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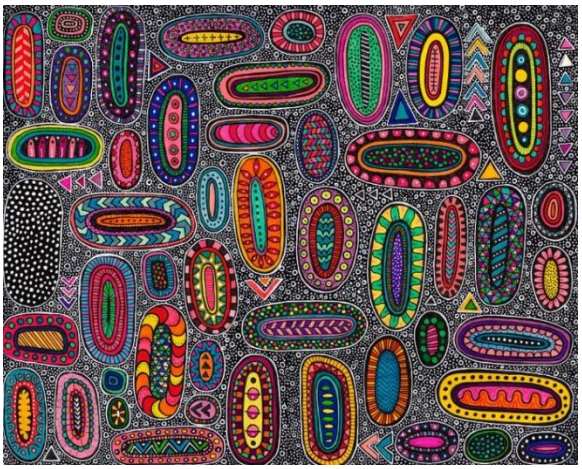
stress

Vivienne Baillie Gerritsen

Stress is a warning signal. It is like setting off a fire alarm or dialling an emergency phone number. The point is to trigger a reaction which, in the best of cases, will set things right again. We have all sensed stress at various times in our lives and, if we are attentive, our bodies react by firing off different signals: muscle stiffness, fatigue, headaches, indigestion… Though we may instinctively think of stress as something which emerges from external sources – such as busy timetables, relationships, disease or starvation – stress can also arise from sources within us. In fact, living organisms recognised the benefits of stress as a warning signal long before the word existed. One example are mitochondria. Mitochondria are small organelles whose major role is to produce biological energy, otherwise known as ATP. Consequently, healthy mitochondria are paramount to life. If, for one reason or another, they become malfunctional, they may choose to trigger off what is known as an 'integrated stress response', or ISR. This indicates to the cell that they need help, and the cell will do its best to fix the situation. A key protein involved in activating mitochondrion-induced ISR is known as 'death ligand signal enhancer', or DELE1.



"microscopic" by Hello Angel

courtesy of the artist

Mitochondria are intriguing organelles, almost bestowed with a mind of their own. They are found in eukaryotic cells where they differ considerably in size and number – from one copy to thousands –, depending on the type of cell, its cycle and the physicochemical environment. They are supported by microtubules, and their rounded shape – from spherical to pellet-like – changes continuously depending on whether they are dividing (mitochondrial fission), fusing (mitochondrial fusion), or indeed dying (mitophagy). Characteristically, they have two membranes, an outer membrane and an inner membrane – both structurally and chemically similar to a cell's plasma membrane – which are separated by an intermembrane space. As the inner membrane has a greater surface than its outer counterpart, it looks as though it has been squeezed into a space too tight, which lends it this distinctive zig-zagged aspect, like a long neatly-packed sausage.

A surprising fact: mitochondria carry their own DNA. The vertebrate mitochondrial genome is invariably circular and stored within the inner membrane, known as the matrix. Unlike a cell's nucleus, mitochondria are usually equipped with several copies of their own DNA, on which are found a few of the genes for proteins required for ATP synthesis as well as the rRNA and tRNAs required for synthesizing proteins. Other proteins needed by mitochondria are imported from the cell's cytosol – such as DELE1, the protein involved in dealing with mitochondrial stress.

Though a mitochondrion's most distinctive job is to produce biological energy (ATP) by a pathway known as cellular respiration, it is also involved in many other metabolic pathways. Among them: programmed cell death, the regulation of cellular metabolism, steroid synthesis and hormonal signalling. Mitochondria were first observed in the

1840s and established as cell organelles – or bioblasts – *per se* in the 1890s. In 1898, they were termed mitochondria, from the Greek *mitos*, meaning 'thread', and *chondrion*, 'granule', which is what they look like under the microscope. The respiratory chain –the seat of ATP production, to cut a long story short – was discovered in the 1920s, but it took another 30 years or so before scientists realised that mitochondria, themselves, were the actual orchestrators of ATP production.

Mitochondrial fusion and fission are frequently an answer to various forms of stress. A damaged mitochondrion can fuse to a healthy one, thus mingling their contents, diluting the damage and replacing it by healthy components. Fission, on the other hand, can be used as a means of disposing of a mitochondrion's damaged elements which are transferred to one extremity, which then buds off. Each of these reactions arise from sending out a stress warning signal, or integrated response signal (IRS), which – in the best of cases – will lead to the restoration of cellular homeostasis. DELE1 is intimately involved in this process.

When a mitochondrion senses stress, DELE1 binds to its inner membrane where it is cleaved into a shorter active form: DELE1s. This shorter form is composed mainly of tetratricopeptide repeats (TPRs). These are structural motifs – typically bunches of alpha-helices – which form scaffolds that mediate protein-protein interactions. The active form of DELE1 is able to exit the mitochondrion and accumulates in the cell's cytosol where it binds – via its TPR domains – to an enzyme known as HRI. HRI is the first component of a pathway which ultimately leads to an integrated response signal. In this light, DELE1 can be seen as a messenger capable of relaying a stress signal from the mitochondrion to the cell.

Mitochondrion dynamics is a fascinating paragraph of cell biology, as is the origin of mitochondria. The most widely accepted hypothesis today is known as the endosymbiotic hypothesis. This hypothesis suggests that mitochondria were once prokaryotic cells, such as bacteria, with metabolic pathways – like cellular respiration – which eukaryotic cells then lacked. By becoming endosymbionts, these prokaryotic cells will have offered their hosts the ability to produce their own energy, which would have been an undeniable evolutionary advantage. Such a hypothesis is supported by several facts, one being that bacterial genomes are also circular. In the past years, ageing and age-associated diseases have been linked to mitochondria – or, perhaps more specifically, to the ability cells still have of reacting to mitochondrion damage. Understanding the intricacies of the ISR pathway could pave the way to therapeutic strategies – not to postpone ageing, but to subdue age-associated diseases.

Cross-references to UniProt

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