Life(span) in balance: oxygen fuels a sophisticated neural network for lifespan homeostasis in *C. elegans*

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A key finding of modern ageing research is that our limitation in lifespan is more than the result of accumulated organismal decay. Lifespan is regulated by genetically defined chemosensory and endocrine pathways, which integrate signals that reflect the internal and external status of the animal. New findings by Liu and Cai unravel a role for the environmental gases oxygen and carbon dioxide in the regulation of lifespan homeostasis and thus a novel function of oxygen-chemosensory neurons in *C. elegans*.

Which factors define our lifetime? Along the quest for answers, the soil nematode *C. elegans* has become a popular model to address this question, as is demonstrated by the rapidly growing number of journal articles on lifespan regulation solely in *C. elegans*. Importantly, due to evolutionary conservation of the implicated genes, these findings are transferable to higher organisms including humans.

Environmental circumstances such as nutrient availability and temperature directly feed into endocrine mechanisms that regulate lifespan. The importance of chemosensation in these processes has long been understood and efforts were focused on elucidating its various roles affecting longevity. For instance, ablating specific sensory neurons involved in the detection of stress and starvation pheromones causes pronounced effects on lifespan, both positive and negative (Alcedo and Kenyon, 2004). Specifically, functional loss of neuron classes called ASI or ASG promotes lifespan, an effect which is suppressed by ablation of other neuron classes called ASJ and ASK. This lifespan modulation was found to be dependent on hormonal signalling via the insulin receptor homologue DAF-2, which negatively regulates the FOXO transcription factor DAF-16.

The hypoxia-inducible factor 1 (HIF-1) transcriptional pathway presents another well-described mechanism affecting longevity. Although predominantly known for its importance for survival of hypoxic conditions, HIF-1 has gained recognition as a key player in lifespan regulation. Activation of HIF-1 promotes longevity via the classical hypoxic response pathway (Mehta *et al.*, 2009), whilst functional loss of HIF-1 promotes lifespan in a temperature- and DAF-16-dependent manner (Leiser *et al.*, 2011). Generally, DAF-16 proved to play a leading role in lifespan regulation, both dependent and independent of DAF-2. For instance, recent work demonstrated that cold-induced longevity via DAF-16

occurs independent of DAF-2 and is initiated by the activation of the temperature-sensitive TRP family ion channel TRPA-1 in cold-sensitive neurons and the intestine (Xiao *et al.*, 2013).

Figure 1 Negative feed-forward loops establish lifespan homeostasis. Low O₂ concentrations (<8%) increase lifespan. Concurrently, these low O₂ concentrations activate the soluble guanylate cyclases (sGCs) GCY-31 and GCY-33 in BAG neurons, which antagonise this lifespan-promoting effect. High CO₂ concentrations (more than atmospheric 0.038%) also increase lifespan. CO₂-dependent BAG activation occurs in a GCY-9-dependent manner, a mechanism that counteracts the lifespan-promoting effect. High O₂ concentrations (>12%) shorten lifespan. Increases in O₂ concentrations are perceived by URX neurons and depend on the sGCs GCY-35 and GCY-36 in URX. O₂ binding on these sGCs antagonises the lifespan-inhibiting effect of high O₂. Taken together, BAG and URX neurons serve to integrate information on environmental gas concentrations in order to maintain a lifespan that is sensitive yet stable to changing environmental conditions.

Around the same time as the insulin and HIF-1 pathways were deciphered, the molecular underpinnings of dietary restriction, a well-defined cross-species mechanism promoting longevity were identified. The initial step in dietary restriction-induced longevity is the upregulation of the transcription factor SKN-1 in ASI neurons, which subsequently signal to increase metabolic activity in other tissues (Bishop and Guarente, 2007).

Collectively, these recent findings demonstrate the requirement for the nervous system to integrate signals that eventually confer longevity. Asking which other environmental factors might be involved in regulating lifespan, Liu and Cai (2013) turned their attention towards a ubiquitous prerequisite of life: oxygen. Though the concentration of atmospheric O₂ is 21%, concentrations ranging from 0–21% occur in nature. Special emphasis has to be given to soil where O₂ concentrations can differ substantially within a small area. Accordingly, the soil nematode *C. elegans* has evolved sophisticated sensory systems to detect small changes in ambient O₂ concentrations. Feeding on O₂-consuming bacterial organisms, *C. elegans* shows preference for O₂ concentrations in an intermediate range (Gray *et al.*, 2004), which indicate the presence of bacteria. A look back into the year 1992 reveals that one of the first studies engaged with research on lifespan regulation in *C. elegans* already suggested a leading role for O₂, reporting a decrease in lifespan to occur under conditions of high O₂ concentrations (Honda and Matsuo, 1992). Liu and Cai (2013) started over with a simple yet illuminating assay: assuming a normal lifespan at intermediate 12% O₂, wild-type worms lived longer when raised at 4% O₂ and had a shortened lifespan when raised at 21% O₂. O₂ sensation, as shown previously (Zimmer *et al.*, 2009), requires the opposing actions of BAG and URX sensory neurons. BAG neurons sense decreases in O₂ concentrations, while URX neurons sense increases. The interaction of these neurons results in locomotion responses allowing the worm to find and settle at places of preferred O₂ concentrations. The O₂-sensing abilities of BAG and URX neurons are attributed to specific oxygen-binding soluble guanylate cyclases (sGCs) residing within those neuron classes, namely GCY-31 and GCY-33 in BAG neurons, and GCY-35 and GCY-36 in URX neurons (Zimmer *et al.*, 2009). Liu and Cai (2013) performed genetic as well as laser cell ablations of either BAG, URX, or both neuron classes and confirmed these neurons as mediators of O₂-dependent lifespan effects. These experiments additionally revealed the intriguing finding of counterbalanced effects of BAG and URX neurons on O₂-mediated lifespan effects: ablation of low O₂-sensing BAG neurons increased lifespan compared with ablation control, indicating that BAG neurons antagonise the lifespan-promoting effects of low O₂ concentrations, while URX ablation decreased lifespan, suggesting that high O₂-sensing URX neurons antagonise the lifespan-decreasing

effect of high O₂ concentrations. Using *C. elegans* mutants deficient in the respective guanylate cyclases, they showed that the lifespan effects of BAG and URX neurons are dependent on their respective sGCs. In summary, Liu and Cai (2013) establish the existence of a counterbalanced neural network that maintains lifespan balance (see Figure 1).

Being incapable of regulating its internal milieu, *C. elegans* is dependent on O₂ diffusion from the outside through the tissue (Van Voorhies and Ward, 2000). The functional antagonism of BAG and URX neurons shown by Liu and Cai (2013) puts forward the idea of feed-forward loops aimed at keeping lifespan in a narrow range. As a result, this mechanism allows lifespan regulation independent of the ever-changing environment.

Having identified the O₂-dependent lifespan regulation by BAG and URX neurons, Liu and Cai (2013) addressed the signalling pathway downstream of BAG and URX sensory neurons. Performing epistasis experiments, the authors demonstrated that O₂-mediated lifespan modulation occurs independent of any lifespan-regulating pathway known to date, namely insulin and germline signalling as well as sensory perception and dietary restriction. The finding that *C. elegans* has an additional O₂-dependent mechanism besides the HIF-1 pathway is unexpected yet compelling, underlining the importance of environmental signals for *C. elegans* lifespan regulation. Conclusively, O₂ fuels a yet unidentified mechanism by which *C. elegans* maintains lifespan homeostasis. It will be an exciting project for future research to identify the downstream signalling mechanism that mediates O₂-dependent lifespan effects.

On top of that, Liu and Cai (2013) paid tribute to the fact that BAG neurons have been reported to sense carbon dioxide, which involves the transmembrane guanylate cyclase GCY-9 (Hallem *et al.*, 2010), opening the possibility of CO₂ as a further regulator of lifespan. Indeed, raising wild-type worms at 5% CO₂ significantly increased their lifespan compared with worms grown at atmospheric CO₂ concentrations. Furthermore, this effect is abolished in *gcy-9* mutant worms, indicating that CO₂-mediated lifespan effects are dependent on GCY-9 (Figure 1).

In conclusion, this study adds a new chapter to the age-old story of lifespan regulation. The thorough experiments by Liu and Cai (2013) demonstrated that lifespan homeostasis can be achieved by the action of a counterbalanced network of BAG and URX neurons, which is fuelled by the differential effect of environmental O₂ concentrations on these neuron types. This network receives additional modulatory input from environmental CO₂. All in all, this study advances the idea of a network that works to maintain lifespan balance in the face of frequently changing environmental conditions.

Conflict of interest

The authors declare that they have no conflict of interest.

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