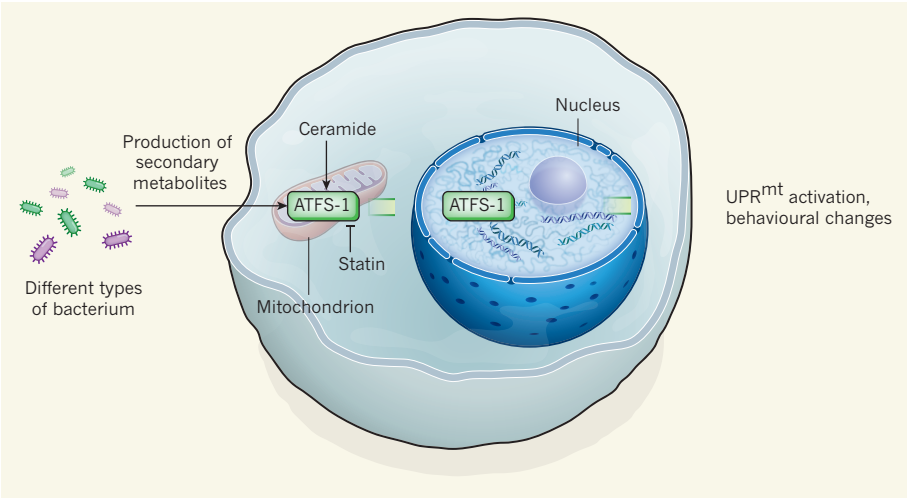

Figure 1 | Cellular and bacterial metabolites influence mitochondrial behaviour. When cellular mitochondria sense stressful changes in their environment, they activate a protective program known as the mitochondrial unfolded protein response (UPR^{mt}). This occurs owing to movement of the transcription factor ATFS-1 from the mitochondrion to the nucleus, where it activates UPR^{mt} genes, causing changes in cellular behaviour. Liu *et al.*[1] report that metabolic products secreted from bacterial cells can induce the UPR^{mt}. The authors find that the same response can be brought about by intracellular synthesis of metabolites such as ceramide or products of the mevalonate pathway, which is inhibited by statin drugs.

genome-wide screening, the authors identified 45 genes that are needed for the mitochondrial stress response. In this analysis, they found two metabolic pathways required for activation of the UPR^{mt}.

The first, the sphingolipid biosynthesis pathway, is responsible for production of ceramide, a waxy lipid molecule typically found in the cell membrane after being synthesized in another organelle, the endoplasmic reticulum (ER). Ceramide plays a part in multiple physiological processes, including mitochondrial degradation[7] and the cell-death program apoptosis[8]. Although the authors report that ceramide synthesis is required for UPR^{mt} induction, a loss of ceramide synthesis has also been linked to increased longevity in several organisms[9–11], suggesting a complex role for this molecule in health.

Disruption of a second metabolic pathway, the mevalonate pathway, also blocks activation of the UPR^{mt}. This pathway is required for the synthesis of cholesterol in most multicellular animals, but not in *C. elegans*[12], indicating that alternative metabolic outputs of this pathway (rather than cholesterol synthesis) are required for the mitochondrial stress response in this worm.

The mevalonate pathway is inhibited by statins, drugs that are used in humans to lower cholesterol. Previous work has demonstrated that statins have adverse effects on longevity in *C. elegans*, affecting the function of the ER and inducing a robust ER stress response[13], which acts to protect the ER in the same way as the UPR^{mt} protects mitochondria. Likewise, Liu and co-workers demonstrated that statins affect mitochondrial health. However, in contrast to what is seen in the ER, they found that after treatment with statins the worms could no longer respond to mitochondrial stress. In agreement with this observation, earlier data showed that forcing ATFS-1 to enter the nucleus protects worms from the harmful effects of statins[14], suggesting that a breakdown in mitochondrial stress sensing is responsible for the harmful effects of statins in *C. elegans*. This may have consequences for our understanding of the side effects of statins in humans.

As with statins, Liu *et al.* found that forcing ATFS-1 to move to the nucleus was sufficient to induce the UPR^{mt} when the sphingolipid biosynthesis pathway was blocked. Clearly, the typical regulation of ATFS-1 is broken after disruption of these two metabolic pathways. But what exactly prevents ATFS-1 from functioning properly?

The authors' data suggest that reducing mitochondrial import of ATFS-1 may not be sufficient to ensure its transportation into the nucleus. Alternatively, mitochondrial import and degradation of ATFS-1 may be directly controlled by metabolite changes in the cell. A closer look at the effect of these metabolites on ATFS-1 import and stability will offer a better understanding of how they affect the function of the UPR^{mt}. Moreover, these results suggest an effect of UPR^{mt} activation, and potentially of ATFS-1, on *C. elegans* behaviour in response to food sources. How this plays into the general sensing of food availability — for instance, through control of the nervous system[15] — is not yet known.

The extent to which this is a general phenomenon or one specific to these particular metabolites also remains unclear. The authors find that a remarkably high percentage of bacterial species in a large panel can induce the UPR^{mt} in *C. elegans* in the absence of other stressors. By contrast, they find that some classes of microbe are capable of blocking UPR^{mt} activation even during stress. The authors leave the mechanism behind these varying effects open, but the overarching message of this study is clear: different metabolites produced in these differing conditions are most likely to be responsible.

Mitochondria are ancient relics of a purely single-celled world. It is possible that the systems that protect mitochondria were the same as those used to protect colonies of bacteria from their invading neighbours. Perhaps bacterial metabolites have retained the ability to communicate with their long-lost relative, the mitochondrion, which in turn has gained the ability to communicate with its host to alter such complex processes as behaviour. Human physiology also relies on complex interactions with thousands of species of bacterium. It is possible that our own mitochondria will sense and respond to the secondary metabolites produced by these species, and possibly change the behaviour of our cells. ■

Suzanne Wolff *and* **Andrew Dillin** *are in the Department of Molecular and Cell Biology and the Howard Hughes Medical Institute, University of California, Berkeley, Berkeley, California 94720-3200, USA.*
e-mail: dillin@berkeley.edu

1. Liu, Y., Buck, S. S., Breen, P. C. & Ruvkun, G. *Nature* **508,** 406–410 (2014).
2. Zhao, Q. *et al. EMBO J.* **21,** 4411–4419 (2002).
3. Haynes, C. M., Petrova, K., Benedetti, C., Yang, Y. & Ron, D. *Dev. Cell* **13,** 467–480 (2007).
4. Nargund, A. M., Pellegrino, M. W., Fiorese, C. J., Baker, B. M. & Haynes, C. M. *Science* **337,** 587–590 (2012).
5. Virk, B. *et al. BMC Biol.* **10,** 67 (2012).
6. Pang, S. & Curran, S. P. *Cell Metab.* **19,** 221–231 (2014).
7. Sentelle, R. D. *et al. Nature Chem. Biol.* **8,** 831–838 (2012).
8. Stiban, J., Caputo, L. & Colombini, M. *J. Lipid Res.* **49,** 625–634 (2008).
9. D'Mello, N. P. *et al. J. Biol. Chem.* **269,** 15451–15459 (1994).
10. Huang, X., Liu, J. & Dickson, R. C. *PLoS Genet.* **8,** e1002493 (2012).
11. Mosbech, M. B. *et al. PLoS ONE* **8,** e70087 (2013).
12. Kurzchalia, T. V. & Ward, S. *Nature Cell Biol.* **5,** 684–688 (2003).
13. Morck, C. *et al. Proc. Natl Acad. Sci. USA* **106,** 18285–18290 (2009).
14. Rauthan, M., Ranji, P., Pradenas, N. A., Pitot, C. & Pilon, M. *Proc. Natl Acad. Sci. USA* **110,** 5981–5986 (2013).
15. Schwartz, M. W., Woods, S. C., Porte, D. Jr, Seeley, R. J. & Baskin, D. G. *Nature* **404,** 661–671 (2000).

This article was published online on 2 April 2014.

CORRECTION

The News & Views article 'Tuberculosis: Drug discovery goes *au naturel*' by Clifton E. Barry (*Nature* **506,** 436–437; 2014) incorrectly described the pharmaceutical company Lepetit as being French. It is an Italian firm.