accretion flow? There is one viable mechanism (Fig. 1): that, hidden from view deep within the disk, comet-like bodies rich in water ice are sent towards the inner disk through gravitational interactions. In the inner disk, the water is released as the icy bodies evaporate. If these bodies form at the temperatures of 20–150 kelvin found in almost the entire disk of MWC 480, water will be ice, but CO will still be gaseous. Such bodies will therefore contain lots of water, but little or no CO.

The idea that icy bodies are on the move in the innermost regions of a solar system in the making would confirm theories of Earth's own formation. Earth is thought to have been produced through the merging of large numbers of smaller bodies, some of which came from larger distances and contained water ice, thus supplying large quantities of water: Earth's interior is estimated to contain between one and ten times more water than its oceans[8]. Where Earth's surface water came from is, incidentally, a matter of debate: rival theories hold that the oceans were 'sweated' by the young planet through volcanic eruptions, or that they were the product of comet-like bodies that collided with the planet after it had formed[9,10]. Unfortunately, MWC 480 is much younger than our Solar System was when Earth's formation was complete, and so Eisner's observations do not provide any new handle on this controversy.

One factor speaks against the interpretation of Eisner's results as the signature of comet-like icy bodies. This is the reasonably high rate at which material is falling onto MWC 480's central star, which makes an intermittent, cometary origin of the accreting material less likely than a steady, gaseous accretion flow. Such steady accretion would be more in line with existing ideas and observations of other stars, but puts us back to square one with the problem of why we see water, but no CO. High-resolution spectroscopy to confirm the detection of hot water vapour and to put stringent limits on the CO emission in the MWC 480 system are urgently needed as the next steps towards solving the puzzle. ■

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AGEING

When less is more

Adam Antebi

Restricting dietary intake is one way to promote longevity. The identification of two genes that specifically mediate this effect in worms provides insight into the molecular mechanisms underlying ageing.

Dietary restriction — a reduction of food intake by 40–60% without malnutrition — has remarkable benefits for health and lifespan, extending the survival of species as diverse as yeast, worms, flies, rodents and perhaps even primates. Yet despite intensive study, the molecular basis of the effects of dietary restriction in animals has remained largely elusive. Elsewhere in this issue, two groups[1,2] report a role for a pair of evolutionarily conserved proteins — PHA-4 and SKN-1 — in conferring extended survival under dietary restriction in the small roundworm *Caenorhabditis elegans*. Both PHA-4 and SKN-1 are transcription factors, regulating the expression of many genes. Moreover, evidence suggests that they may also trigger hormones that coordinate physiological responses to dietary restriction.

Restricting dietary intake in worms can be achieved by diluting their bacterial food. At optimum conditions for dietary-restriction-induced longevity, worms typically live 20–50% longer than fully fed animals. The PHA-4 protein, which was originally described for its role in specifying the pharynx in worm embryos, is a member of the forkhead family of transcription factors, and is very similar to mammalian FOXA proteins[3,4]. In mammals, FOXA proteins have developmental roles, and regulate glucose metabolism later in life[5]. In *C. elegans*, PHA-4 is present from embryo to adult, but its functions in later life were largely unknown.

To examine PHA-4 function in adult worms, Panowski and colleagues (page 550)[1] used genetic manipulations to inactivate the *pha-4* gene in adult worms, without affecting its embryonic activity. Intriguingly, they found that *pha-4* mutants did not respond to dietary manipulations, showing a similar median adult lifespan at all tested food concentrations; however, other processes such as food ingestion and feeding behaviour appeared normal. By inference, therefore, PHA-4 function in adult worms is to respond to dietary changes, and to increase survival under conditions of dietary restriction.

The authors also found that the requirement for PHA-4 was very specific. Systematic knockdown of the other 14 forkhead transcription factors expressed in the worm — including DAF-16/FOXO — had little effect on longevity induced by restricting dietary intake. The DAF-16/FOXO transcription factor works in another well-known longevity pathway — that of insulin/IGF signalling, which dramatically influences lifespan in worms, flies and mice[6]. A modest reduction of insulin/IGF signalling activates DAF-16/FOXO, which mediates a twofold extension of worm lifespan. Similarly, inactivation of DAF-16 completely abolishes insulin/IGF-signalling-mediated longevity[6].

Panowski *et al.* found that, by contrast, mutants lacking DAF-16/FOXO still showed a normal response to dietary restriction, indicating that longevity induced by restricted food intake is DAF-16/FOXO independent. Conversely, PHA-4 had little or no effect on longevity induced by insulin/IGF signalling, because with a reduction in this pathway animals lived longer in the presence or absence of PHA-4 function. Thus, PHA-4/FOXA seems to specifically affect dietary-restriction-mediated longevity, whereas DAF-16/FOXO is involved in regulating longevity induced by insulin/IGF signalling. The authors also found that a conserved nuclear factor called SMK-1 is required for longevity in both pathways[1,7].

Other observations by these authors[1] also support a role for a PHA-4-mediated effect of dietary restriction. First, dietary restriction increased the levels of PHA-4 messenger RNA, indicating a cause-and-effect relationship. In addition, dietary restriction triggered the expression of several genes encoding superoxide-dismutase enzymes, which protect animals from oxidative damage — a cause of ageing. The expression of these genes in response to dietary restriction required PHA-4 activity, suggesting that they could be transcriptional targets of PHA-4.

In adult worms, PHA-4 is found in the intestine, gonad and a handful of neurons. Nevertheless, it influences survival of the whole organism, probably by controlling the production of hormones in some of these tissues, which then signal throughout the body. Indeed, mammalian FOXA regulates glucagon[8], a hormone that is released during fasting in higher organisms. Although worms lack a glucagon homologue, they have several hormone-like proteins that could subsume a similar role.

Like PHA-4, SKN-1 also functions early in embryonic development, where it specifies the formation of the intestine and related tissues[9]. Later in life, it helps to protect animals from oxidative stress[10]. This transcription factor is related to NRF2 transcription factors, which perform similar functions in mammals[11]. Mutant worms lacking SKN-1 have a shortened lifespan[10], but a direct role for SKN-1 in

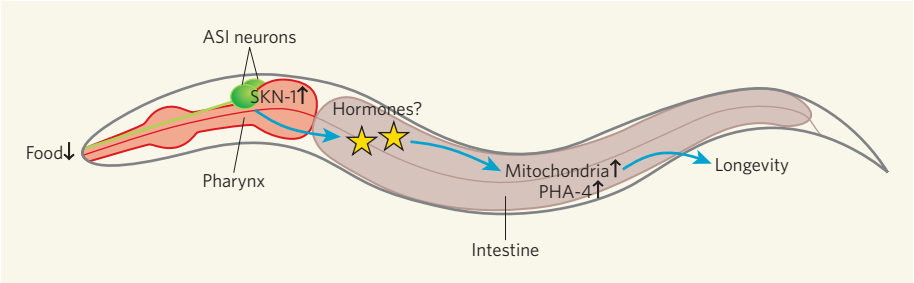

Figure 1 | Dietary restriction and longevity in *C. elegans*. Two studies[1,2] show that, in response to dietary restriction, the activities of SKN-1 and PHA-4 gene-transcription factors increase (black arrows). Neuronal, but not intestinal, SKN-1 mediates longevity in response to reduced dietary intake, where it triggers the release of unidentified hormones (stars) from the pair of ASI neurons to increase mitochondrial activity throughout the body. The PHA-4 transcription factor may also induce hormonal production in the tissues where it is expressed — neurons, intestine and gonad.

mediating dietary restriction was unknown.

Bishop and Guarente (page 545)[2] discovered that a lack of SKN-1 abolishes dietary-restriction-induced longevity over a wide range of food concentrations. Again, the role of SKN-1 in mediating longevity through dietary restriction was specific, because its removal had little effect on lifespan enhanced through a reduction of insulin/IGF signalling. In adult worms, a different form of SKN-1 resides in the intestine from that found in the single pair of neurons known as the ASIs[10]. The authors found that the SKN-1 from the ASI neurons, and not from the intestine, was required for dietary-restriction-induced longevity (Fig. 1), and that restriction of dietary intake promoted increased SKN-1 expression specifically in these two cells. The ASIs are neurosensory cells that integrate cues from the environment and produce various hormones that are relayed to the whole body[12,13]. This indicates that SKN-1-dependent hormonal signals that are released from the ASIs coordinate organism-wide physiological responses to dietary restriction.

Indeed, Bishop and Guarente[2] observed global metabolic changes in response to dietary-restriction-induced activation of *skn-1*, indicative of an organismal response. In particular, restricting dietary intake increased the rate of oxygen consumption — a marker of mitochondrial respiration — in a SKN-1-dependent manner. Mitochondria are the powerhouses of the cell, deriving cellular energy from various metabolites and consuming oxygen in the process. The authors found that, when mitochondrial activity was chemically inhibited, the beneficial effects of dietary restriction on survival were also abolished. Evidently, dietary restriction seems to increase mitochondrial activity, presumably to efficiently extract energy from a limited amount of food. How increased mitochondrial activity might promote longevity is not known. Conceivably, it may trigger mechanisms that protect cells against oxidative stress, or stimulate turnover of damaged cellular components.

Together, these findings[1,2] indicate that dietary restriction activates a highly regulated process, rather than passive metabolic changes. A role for PHA-4 and SKN-1 transcription factors in mediating the effects of dietary restriction on longevity is exciting because, so far, only a handful of molecules have been described that regulate physiological responses to dietary restriction. Moreover, because *pha-4* and *skn-1* genes are evolutionarily conserved, similar mechanisms may hold in higher organisms.

These findings also raise a host of other questions. Although both PHA-4 and SKN-1 are required for dietary-restriction-induced longevity, neither is truly sufficient. Are other factors involved? Must PHA-4 and SKN-1 work together? Moreover, what is the nature of the hormonal pathway that coordinates the effects of dietary restriction? Do the vertebrate counterparts of these transcription factors also have a role in regulating survival? Potentially, the answers to these questions may illuminate the path to increased human health and longevity. ■

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HIGH-TEMPERATURE SUPERCONDUCTIVITY

Local pairs and small surfaces

Stephen R. Julian and Michael R. Norman

Mapping out the strange territory of high-temperature superconductors has proved a challenge. In the latest tour de force, two experiments take big steps forward, in complementary directions, to chart the lie of the land.

More than 20 years after they were first discovered, high-temperature superconductors remain fundamentally baffling. In superconductors, conduction without electrical resistance arises through the pairing of electrons so as to overcome obstacles to current flow. But whereas the better-understood 'conventional' superconductors confine their superconducting behaviour to temperatures within a few degrees of absolute zero, certain metallic oxides of copper conduct without electrical resistance at temperatures up to 150 kelvin. Two papers in this issue[1,2] substantially advance our understanding of these bizarre materials. First, in a beautiful study, Doiron-Leyraud *et al.* (page 565)[1] describe the emergence of the classic signature of a metal, a Fermi surface, in a high-temperature superconductor. Second, Gomes *et al.* (page 569)[2] take the most probing look yet at what happens to the electron pairs at temperatures above the transition from the high-temperature superconducting state (Box 1, overleaf).

Doiron-Leyraud and colleagues' measurements[1] have an echo of the old-fashioned physics of metals; however, the small size of the Fermi surface they observe strongly suggests that entirely new physics is in play.

The Fermi surface is named after the Italian physicist Enrico Fermi, who in 1926 suggested that current-carrying electrons fill up available energy states in a metal rather like water fills a lake. The Fermi surface — a strange, often geometrically beautiful, structure that separates filled states from unfilled states in an abstract energy space known as *k*-space — is the shoreline of this lake. For simple metals, its size and shape depend only on the electron density and the crystal structure of the metal.

In the 1960s, the combination of measurements in high magnetic fields and computer-aided calculations allowed the Fermi surfaces of many metals to be mapped out. It became apparent that the existence of the Fermi surface explains more than just the universal features of metals, such as the dependence of their electrical resistance on temperature. Its detailed