in a mouse model of amyotrophic lateral sclerosis (ALS), in which trehalose administration enhanced autophagic clearance of aggregates of mutant superoxide dismutase 1 (SOD1). This trehalose-mediated increase in autophagy was associated with higher expression of key autophagy-related genes and activation of the transcription factor FoxO1, a regulator of autophagy in neurons (*9*). Likewise, trehalose induced autophagy and had protective effects in a mouse model of tauopathy (*10*), one of the hallmarks of Alzheimer's disease. These examples illustrate the beneficial effects of trehalose in a disease context and point to an alternative route of autophagy induction, which could circumvent the side effects of mTOR inhibition (*2*, *6*).

In the context of NAFLD, the study by DeBosch and coworkers brings new insights into the biological activity of trehalose. Trehalose inhibited glucose transporters of the SLC2A family, which mediate hexose import to hepatocytes and other cell types. The reduction in glucose availability triggered a starvation signal, causing the rapid phosphorylation and activation of AMPK and a concomitant increase in ULK1 phosphorylation and activation, which induced autophagy. Although canonical mTOR targets were not evaluated directly, the dephosphorylation of ULK1 in the site regulated by mTOR (Ser^{757}) suggests a potential connection between both autophagy-regulating pathways. It would not be completely unexpected to observe some cell- or tissue-specificity in the biological activity of trehalose, although a more thorough examination of direct effectors of mTOR in the liver is necessary in order to draw a definitive conclusion regarding the role of mTOR inhibition in trehalose-mediated autophagic induction. Conversely, it would be interesting to investigate whether trehalose compromises glucose transport into neurons through GLUT3. If so, this mechanism of enhancing neuronal autophagy through the AMPK pathway may explain some of the broad neuroprotective effects of trehalose.

A general consideration of the study highlights the potential influence of trehalose on global carbohydrate and energy metabolism, depending on its administration route. The inhibition of GLUT transporters predicts additional metabolic consequences in vivo because GLUT2 is also involved in facilitating transepithelial hexose transport in the gut, whereas GLUT8 facilitates fructose import into hepatocytes, and GLUT4 mediates the regulated transport of glucose into adipocytes

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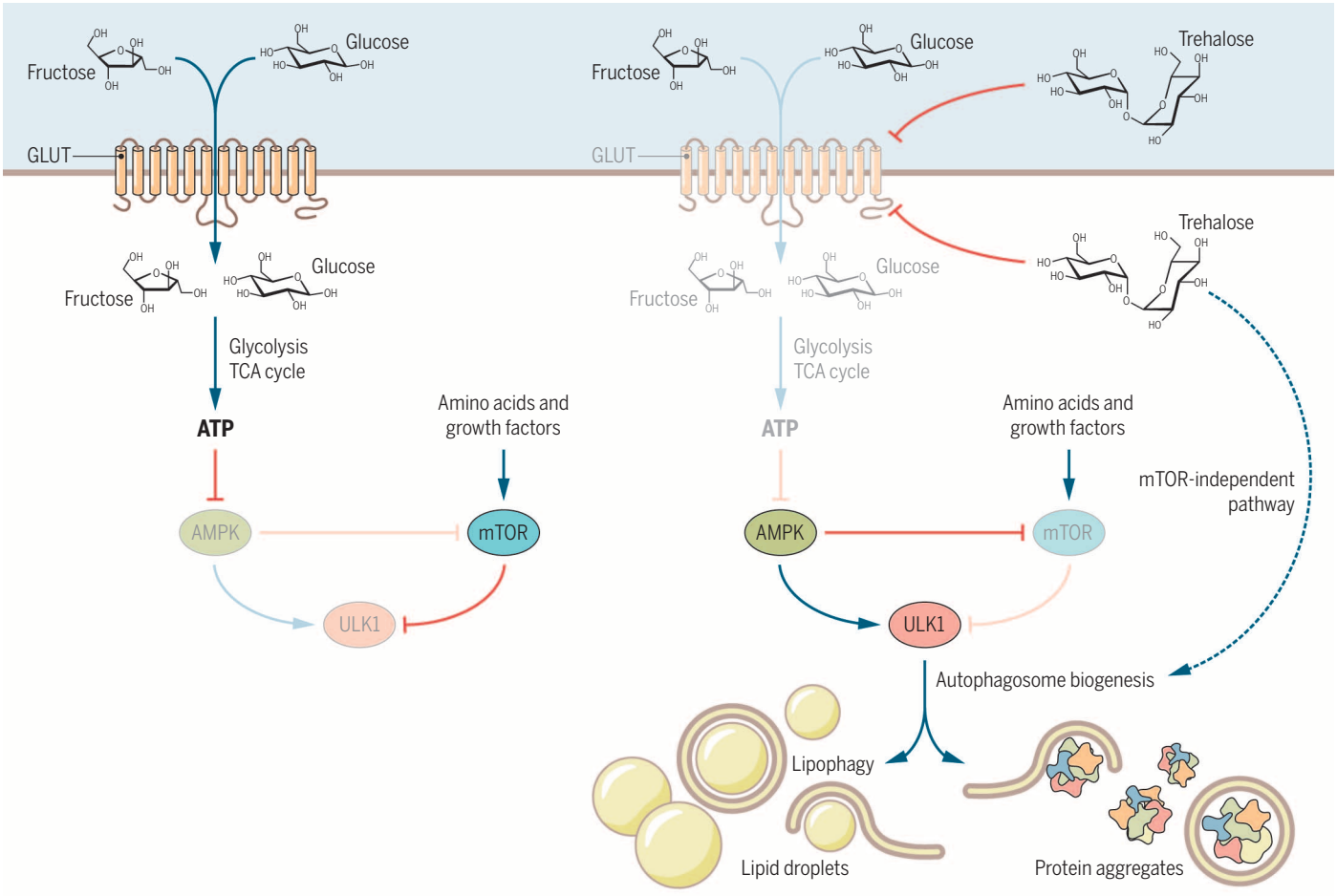

Fig. 1. The molecular link between trehalose and autophagy. Trehalose inhibits cellular import of glucose and fructose through SLC2A (GLUT) transporters, generating a starvation-like (low adenosine triphosphate) state that stimulates autophagy through AMPK and activation of ULK1. This pathway triggers autophagosome biogenesis and autophagic flux, which favors the clearance of pathological protein aggregates and lipid stores. Conversely, autophagy is inhibited by mTOR, a sensor of nutrient availability and recipient of growth factor signaling. AMPK activation may interfere with mTOR-mediated inactivation of ULK1. Trehalose may induce autophagy through additional unidentified mTOR-independent mechanisms.

and muscle cells. Trehalose-mediated inhibition of glucose absorption in the intestine might explain, for example, the absence of hyperglycemia in high-trehalose-fed mice with normal levels of trehalase, the enzyme that breaks it down into glucose monomers. Potential competitive inhibition of hexose transport may provide an additional advantage for the use of oral trehalose in the context of insulin resistance and obesity by simultaneously tackling systemic and cellular aspects of these complex diseases.

Regardless of the precise molecular mechanism behind the pro-autophagy activity of trehalose in the liver, the impressive reversal of lipid storage and gene expression changes reported by DeBosch *et al*. in experimental models of hepatic steatosis offer great promise for the clinical use of a relatively safe molecule that may soon become a silver bullet in the therapeutic arsenal against proteostasis and metabolic disorders.

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Funding: This work was supported by Millennium Institute No. P09-015-F, Fondo de Financiamiento de Centros de Investigación en Áreas Prioritarias (FONDAP) 15150012, the Frick Foundation No. 20014-15, ALS Therapy Alliance 2014-F-059, Muscular Dystrophy Association 382453, Comisión Nacional de Investigación Científica y Tecnológica (CONICYT) CONICYT-USA2013-0003, the Michael J. Fox Foundation for Parkinson's Research No. 9277, Fundación Copec–Universidad Católica No. 2013.R.40, Ecos-Conicyt C13S02, Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT) no. 1140549, Office of Naval Research–Global (ONR-G) N62909-16-1-2003 and Amyotrophic Lateral Sclerosis Research Program Therapeutic Idea Award AL150111 (to C.H.), FONDECYT-3140388 (to P.M.), the Wellcome Trust 095317/Z/11/Z Principal Research Fellowship (to D.C.R.), and the National Institute for Health Research Biomedical Research Unit in Dementia at Addenbrooke's Hospital (D.C.R.). **Conflict of interest declaration:** D.C.R. consults for BioBlast.

10.1126/scisignal.aaf1937

Citation: P. Mardones, D. C. Rubinsztein, C. Hetz, Mystery solved: Trehalose kickstarts autophagy by blocking glucose transport. *Sci. Signal.* **9**, fs2 (2016).

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Sci. Signal. **9** (416), fs2.
DOI: 10.1126/scisignal.aaf1937