CELL BIOLOGY

Ageing theories unified

Ageing is a complex process involving defects in various cellular components. The latest evidence suggests a unifying mechanism for cellular ageing that is relevant to the development of common age-related diseases. SEE ARTICLE P.359

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The effects of ageing are myriad and insidious, leading to progressive multi-organ deterioration. Prominent theories regarding the 'wear and tear' aspects of ageing implicate events in two cellular organelles — the nucleus and the mitochondrion. The connection between these seemingly distinct sets of processes, however, has remained a mystery. An intriguing study by Sahin *et al.*[1] (page 359 of this issue) unveils a potentially unifying mechanism for cellular ageing*.

With age, chromosomes become increasingly damaged[2]. Normally, telomeres — cap-like nucleoproteins at the tips of chromosomes — prevent such damage. When the protective function of telomeres fails, a standard cellular response is triggered that activates the DNA-repair machinery. This response, which involves the protein p53, halts DNA replication and other cellular proliferative processes. If repair fails, the cell may undergo apoptotic cell death. The telomere theory of ageing holds that progressive loss of telomere function triggers chronic activation of p53, which in turn stops cellular proliferation and triggers cell death — an effect that is especially deleterious for cells that have rapid turnover rates, such as blood cells[3].

Mitochondria are the cell's chief energy-producing organelles. A cell can contain hundreds of mitochondria, the DNA of which encodes a subset of mitochondrial RNA and proteins. The mitochondrial theory of ageing proposes that mutations progressively accumulate within the mitochondrial DNA, leading to a cellular 'power failure'[4,5]. The consequences are predicted to be particularly dire for non-proliferative cells in organs that have a minimal capacity to regenerate (quiescent tissues), such as the heart and brain. Recent studies[6] have also suggested that the activity of master regulators of mitochondrial function and number diminishes with ageing, further contributing to mitochondrial deficiency.

Sahin *et al.*[1] unveil a fascinating connection between the nuclear and mitochondrial ageing processes. Previous work[7] has shown that mice genetically engineered to develop progressive telomere dysfunction exhibit many features of ageing that are relevant to proliferative cells. Sahin and colleagues report that, in addition to the expected nucleus-related features of ageing, these mice develop mitochondrial dysfunction as a result of the reduced activity of master regulators of mitochondrial function — the proteins PGC-1α and PGC-1β (ref. 8). The animals also display many features of mitochondrial ageing, such as heart failure and liver dysfunction. This evidence is pertinent, as deactivation of PGC-1 factors has been strongly suspected[9] of contributing to mitochondrial ageing in quiescent tissues.

So how does telomere abnormality in the nucleus deactivate PGC-1 proteins in the mitochondria? It seems that activation of p53 by telomere dysfunction[10] provides the link. Sahin *et al.* find that p53 activation results in the direct suppression of *PGC-1* genes in telomere-deficient mice. What's more, reducing p53 levels in these animals reverses PGC-1 suppression associated with telomere deficiency. Low p53 levels also reduce cardiac dysfunction in a metabolic form of cardiomyopathy and enhance the metabolic capacity of the liver. These fascinating results suggest a unifying mechanism whereby ageing-related changes in the nucleus trigger mitochondrial dysfunction that is relevant not just to proliferating tissues, but also to quiescent organs such as the heart (Fig. 1). As with all provocative discoveries, however, a number of questions arise.

For instance, p53 is known to enhance mitochondrial function: in certain cancers, deficiency in this factor has been linked[11] to reduced mitochondrial function. How can this be reconciled with Sahin and co-workers' findings? Could it be that the effects of p53 on mitochondrial function vary according to cell type?

Also, how do these data relate to the mitochondrial model of cellular ageing, which defines mutations in mitochondrial DNA as the primary event? Although the present study does not resolve this chicken-and-egg conundrum, it does not exclude a role for mitochondrial-DNA damage. Loss of PGC-1 function can lead to the generation of toxic reactive oxygen species, which can cause mutations in mitochondrial DNA (Fig. 1).

Furthermore, is the described[1] telomere–mitochondrial response adaptive or maladaptive? At first glance, reduction of mitochondrial function would seem a deleterious response. Nonetheless, dysfunctional mitochondria working overtime may themselves trigger cell injury and death. Does deactivation of PGC-1 factors lead to mitochondrial 'hibernation', which protects the cell from even worse consequences associated with the stress of ageing? This question must be answered if rational proof-of-concept studies are to be developed to find ways of preventing ageing-related diseases such as heart failure,

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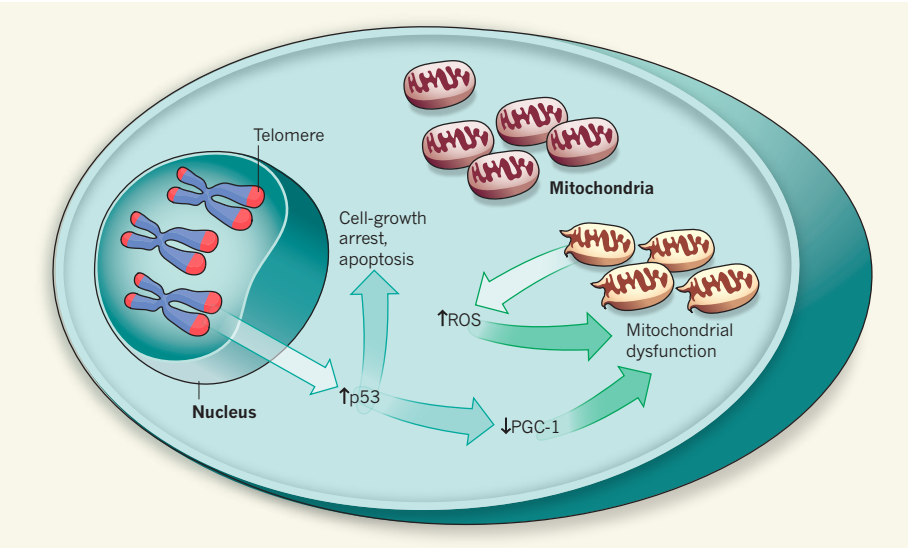

Figure 1 | The nucleus, mitochondria and ageing. With age, telomere damage in the nucleus triggers the activation of p53, which can have different effects. In proliferative cells, p53 halts both cell growth and DNA replication, potentially causing apoptotic cell death. Sahin *et al.*[1] report that p53 also represses the expression of PGC-1 in mitochondria, reducing the function and number of these organelles, and so leading to age-related dysfunction of mitochondrion-rich, quiescent tissues. The mitochondrial derangements driven by loss of PGC-1 activity may independently lower the threshold for the generation of toxic intermediates such as reactive oxygen species (ROS), which damage mitochondrial DNA, thus setting up a vicious cycle of further mitochondrial dysfunction.

insulin resistance and neurodegenerative disorders. ■

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APPLIED PHYSICS

Extreme light-bending power

Metamaterials are best known for their ability to bend light in the opposite direction to that of all materials found in nature. A hidden ability of these man-made materials has now been discovered. SEE LETTER P.369

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You've probably noticed that, if you look at it from the side, a straw in a glass of water seems to bend. This is because light bends and slows down when it travels from air into water or other substances. How much the light bends depends on the type of material through which it travels or, more specifically, on the material's refractive index. Ideally, with a view to applications, we would want unlimited power to control the refractive index. A computer-chip maker, for example, would be thrilled to have a lens of huge refractive index in their lithographic machine, because such a lens would allow chips to be made that are much smaller and perform better than those currently available. But nature cannot always supply our ideals: naturally occurring materials have only a limited range of optical refractive indices, typically between 1 and 3. However, on page 369 of this issue, Choi and colleagues[1] bring us good news: they have found a way to create metamaterials with an unnaturally high refractive index.

During the past decade, metamaterials[2] have generated great enthusiasm among scientists and engineers. These artificially engineered composite materials gain their unique properties, which are not attainable with naturally occurring materials, from their physical structure rather than their chemical composition. The very ability of metamaterials to reach beyond nature's limitations is not only scientifically exciting, but also technologically important: scientists have achieved intriguing physical phenomena and properties in these composite materials that their parent materials do not possess. For example, strong magnetic responses in the terahertz frequency regime have been engineered[3] with a composite material containing split-ring structures made of copper. Such strong magnetic responses do not occur in natural materials.

Metamaterials research has made it possible to create the negative-refractive-index materials first envisioned[4] by the Russian scientist Victor Veselago in 1968. The negative electrical and magnetic responses of these materials cause them to bend light in the 'wrong' direction[5,6]. Consider a fish in a tank of water. If water had a negative refractive index — which it doesn't — the fish would seem to an observer to be swimming upside down above the water. Naturally occurring materials have an index with a small positive value, which fundamentally limits the resolution of optical-imaging lens systems to about half the wavelength of the incident light, and so prevents the tiny details of an object from being imaged. Negative-index materials can overcome this limitation. The 'perfect imaging' capability of metamaterials would open the door to many exciting applications, including ultra-high-resolution medical imaging and data storage, and revolutionary miniaturization of computer chips[7].

At the other end of the metamaterials spectrum would be materials with a very large positive index — beyond that of naturally occurring materials. A lens with such an index would allow more details to pass through an imaging system. Recently, an ultra-high-index metamaterial has been proposed theoretically[8] that uses metallic (conducting) structures embedded in a dielectric (insulating) host. However, its experimental implementation has been impeded by its complicated three-dimensional geometry. Inspired by this idea, Choi *et al.*[1] stacked centimetre-