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Longevity: Mapping the path to a longer life

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Understanding how cellular nutrient-sensing and homeostasis affect an organism's lifespan and susceptibility to cancer and degenerative diseases is clinically important but scientifically difficult. Work in model organisms, first in nematode worms¹ and then in fruit flies², has established that increasing the activity of the transcription factor FOXO, by reducing insulin and insulin-like growth factor signalling (IIS), can protect against cellular damage and ageing. Writing in *Cell*, Slack *et al.*³ now show that selective mutation of the fruit fly IIS adaptor protein Chico to disrupt either of the two major IIS pathways — the RAS–ERK or the PI3K–AKT cascades — can extend the flies' lifespan. They find that inhibiting ERK signalling activates the transcriptional-repressor protein AOP, which, surprisingly, extends lifespan by just as much as the activation of FOXO that occurs during PI3K inhibition. This finding may have uncovered a new target for extending lifespan that lacks the adverse effects associated with PI3K inhibition, which include dysregulated metabolism, reduced growth and infertility.

From a clinical perspective, a reduced IIS pathway that extends lifespan is different from the resistance to the hormone insulin that leads to metabolic syndrome — the medical term for a combination of diabetes, high blood pressure and obesity. The most frequent misconception is that increasing the amount of circulating insulin to overcome insulin resistance is a healthy goal. Although increasing circulating insulin levels can prevent high blood glucose levels and slow the progression to type 2 diabetes, it is associated with obesity and abnormal lipid levels and cardiovascular disease. Moreover, at the cellular level, chronic high insulin or long-term insulin therapy can retard tissue repair and maintenance by inhibiting autophagy, the process that removes damaged intracellular proteins. How to safely achieve a longer lifespan by reducing IIS in the face of high-sugar diets that promote insulin resistance and increase insulin levels is a challenging conundrum.

The fruit fly *Drosophila melanogaster* is useful for investigating the relationship between the IIS pathway and lifespan because it has a short life cycle and its genome encodes single copies of many IIS components. However, translating discoveries in fruit flies to other organisms can be tricky, because in people and other animals the IIS pathway is distributed between two homologous receptors (InsR and IGF1R), three or four adaptor proteins (IRS1, IRS2, IRS3 in rodents, and IRS4) and several effector proteins of the MAPK, PI3K, ATK and FOXO families. Some variants in the genes encoding IGF1R⁴ and FOXO3A⁵ have been

associated with human longevity; however, complete loss of InsR or IGF1R function is fatal after birth for mice and people. Yet inactivation of InsR in murine adipose tissue extends lifespan⁶, as does deletion of IGF1R in the brain⁷. Thus the window for increasing lifespan by modulating IIS in mammals seems to be tissue specific.

The natural loss of growth-hormone receptors in humans with Laron syndrome (a type of dwarfism) causes obesity and reduces circulating insulin and IGF1, as well as decreasing the incidence of diabetes or cancer⁸. Notably, mice without growth-hormone receptors share similar traits and are the longest-lived laboratory mouse strain. Clearly, it is essential to understand the tissue-specific effects of reduced IIS in mammals to modulate lifespan with the fewest possible adverse effects.

A major problem with reduced IIS is the risk of dysregulated metabolism and growth associated with inhibiting the PI3K cascade⁹. Despite this, efforts to target the PI3K branch of IIS in ageing might be successful with a better understanding of which protein isoforms to target and with improved inhibitors. In the meantime, Slack *et al.* find that exposing flies to the small molecule trametinib, currently used for cancer therapy, achieves similar lifespan extension to the inhibition of the PI3K pathway. Trametinib inhibits the ERK branch of the IIS pathway by inhibiting the protein kinase enzyme MEK (Fig. 1).

The authors also show that the extension of fly lifespan by ERK or PI3K inhibition is not additive, which suggests that the two branches of the pathway might converge on modulating the expression of common genes that regulate lifespan¹⁰. Inhibition of ERK activates AOP, whereas inhibition of PI3K activates FOXO; both transcription factors do indeed bind a common subset of genes, but the exact targets that control lifespan are unknown¹⁰ (Fig. 1). Moreover, FOXO is usually a transcriptional activator, whereas AOP is a repressor that opposes the activity of another factor, PNT, in *Drosophila*. Interestingly, coactivation of FOXO and PNT can have detrimental effects that are attenuated by AOP¹⁰, indicating that favourable crosstalk between AOP and FOXO might modulate common genes needed to extend lifespan.

Despite the potential to bypass PI3K inhibition, it remains to be investigated whether inhibiting the ERK cascade can extend mammalian lifespan without any adverse effects. ERK is a member of the MAPK enzyme family, which mediates cellular responses to a wide range of extracellular cues to regulate cell growth, differentiation and survival. Although MEK inhibition has been shown¹¹ to improve glucose tolerance in diet-induced obese mice, the tissues in which this is beneficial are ill defined. Further work is needed to establish whether inhibiting the ERK signalling branch is a plausible mechanism-based strategy for extending lifespan, especially when started in adults.

While work continues to devise medical strategies to extend lifespan, calorie restriction remains the best-known way to increase lifespan in yeast, nematodes, fruit flies, rodents and some primates¹². Calorie restriction can reduce the progression of age-related diseases, including obesity, insulin resistance, type 2 diabetes, cardiovascular disease and cancer, but it is difficult for people to use in the long term and can be dangerous if unmonitored or used to excess; furthermore, its beneficial effects on human lifespan are unproven¹³. Recent work

suggests that a fasting-mimicking diet that produces intermittent, brief bouts of calorie restriction can produce health benefits in people and extend the lifespan of mice¹⁴.

Both these approaches increase insulin sensitivity and reduce circulating insulin and IGF1 concentrations, and so reduced IIS might be involved in the observed effects. Whether medical strategies — such as using the drug rapamycin to inhibit the enzyme TOR¹⁵, the antidiabetic drug acarbose to mimic calorie restriction¹⁶, or inhibiting the ERK cascade as described by Slack and colleagues — can exploit or augment the underlying molecular mechanisms engaged by calorie restriction and reduced IIS in the face of nutrient excess is an important area for future investigation.

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Fig. 1.

Insulin and insulin-like growth factor signalling (IIS) is triggered by binding of the insulin receptor (InsR) or insulin-like growth factor 1 receptor (IGF1R) and activation of an adaptor protein, which can be one of three or four IRS proteins in mammals or the Chico protein in *Drosophila* fruit flies. The pathway then splits into two main branches. One activates the proteins PI3K and AKT to cause inhibition of the transcription factor FOXO, an activator of gene transcription. The other branch activates the protein RAS, which then triggers a cascade involving RAF, MEK and ERK to inhibit the transcription factor ETV6 (or its

equivalent in flies, AOP), a repressor of gene transcription. Slack et al.³ show that, in *Drosophila*, mutating chico to disrupt either of these pathways, or inhibiting the RAS–ERK pathway by treating flies with the MEK inhibitor trametinib, leads to extended lifespan. Adapted from ref. 3 (CC BY 4.0).