AGEING

Beneficial miscommunication

Natural variations in the rate of protein translation in cellular organelles called mitochondria have been found to correlate with lifespan, suggesting a unified mechanism for the effects of metabolic alterations on longevity. SEE ARTICLE P.451

SUZANNE WOLFF & ANDREW DILLIN

Our existence depends on a small interloper that resides within our cells — the persistent and phantom-like presence of a once autonomous organism. More than 2 billion years ago, as one bacterium tried, but failed, to consume another, two cells forged a relationship that eventually resulted in the evolution of one into a subcellular organelle — the mitochondrion — of the other. As time passed, this organelle became a small metabolic factory for its host cell, allowing the host to produce enough energy to differentiate and to evolve into the intricate networks of cells and tissues that form the basis of a complex organism[1]. What happens to the organism when this endosymbiotic relationship is disrupted, and the surprising effects of this disruption on lifespan, are the focus of a study by Houtkooper *et al.*[2] on page 451 of this issue.

Across the ages, the mitochondrion has stubbornly tried to retain its identity. It has held on to its own DNA and replicates independently of the rest of the cell. And it defies the rules of Mendelian inheritance. Hundreds or even thousands of these organelles now exist within each cell, and live in a constant physical flux driven by fusion and fission, whereby separate mitochondria join to form one larger mitochondrion or individual ones suddenly split apart[3].

During this time, however, the mitochondrion has lost much of its autonomy; both its basal composition and the cellular distribution of its DNA have changed[4]. Today, most of the proteins that comprise a mitochondrion are encoded by the cell nucleus, and mitochondrial DNA encodes only 13 proteins — less than 1% of its total protein composition[5,6].

To build a mitochondrion, the nucleus must know which mitochondrial genes are needed, and when. It must also recognize what type of mitochondrion to build, because specific tissues — and perhaps even different subcellular locations — contain mitochondria of markedly different protein composition[7]. The nucleus must be ready to respond to fluctuations in the environment and to initiate mitochondrial biogenesis when metabolic conditions so necessitate. Finally, the cell must be poised to translate these genes into proteins in its cytoplasm, and must have sufficient chaperone proteins to help to fold and translocate the nascent proteins to the mitochondria. Synthesis and maintenance of mitochondria is thus a dazzlingly elaborate process — one that necessarily requires complex communication between the mitochondria and the nucleus to ensure synthesis of the proper ratios of proteins required for mitochondrial construction and function.

It seems impossible that a cell could keep track of all these individual fluctuations. Perhaps not surprisingly, therefore, cells have evolved intricate mechanisms specifically for detecting and responding to stress that affects their mitochondria[8–10]. An imbalance between the production of proteins encoded by the nucleus and those encoded by the mitochondria will quickly initiate defence mechanisms to restore homeostasis. During such events, mitochondria release signals that travel to the nucleus to alter the proliferation of mitochondria by affecting the expression of nuclear-encoded mitochondrial genes. This signal also increases the translation of a network of stress-related proteins designed to protect mitochondria from further damage (Fig. 1).

It is the upregulation of one such defence mechanism, the mitochondrial unfolded protein response (UPR^{mt}), that is the focus of Houtkooper and colleagues' study[2]. The authors discovered that partial loss-of-function of the mitochondrial translational machinery correlated with as much as a 2.5-fold increase in lifespan among dozens of inbred lines of mice originating from a single ancestral mating. Specifically, variation (polymorphism) in a gene encoding a single mitochondrial ribosomal protein (MRP) involved in protein translation, Mrps5, correlated with an increase in lifespan in these lines. A decrease in mitochondrial translation was also sufficient to extend lifespan and to activate

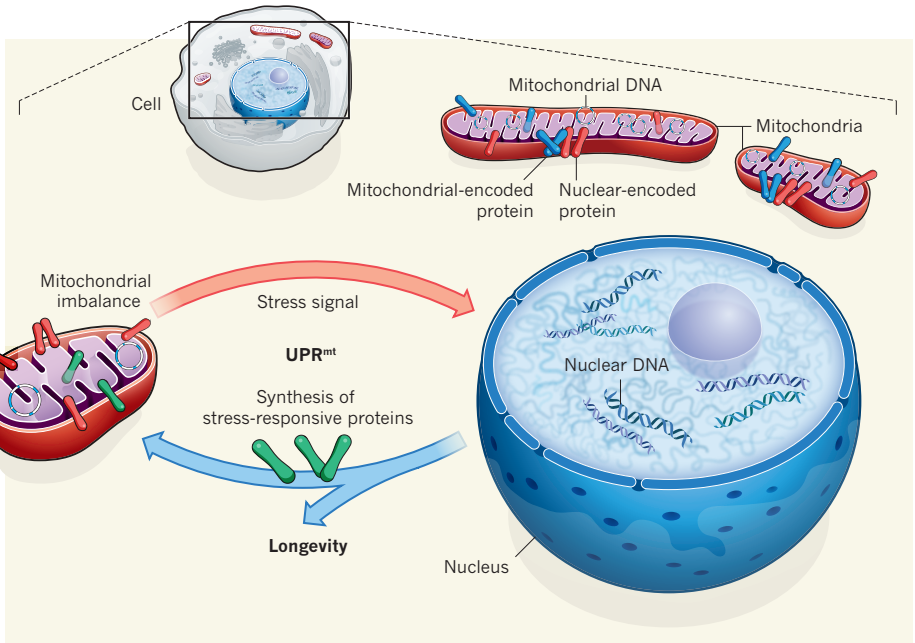

Figure 1 | Consequences of a cellular imbalance. Mitochondria carry a full complement of nuclear-encoded and mitochondrial-encoded proteins. An imbalance between mitochondrial and nuclear proteins triggers the mitochondrial unfolded protein response (UPR^{mt}), whereby mitochondria send a signal to the nucleus to induce the production of stress-related proteins, which restores the mitochondrial balance. Houtkooper *et al.*[2] find that increased UPR^{mt} is correlated with longer lifespan in mice and nematode worms.

the UPR^{mt} in the nematode *Caenorhabditis elegans* in a dose-dependent manner.

The authors hypothesized that a deficiency in the function of MRPs might cause an imbalance in the relative levels of mitochondrial- and nuclear-encoded components of the electron transport chain, the mitochondrion's energy factory. This imbalance may secondarily activate the UPR^{mt}. Importantly, this effect seemed reciprocal: addition of rapamycin or resveratrol (pharmacological agents associated with attenuated cytoplasmic, rather than mitochondrial, translation, but which alter the metabolic state of the cell through the regulation of mitochondrial biogenesis) was sufficient to both upregulate the UPR^{mt} and extend lifespan.

This work is extremely suggestive, but it is only a start. Mitochondrial dysfunction has proved far from beneficial in most known contexts: in humans, mutations in mitochondrial genes cause a large number of extremely debilitating and life-shortening diseases[11]. And, until now, mutations in mitochondrial genes have not been associated with increased health or longevity in mammals. Therefore, the association of a natural variation in the function of MRPs with increased lifespan seems extraordinary.

The regulation of mitochondrial function and the synthesis of its proteins are necessarily complicated, however. It will be important to examine how a loss of MRPs affects the overall molar ratio of the different components of the electron transport chain. Whether other changes that affect mitochondrial proliferation affect lifespan with a dependency on the UPR^{mt} should also be tested. Nevertheless, the current paper illustrates the extent to which the balance of communication between the nucleus and mitochondria remains absolutely necessary for a cell to maintain its homeostasis.

After 2 billion years of partnership, then, communication between mitochondria and the nucleus may remain a core determinant of an organism's lifespan. By definition, endosymbiosis involves a balance between the needs of distinctly functioning subparts to provide a greater benefit to the whole. Our cells may be so sensitized to a loss of this equilibrium that a rapid and effective defence becomes necessary. The ageing-research community must continue to search for an understanding of the specific effects of the UPR^{mt} on the factors that cause ageing, and how such a response is disseminated and communicated across extremely complex organisms. We should also further our understanding of methods by which UPR^{mt} induction might alleviate age-onset diseases. ■

Suzanne Wolff *and* **Andrew Dillin** *are in the Department of Molecular and Cell Biology, University of California, Berkeley, Berkeley, California 94720-3370, USA, and at the Howard Hughes Medical Institute.*
e-mail: dillin@berkeley.edu

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DENGUE VIRUS

Two hosts, two structures

Dengue virus has a highly ordered structure when grown in mosquito cells at 28 °C. The finding that the virus expands into a less ordered form at 37 °C indicates that the human immune system does not see it as we previously thought.

FELIX A. REY

Dengue disease is caused by four viruses of the flavivirus genus that are transmitted to humans by infected mosquitoes[1]. Dengue infections impose a formidable burden: about 5.5% of the world's population is infected each year, and one infection in four is symptomatic[2]. But in spite of its impact, no effective antiviral treatment[3], nor a licensed vaccine[4], is available. Writing in *Journal of Virology* and in *Proceedings of the National Academies of Sciences*, respectively, Fibriansah *et al.*[5] and Zhang *et al.*[6] report that dengue virus particles display a different organization of surface glycoproteins when they are at temperatures above 34 °C, as in a human body, than they do at lower temperatures, such as those found in mosquitoes. These results have important implications for understanding how the virus particles are presented to the human immune system, and how to use this knowledge to develop an effective vaccine.

The difficulties in developing an anti-dengue vaccine stem from the interplay of the four related viruses (called viral serotypes) that cause dengue infections. Infection with any one of these viruses induces lifelong immunity against that serotype. Although some of the antibodies elicited during this response are cross-reactive and can neutralize the other serotypes to a degree, they do not mediate long-lasting cross-protection. Moreover, animal experiments show that the cross-reactive antibodies can actually enhance a subsequent infection with another serotype[7], which is thought to contribute to the severe forms of dengue disease seen in humans[8].

In this context, it is clear that only a vaccine that protects against all serotypes simultaneously would be successful. Although one promising candidate — which comprised four vaccines, each targeting one serotype — was shown by a large vaccine trial[7] to be safe and to confer some protection against serotypes 1, 3 and 4, it did not protect against serotype 2 despite eliciting neutralizing antibodies against all four serotypes[9]. These results highlight the importance of understanding the actual mechanisms of virus neutralization by antibodies and the correlation with protection from disease.

The main antigen targeted by neutralizing antibodies against dengue viruses is a glycoprotein called protein E, which exists as protein dimers at the virus surface. This protein is the main player during viral entry to a cell: it is responsible for receptor binding and for inducing fusion of viral and cellular membranes to release the viral RNA into the cytoplasm. Protein E contains a fusion loop that inserts into the membrane of cellular organelles called endosomes; this loop is concealed at the E-dimer interface in the mature virus particle. Receptor binding at the cell surface leads to uptake into the endosome, where the acidic environment triggers E-dimer dissociation and exposure of the fusion loop, which is accompanied by a major structural rearrangement. Antibodies against protein E can therefore block infection by interfering with receptor binding or with this conformational change.

However, the picture is complicated by another viral glycoprotein, prM, which associates with protein E during viral synthesis. PrM is cleaved during viral maturation, but a substantial amount of the protein is still found in dengue virus particles circulating in an infected host, and it elicits antibodies that are non-neutralizing and contribute to antibody-mediated enhancement of the infection[10]. This observation highlights the complexity of devising a vaccine to generate