Trends in
Endocrinology & Metabolism

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Spotlight

Shifting metabolism to increase lifespan

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Lionaki *et al.* report that reducing mitochondrial protein import increases *Caenorhabditis elegans* lifespan, through a metabolic shift that enhances the conversion of glucose into serine. Here, I discuss the promise held by these findings in the framework of therapeutic approaches to metabolic and neurodegenerative diseases.

Excessive sugar intake

A large percentage of the human population consumes excessive amounts of sucrose, the digestion of which releases glucose and fructose. Consequently, conditions including diabetes, obesity, fatty liver, and cardiovascular diseases have become a global healthcare burden. In conjunction with educational approaches, understanding and modulating the mechanisms mediating the toxic effects of excessive sugar intake is an essential investment to mitigate that burden.

In a recent article, Lionaki and colleagues [1] report the induction of a metabolic shift that alleviates the toxic effects of glucose and increases the lifespan of the nematode *C. elegans* (Figure 1A). This metabolic shift was induced through inhibition of protein import into mitochondria (Figure 1B), the major subcellular compartments involved in energy conversion.

Increasing *C. elegans* lifespan

To inhibit mitochondrial protein import in *C. elegans*, Lionaki and colleagues blocked the biosynthesis of the channel-forming subunits of protein complexes that translocate proteins across mitochondrial membranes or enclosed compartments. Wild-type *C. elegans* animals were grown from hatching in culture media containing bacteria (Figure 1C) engineered to produce RNAi molecules targeting the mRNA encoding one of the channel-forming subunits, thus blocking its biosynthesis (Figure 1D) [1,2]. The percentage of living animals was monitored and, 22 days after egg laying, 50% of control animals were dead [1], and a normal mitochondrial protein content correlated with a normal lifespan (Figure 1E). Strikingly, upon inhibition of the biosynthesis of the translocase of inner membrane 23 (TIM23) or the translocase of outer membrane 40 (TOM40) (two of the channel-forming subunits), 50% of animals were still alive after 25 days [1]. Decreased mitochondrial protein import correlated with increased lifespan (Figure 1F).

The metabolic shift

Lionaki and colleagues sought to uncover the molecular basis of the increase in *C. elegans* lifespan. Such an increase was not directly caused by protein chaperone activation in response to reduced mitochondrial protein content. Interestingly, the driving process was a metabolic shift [1]. Under normal conditions, glucose is internalized by cells, phosphorylated, and converted into pyruvate through glycolysis. Pyruvate is further imported into mitochondria where it is fully degraded through mitochondrial respiration (Figure 1G). The impairment of mitochondrial function, by blocking protein import, restricts sugar metabolism to the cytoplasm. In the cytoplasm, pyruvate accumulation enhances its conversion into lactate (Figure 1H) and also increases the cellular levels of the glycolysis intermediate glycerate-3-phosphate (glycerate-3P). Increased glycerate-3P enhances its conversion into serine (Figure 1H). The expression levels of genes involved in glycolysis and related metabolic pathways, such as glycogen metabolism and the pentose phosphate pathway, were generally increased [1]. These observations indicate a clear metabolic shift in *C. elegans* that correlated with increased lifespan.

Another effect of inhibiting mitochondrial protein import was an increase in glucose uptake (Figure 1H) and glycolysis that were also crucial for lifespan increase. Accordingly, inhibiting mitochondrial protein import only in neurons or the hypodermis (that unresponsive to insulin-induced glucose uptake) failed to increase *C. elegans* lifespan [1].

The observed metabolic shift could increase lifespan most likely through removal of excess glucose levels and *de novo* serine biosynthesis. Growing *C. elegans* in the presence of D-glucose decreased its lifespan; however, inhibiting mitochondrial protein import could overcome this effect [1]. Moreover, simultaneous depletion of mitochondrial protein import and phosphoglycerate dehydrogenase (the enzyme catalyzing the rate-limiting step in the conversion of glycerate-3P into serine) completely abolished the lifespan increase [1], confirming the essential role of serine biosynthesis.

These findings are supported by previous reports relating increased *C. elegans* lifespan to decreased mitochondrial protein import [3] or function [4], and linking mitochondrial dysfunction to increased serine biosynthesis [5].

Therapeutic perspectives

The findings by Lionaki and colleagues might be useful in treating diseases caused by excessive glucose intake. Reducing mitochondrial protein import to decrease glucose levels through conversion into serine could be a therapeutic approach.

Excessive fructose intake also causes toxic effects, including insulin resistance. After cellular uptake, fructose is first converted into fructose-1-phosphate, and then into dihydroxyacetone phosphate and D-glyceraldehyde. This pathway bypasses the phosphofructokinase-catalyzed reaction [6], the rate-limiting step of glycolysis. The uncontrolled cellular degradation of large amounts of

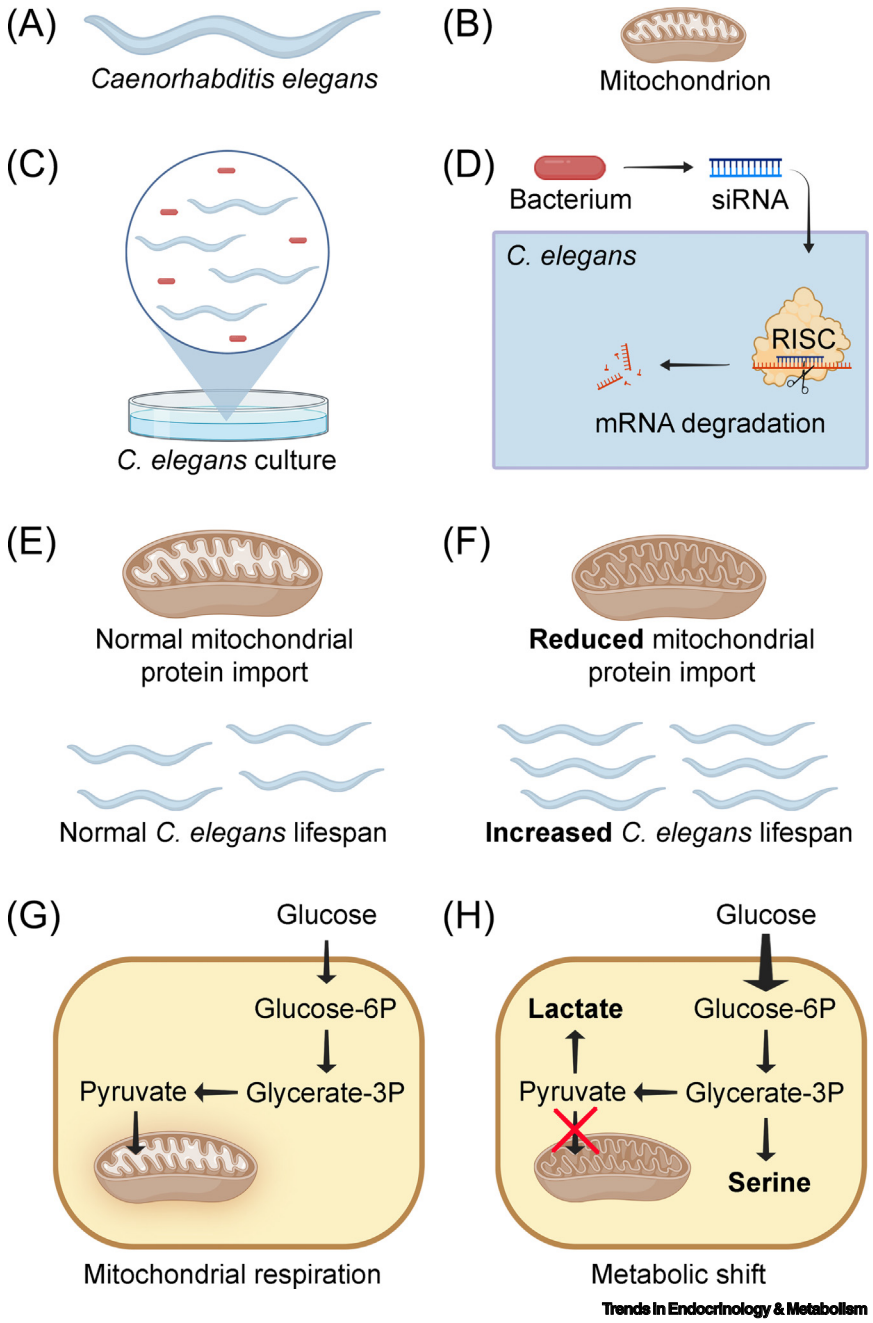

Figure 1. Lifespan increase and metabolic shift in *Caenorhabditis elegans*. (A,B) Drawings of (A) a *C. elegans* animal and (B) a mitochondrion. (C) A Petri dish containing a culture of *C. elegans* and bacteria (represented in red). (D) Schematic representation of the RNAi mechanism in *C. elegans*. siRNA produced by genetically modified bacteria is internalized by *C. elegans* cells, forming the RNA-induced silencing complex (RISC) which degrades a specific mRNA, thus preventing its translation into a channel-forming subunit of a mitochondrial protein import complex. (E,F) Drawings of mitochondria, representing (E) normal protein import levels that are associated with normal *C. elegans* lifespan, and (F) reduced protein import levels related to increased *C. elegans* lifespan. (G,H) Simplified schematic representations of the (G) glucose degradation pathway in *C. elegans*, where glucose is internalized by a cell (represented in yellow), phosphorylated into

(Figure legend continued at the bottom of the next page.)

fructose can cause dangerous effects, including the production of uric acid and a shortage of ATP, the main energy biomolecule [6]. Therefore, it would be interesting to test whether the metabolic shift described by Lionaki and colleagues can also protect against fructose toxicity.

Accelerating glucose uptake and metabolic degradation could also be a potential therapeutic approach for neurodegenerative diseases. These diseases originate in neurons, which have a high energy demand. Although their causes are poorly understood, they are generally related to insufficient glucose uptake and metabolism caused by dysfunctional mitochondria [7]. The induction of conditions mimicking hypoxia (reduced cellular oxygen availability) has been proposed as a possible treatment [8]. As hypoxia increases glycolysis and decreases mitochondrial respiration, it could be mimicked in neuronal cells through the inhibition of mitochondrial protein import.

Nevertheless, as a therapeutic approach, reducing mitochondrial protein import should be induced only in specific cell types to prevent side effects. As an example, several drugs reducing mitochondrial function have anticancer effects; however, they can also be cardiotoxic in patients [9].

Concluding remarks

By inhibiting mitochondrial protein import in *C. elegans*, Lionaki and colleagues increased its lifespan. The associated metabolic shift led to reduced glucose toxicity by enhancing its cellular uptake and conversion into serine. Future research will certainly deepen our understanding of these mechanisms and their therapeutic potential against diseases related to excessive sugar intake or deficiencies in its metabolism.

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Declaration of interests

The author declares no conflicts of interest.

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glucose-6-phosphate (glucose-6P), and converted into pyruvate, which is further degraded in mitochondria. (H) Under conditions of reduced mitochondrial protein import, glucose uptake is enhanced (represented by a larger arrow), and pyruvate fails to be degraded in the mitochondrion, and is instead converted into lactate. Notably, the glycolysis intermediate glycerate-3-phosphate (glycerate-3P) is extensively converted into serine. Elements not drawn to scale. This figure was created using BioRender (biorender.com).