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Death and dessert: Nutrient signalling pathways and ageing

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Abstract

Reduction in nutrient intake without malnutrition can delay ageing and extend healthy life in diverse organisms from yeast to primates. This effect can be recapitulated by genetic or pharmacological dampening of the signal through nutrient signalling pathways, making them a promising target for intervention into human ageing and age-related diseases. Here we review the current knowledge of the interactions between nutrient signalling pathways and ageing, focusing on the findings emerged in the last few years.

Dietary restriction and ageing

What you eat and how much may determine not just what you are but also how long you live. Reduction in nutrient intake without malnutrition, often referred to as caloric or dietary restriction (DR), has for over 70 years been known to retard ageing in rodents [1]. This effect is conserved during evolution and can be observed in model organisms from yeast to mice, including the nematode worm *C. elegans* and the fruit fly *Drosophila* (reviewed in [2]). The strong evolutionary conservation of the effects of DR has long hinted that it could extend lifespan and, more importantly, improve health into old age in primates. Indeed, a recent study has confirmed this idea, showing that DR can extend lifespan in Rhesus monkeys [3]. Importantly, DR can delay the onset of age-associated pathologies and induce a broad-spectrum improvement in health during ageing in mammals, including humans [4,5].

DR can be implemented in multiple ways for a single organism, and different types of DR applied to *C. elegans* clearly extend lifespan through non-identical underpinning molecular mechanisms [6]. Recent work in the fruit fly *Drosophila* has shown that the main nutritional effector is not necessarily the total amount of calories or nutrients eaten, but rather the balance between specific nutritional components, particularly amino acids [7]. It will be essential to understand the nature of nutritional manipulations that could improve human health into old age. However, other obstacles could prevent implementation of DR itself in humans. While yeast, worms and flies do not complain of the reduction in food intake,

hungry humans are much more vocal and can lack discipline at tea time. So how could humans be tricked into DR?

Nutrient sensing and ageing

Evolutionary theory has long postulated that the effects of DR on lifespan come about through readjustment of a trade off between reproduction and longevity-assurance mechanisms, brought about by competition for nutrients [8]. However, recent work suggests that such a trade-off is not obligatory [7], and that the effects of reduction in food intake on lifespan are not a direct, mechanical consequence of reduced nutrient availability, but rather of the changes in animal physiology resulting from altered nutrient signalling.

The importance of nutrient signalling, rather than nutrient intake, for lifespan is vividly illustrated by the effect of chemosensation of food. In the fruit fly, the simple presence of food-derived odours can modulate lifespan and partially reverse the effects of DR [9]. A specific sensory cue, namely CO₂, and its cognate receptor appear to be involved, and the expression pattern of the receptor implicates a specific neural circuit in regulation of adult physiology and lifespan [10]. This effect of environmental sensing on lifespan is evolutionarily conserved. Neurosensory organs in the worm can modulate lifespan [11] and laser ablation of individual cells revealed that removal of specific gustatory or olfactory neurons could increase or decrease lifespan [12]. The worm sensory system is capable of recognising food types and relaying this information to whole organism physiology. The bacterium *Escherichia coli* is the food source for the worm, and the lipopolysaccharide structure on the bacterium provides a cue whose affect on lifespan appears to be mediated by a neuropeptide receptor resembling the Neuromedin U receptor [13]. The sensory regulation of lifespan extends beyond chemosensation, and a recent report demonstrates that thermosensory neurons modulate the response of lifespan to temperature in *C. elegans* [14].

Nutrient signalling pathways and ageing

Sensory information about food is relayed to the rest of the organism by various nutrient-sensing signalling pathways. Thus, pharmacological interventions that alter the flow of information through these pathways could, in principle, be used to mimic the effects of DR and extend healthy lifespan in humans. The strongest indication that this is possible comes from genetic studies in biogerontology, which started later than DR itself, but are rapidly catching up in terms of understanding of mechanisms. Genetic or pharmacological modulation of several interconnected signalling pathways can extend healthy lifespan. The effects on ageing of modulation of one of these, namely the insulin/insulin-like growth factor (IGF) signalling (IIS) and target of rapamycin (TOR) signalling network (Figure 1), show remarkable evolutionary conservation, from yeast to mice [2], and even possibly humans [15-18]. These pathways signal the presence of nutrients, and they will hence be the focus of this review, although of course other pathways can also affect ageing in at least some organisms. Note as well that this signalling network also responds to stimuli other than nutrition, and for example DNA damage dampens the signalling through the IIS pathway in both flies and mammals [19,20].

Mutations that reduce the activity of IIS/TOR extend lifespan in budding yeast, worms, flies and mice [21-28]. Furthermore, components of this neuroendocrine signalling pathway have been implicated in human ageing by gene-association studies [15-18]. Importantly, interventions that reduce IIS/TOR also improve general health as the animals age [28], as well as delaying progression of pathology in genetic models of specific ageing-related diseases, such as Alzheimer's disease [29,30].

The signalling cascade is initiated by insulin/insulin-like growth factor (IGF)-like peptides (ILPs) that are secreted into circulation to coordinate whole animal physiology (Figure 1). There are 40 such ligands in the worm, 7 in the fly and 3 in mammals. Recent work in the fly and worm has started to unravel the roles of the different ligands. For example, 3 worm ILPs have specific roles in entry to and exit from an alternative developmental stage called dauer [31], while removal of only 3 out of the 7 *Drosophila* ILPs extends fly lifespan [32]. Deletion of these 3 ILPs, as well as the ablation of the neuroendocrine cells that produce them, protects against the effects of high food intake [32,33], implicating them in mediating the effects of DR. The availability of the ILPs is regulated by a set of binding proteins that resemble the mammalian IGF-binding proteins. Indeed, over-expression of one of them (IMP-L2) in the fly is sufficient to extend fly lifespan [34]. This effect may be conserved in the mouse, where the deletion of pregnancy associated plasma protein A, a negative regulator of IGF binding protein 4 stability, extends lifespan [35].

The intracellular IIS cascade is initiated by binding of the ligand to an insulin/IGF receptor-like receptor, leading to the eventual activation of the AKT kinase that directly inactivates a transcription factor of the Forkhead Box-O (FoxO) family (Figure 1). Dampening the IIS signal by alterations in the intracellular components of the pathway also results in increased longevity, which in the worm this has long been known to depend upon the worm FoxO orthologue DAF-16 [23]. Recently, this has also shown to be the case in the fly [36,37]. Interestingly, in the fly, lifespan extension and xenobiotic resistance are dependent on *Drosophila* FoxO, while lowered fecundity and body size, delayed development and resistance to paraquat are not [36]. All these may be orchestrated by other transcription factors, since only a part of the transcriptional response to IIS down-regulation depends on *Drosophila* FoxO [38]. It will now be important to investigate the dependence of IIS lifespan effect on FoxOs in mammals.

Tissue-restricted alterations in IIS are sufficient to extend lifespan. The relevant tissues appear to be neuronal and adipose in mammals [27,39], and similar tissues are involved in the worm and the fly [2]. Indeed, in the worm, the DAF-16/FoxO isoform whose expression is predominant in the intestine (which in part functions as the adipose tissue) is the most potent in extending lifespan [40]. Over-expression of *Drosophila* FoxO in the fly gut and fat body is sufficient to extend lifespan [41,42], and recently over-expression in the muscle has been shown to have the same effect [43]. In some cases, this tissue-specific activation of FoxO has been suggested to result in down-regulation of IIS in the whole organisms by reducing availability of *Drosophila* ILPs [42,43], similar to the observations that have been made in worms [44]. However, the involvement of such a whole-organism positive feedback in lifespan remains to be experimentally tested. Interestingly, slight down-regulation of IIS in stem cells that reside in the *Drosophila* gut and in their immediate daughter cells can

extend the lifespan of the whole fly [45], implicating proliferative homeostasis in the effects of IIS on lifespan.

IIS is known to activate the RAS - extracellular signal regulated kinase (ERK) pathway. However, the effect of the down-regulation of this branch of the pathway on lifespan has not been as thoroughly investigated [2]. Down-regulation of the RAS signalling pathway is known to extend yeast lifespan [21,46], and a recent report indicates that knockout of a RAS-guanine nucleotide exchange factor, RASGRF1, can also extend lifespan in mice [47]. It will be important to examine the effects of down-regulation of this pathway in other organisms.

IIS interacts heavily with the TOR signalling pathway forming a complex signalling network, and a genetic reduction of signalling through TOR itself can also extend lifespan in yeast, worms and flies [21,22,48,49]. A recent report established reduced TOR signalling as the most evolutionarily conserved lifespan-extending intervention so far: reduction in TOR signalling by administration of rapamycin in food extends mouse lifespan [50]. Food-administered rapamycin is an exciting lifespan-extending pharmacological intervention that also has an anti-ageing effect in flies, which depends upon both up-regulation of autophagy and down-regulation of the ribosomal S6 kinase (S6K) [51]. Indeed, deletion of S6K1 in mice results in extended lifespan and increased resistance to a number of age-related pathologies [52]. 4E-BP, a regulator of cap-dependent translation, appears to play only a condition-dependent role in the lifespan response to rapamycin in *Drosophila* [51,53], similar to its conditional role in DR [53-55].

IIS, TOR, cancer and ageing: agonistic pleiotropy?

A role of FoxO proteins in tumour suppression has long been postulated and recent work has revealed mammalian FoxOs as *bona fide* tumor suppressors *in vivo* [56-58]. Indeed, positive regulators in the IIS/TOR network are generally oncogenic, while negative regulators, such as PTEN, are tumour suppressive [59]. Two models have been suggested to explain the evolutionary relationship between cancer and ageing [60]. The first sees cancer and ageing as antagonistically pleiotropic where the suppression of growth, proliferation and survival, particularly in dividing tissues, may protect from cancer while resulting in tissue ageing [60]. This is similar to the relationship between growth and ageing, where for example TOR activity early in life is required for growth while later in life it promotes ageing [61]. A second, which we could name agonistic pleiotropy, postulates that mechanisms that protect from cellular damage would simultaneously protect from cancer and ageing [60]. Indeed, one can see how cancer and ageing could have co-evolved: with selection on cancer resistance declining as animals die off from other causes and selection for other causes of continuing survival only possible if the animals are protected from cancer. The functioning of the IIS and TOR pathways appears mostly to support the agonistic relationship between cancer and ageing, while the functioning of other pathways may not [60]. Furthermore, the link may not be a mechanistic one, with protection against cancer slowing ageing, although the same genes may sometimes be involved in both functions. In this respect it is interesting that increased gene dosage of the tumor-suppressing *Ink4/Arf* locus protects against cancer and extends lifespan in mice, while

increased gene dosage of *p53* only protects against cancer [62]. *Ink4/Arf* locus extends lifespan in cancer-free mice, demonstrating that cancer protecting and delayed ageing are separable.

Can you have you cake and live long too?

It is likely that a nutritional intervention such as DR can prolong healthy life in humans, however, most of us would like to have our cake and live long too. It now appears possible that a pharmacological modulation of nutrient signalling pathways could harness the positive effects of DR to allow humans to be healthier at old age. Already, a pharmacological intervention, rapamycin, has been shown effective in slowing mammalian ageing. Further understanding of molecular mechanisms of DR, as well as of the lifespan extension achieved by modulation of signalling pathways, including their evolutionary conservation, will be needed to design potent beneficial drugs without detrimental side-effects. In the meantime, restraint at tea time is the best option.

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Figure 1.

The nutrient signalling network comprised of IIS and TOR signalling pathway in four model organisms (from left): the yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster* and the mouse *Mus musculus*. Orthologous signalling components are indicated with the same symbol in each organism. Duplication of some signalling components in certain organisms are indicated. For example, the insulin/IGF-like peptides (ILPS) are present in numerous copies in worms and yeast, whereas there are four FoxO genes in mammals. RAS is only indicated in the two organisms where modulation of its signalling has been shown to affect lifespan.