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Gut feelings: microRNAs tune protein quality control and ageing to odours

A new study in *C. elegans* identifies a microRNA-dependent mechanism that enables olfactory neurons to rapidly regulate protein degradation in the intestine and therefore organismal ageing.

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One of the important metabolic decisions that an animal must make is how to best match food intake to metabolic rates, catabolism, and cellular quality control. As an animal develops, reproduces, and ages, these metabolic requirements might change. How can an animal take in information about the quality of the food that it is eating and translate that into the correct metabolic choices? In this issue of *Nature Metabolism*, Finger et al.[1] describe one such mechanism that ties odour sensation of different food cues to the regulation of protein-degradation pathways. Unexpectedly, this signalling process includes the activity of a small-RNA-regulated neuronal signalling network that communicates with the major proteolytic tissue in *Caenorhabditis elegans*, the intestine.

Protein homeostasis is a critical factor in cellular quality maintenance with age. Cells rely on a set of proteostasis (protein quality control) mechanisms to prevent the accumulation of dysfunctional, damaged, and aggregated proteins. These mechanisms include processes that decrease mistranslation, misfolding, aggregation, and incorrect trafficking. The unfolded protein response in the endoplasmic reticulum is an example of such proteostasis. The ability to mark damaged proteins with a ubiquitin tag and then degrade them through the proteasome—the ubiquitin–proteasome system—enables the clearance of these damaged proteins. The ubiquitin–proteasome system is critical for maintenance of cellular quality, but this process, and proteostasis activity in general, degrades with age and is associated with diverse age-related diseases[2,3]. Therefore, identifying upstream regulators that increase the proteostasis network's capacity may improve therapeutic intervention strategies.

The current study by Finger et al., from the Hoppe group, implicates a specific miRNA, *mir-71*, in the regulation of proteostasis. miRNAs are 21- to 23-nucleotide non-coding RNAs that post-transcriptionally downregulate their targets, through either translational repression or messenger RNA degradation. miRNAs are known to change in expression with age, and a few have been shown to regulate longevity and stress resistance, particularly in *C. elegans*[4,5]. miRNAs, such as miR-328 and miR-25, have been implicated in the regulation of proteostasis through their direct targeting of regulatory factors or components of the endoplasmic reticulum machinery[6,7].

Finger et al. screened miRNA mutants to search for new candidate regulators of proteostasis by using a clever reporter screen that labels worm guts green if the miRNA in question is required for proteostasis. Loss of a critical regulatory miRNA would prevent normal ubiquitin-dependent degradation in the intestine, thus causing accumulation of fluorescent protein. *mir-71* emerged from the screen as a strong candidate proteostasis regulator.

Surprisingly, unlike miR-328 and miR-25, *miR-71* did not appear to function directly in the tissue where the phenotype was observed. Instead, the authors uncovered a cell-non-autonomous pathway: expression of *mir-71* in neurons, rather than in the intestine, rescued the defective proteostasis of the mutants, thus immediately indicating that the activity was cell non-autonomous.

mir-71 is a particularly interesting candidate, because previous work had already revealed that this miRNA regulates the Toll-like-receptor adaptor protein TIR-1, both of which are expressed in and regulate the activity of a food-odour-sensing neuron called AWC[8]. The data from Finger et al. support a model in which *mir-71* downregulates *tir-1* in the AWC sensory neurons, which then signal (indirectly) to the intestine and regulate proteostasis.

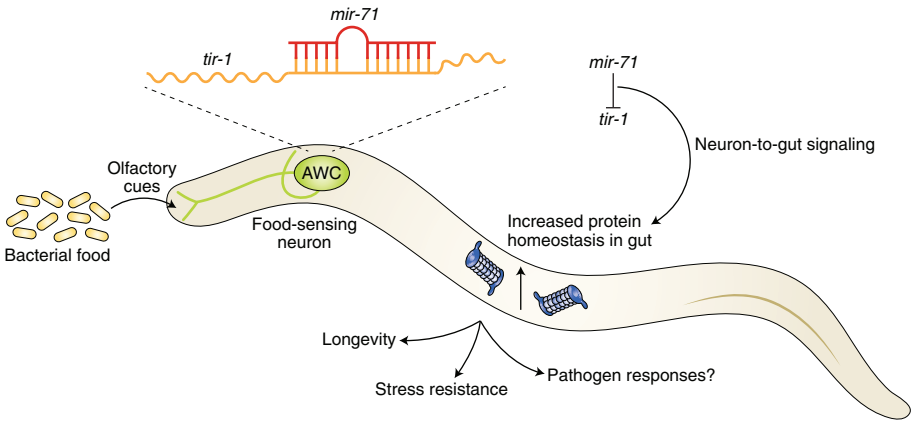

Fig. 1 | Food odour triggers the miRNA *mir-71* in olfactory neurons to regulate gut protein homeostasis and ageing. Finger et al.[1] used the nematode *C. elegans* to show that odours released from bacterial food sources trigger molecular changes in AWC sensory neurons. In response to odour, the *mir-71* miRNA binds and decreases the abundance of *tir-1* mRNA. Loss of *tir-1* in the AWC results in inter-tissue signalling that promotes ubiquitin-dependent protein turnover in the intestine. This increased proteostasis enhances longevity and heat-stress resistance, and may possibly influence other organismal responses such as pathogen resistance.

Finger et al. went on to show that this neuronal *mir-71–tir-1* regulatory network in the food-sensing AWC neurons coordinates food perception and proteostasis, signalling to downstream neurons through two neuropeptides (NLP-9 and NLP-14) whose cellular origins and destinations in response to *mir-71–tir-1* are unknown. Using inedible food, the authors showed that these effects are mediated directly through bacterial odour. Together, these data describe a signalling pathway from odorant-mediated miRNA regulation in AWC neurons to the regulation of proteostasis in the intestine (Fig. 1).

This work is an elegant demonstration of how *C. elegans* can be used to track a signal all the way from neuronal activity (odour sensation) to a systemic response (protein turnover and subsequent longevity). The group not only tracked the signalling from neurons to the intestine but also provided evidence that may hint at the biological utility of the process, given that the AWC neurons are the major food-sensing neurons in *C. elegans*. But why would a worm benefit from sensory neurons that communicate information about food to the protein-quality-maintenance mechanisms in the gut? Sensory-neuron activity has been shown to modulate lifespan in worms[9,10], flies[11] and mice[12]. In fact, different foods (which for worms means different types of bacteria) affect lifespan, and this effect depends on sensory neurons and receptors[13]. The authors previously found that bacterial sources of varying nutrition influence proteostasis activity[14]. The current study demonstrates that varying bacterial sources modifies protein degradation according to the food source, as if different characteristics of the food, such as nutrient composition (carbohydrate, fat, and protein), require precisely tailored levels of proteostasis activity. This distinction between food sources was lost in *mir-71* mutants, thus indicating that food differences in gut proteostasis are mediated by this miRNA–neuron signalling pathway. An intriguing question to be studied in future work is whether, in addition to the non-pathogenic food sources studied here, the neuronal *mir-71–tir-1* system might similarly be responsible for coordinating gut immune responses to pathogenic bacteria, because both *tir-1* and proteostasis maintenance are involved in responses to various bacterial infections[15].

Although such findings might easily be chalked up to being a weird worm event, the observations that TIR-1 has a mammalian homolog (SARM1) that is expressed in mammalian brains and that sensory-neuron activity regulates lifespan in mice[12] suggest that an orthologous pathway may exist in mammals. Importantly, though, whether TIR-1–SARM1 activity in mammalian neurons signals to peripheral tissues and regulates proteostasis activity non-autonomously, as well as whether proteostasis is 'tuned' to nutrient intake, remains to be seen. Similarly, although miRNAs do affect a host of functions in mammals, whether a similar mode of regulation might function outside of invertebrates can now be investigated.

A worm's natural environment is replete with bacteria of varying nutritional content and pathogenicity. Being able to rapidly fine-tune protein homeostasis in the gut is likely to provide metabolic and survival advantages in a constantly changing environment. The ability of miRNAs to reversibly repress mRNA targets, offering the possibility of reactivation, may provide the temporal responsiveness required to rapidly alter proteostasis as food sources (and their smells) change. The odour-responsive *mir-71* regulatory network identified by Finger et al. appears to provide a way for worms to rapidly change their gut metabolism just by smelling food. ❐

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References

1. Finger, F. et al. *Nat. Metab.* https://doi.org/10.1038/s42255-019-0033-z (2019).
2. Ben-Zvi, A., Miller, E. A. & Morimoto, R. I. *Proc. Natl Acad. Sci. USA* **106**, 14914–14919 (2009).
3. Powers, E. T., Morimoto, R. I., Dillin, A., Kelly, J. W. & Balch, W. E. *Annu. Rev. Biochem.* **78**, 959–991 (2009).
4. de Lencastre, A. et al. *Curr. Biol.* **20**, 2159–2168 (2010).
5. Ibáñez-Ventoso, C. et al. *Aging Cell* **5**, 235–246 (2006).
6. Wahlquist, C. et al. *Nature* **508**, 531–535 (2014).
7. Li, C. et al. *Int. J. Cardiol.* **173**, 268–276 (2014).
8. Hsieh, Y.-W., Chang, C. & Chuang, C.-F. *PLoS Genet.* **8**, e1002864 (2012).
9. Apfeld, J. & Kenyon, C. *Nature* **402**, 804–809 (1999).
10. Alcedo, J. & Kenyon, C. *Neuron* **41**, 45–55 (2004).
11. Libert, S. et al. *Science* **315**, 1133–1137 (2007).
12. Riera, C. E. et al. *Cell* **157**, 1023–1036 (2014).
13. Maier, W., Adilov, B., Regenass, M. & Alcedo, J. *PLoS Biol.* **8**, e1000376 (2010).
14. Segref, A., Torres, S. & Hoppe, T. *Genetics* **187**, 1235–1240 (2011).
15. Liberati, N. T. et al. *Proc. Natl Acad. Sci. USA* **101**, 6593–6598 (2004).

Competing interests

The authors declare no competing interests.