SCF expression in osteogenic progenitors to help maintain CLPs, thereby controlling part of the function of the immune system (Fig. 1).

The discovery that mechanosensitive osteogenic progenitors have a role in fighting bacterial infections is exciting. It was known that movement can stimulate the immune system[7], but the advance in Shen and colleagues' work provides one reason why this is the case. If relevant to humans, the work could have direct clinical applications. For example, the pathway uncovered in the current study could be harnessed to develop better therapies to strengthen immune-cell output triggered by movement. A logical next step will be to test whether voluntary running can indeed improve bacterial clearance in mice. Another key question to address will be whether increasing the numbers of Oln$^+$ cells and CLPs in bone marrow would help to provide protection against other disease-causing bacteria, or even viruses, or whether it might also boost vaccination responses.

The authors also found that the number of Oln$^+$ niches, and the number of CLPs, was lower in the bone marrow of 18-month-old mice than in their 2-month-old counterparts. Aged animals are also active[8], so factors other than reduced movement might contribute to this ageing-related decline.

It would be interesting to investigate, for instance, whether the way in which Oln$^+$ niches sense mechanical stimulation changes over time, or whether epigenetic changes (modifications to DNA that can alter gene expression without changing the underlying DNA sequence) in aged Oln$^+$ cells make them less effective in generating signalling molecules such as SCF.

Mechanosensing is well established to play a part in bone physiology, but a crucial role for mechanosignalling has been also described for other cell types — for instance, pancreatic progenitor cells, intestinal stem cells and the endothelial cells that line blood vessels. Although less is known about the niches that support stem cells outside the bone marrow, the vasculature, and so endothelial cells, are prime candidates for forming such niches. It is possible, then, that mechanosensing in niche-forming endothelial cells might contribute to the maintenance of other types of stem and progenitor cell. If so, Shen and colleagues' work could have wide-ranging implications for stem-cell biology.

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Cell biology

Breaks in mitochondrial DNA rig immune response

Nandhitha Uma Naresh & Cole M. Haynes

Damage to DNA in a cellular organelle called the mitochondrion triggers an immune response in the nucleus. Mechanistic insights into this process shed light on how organelles communicate. **See p.477**

Mitochondria are membrane-bound organelles that act as hubs of metabolism and of innate immune signalling in cells. Each mitochondrion contains several copies of the mitochondrial genome (mtDNA), which can be damaged by extrinsic environmental stressors or intrinsic genetic mutations. This can cause degradation of the mtDNA, reducing the total number of mtDNA copies in the organelle and so leading to mitochondrial dysfunction. In addition, healthy mitochondrial function relies heavily on crosstalk between mitochondria and the nucleus[1,2]. Tigano *et al.*[3] uncover a mechanism on page 477 by which cells sense toxic mtDNA damage to initiate an immune response in the nucleus.

Conditions of acute stress, such as viral infection or irradiation, can lead to the activation of pro-death (apoptotic) pathways in the cell. Mitochondria have a key role in these pathways. Pore-forming proteins called BAK and BAX accumulate on the mitochondrial membrane, leading to the release of cell-death factors from the organelle into the cell's cytosolic fluid through a process called mitochondrial herniation[4]. In some instances, cell-death factors are not activated, in which case mitochondrial contents such as DNA and RNA are instead released into the cytosol[4]. The accumulation of cytosolic mtDNA and mtRNA initiates a potent antiviral response[5–7]. But precisely which aspects of mitochondrial dysfunction lead to the extrusion and accumulation of this mitochondrial material has been unclear.

Tigano *et al.* set out to examine one form of stress: cleavage of mtDNA. The group manipulated mammalian cells using 'molecular scissors' constructs called mitochondria-targeted TALENs (mTLNs), which

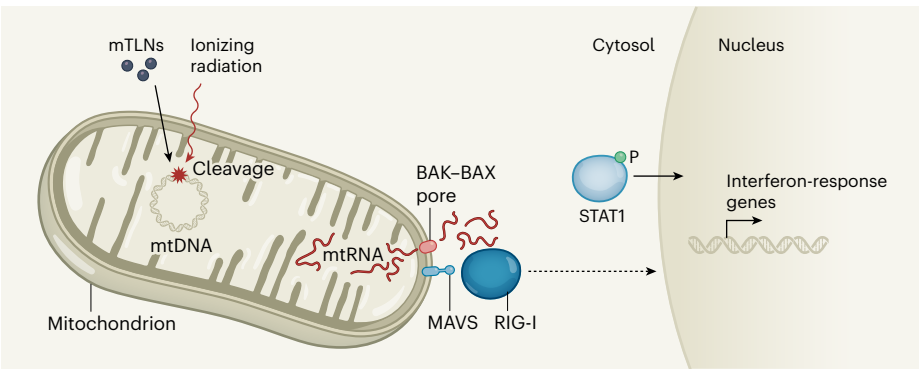

Figure 1 | Communicating damage between organelles. Tigano and colleagues[3] report a mechanism by which damage to DNA in an organelle called the mitochondrion is communicated to the nucleus. The group induced mitochondrial DNA (mtDNA) breaks, either by using 'molecular scissors' constructs called mitochondria-targeted TALENs (mTLNs) or through ionizing radiation. These treatments trigger the release of mtRNA into the cell's cytosol through pores comprising BAK and BAX proteins. Two proteins — the cytosolic RNA sensor RIG-I, acting with its adaptor protein MAVS — sense the mtRNA, triggering signalling pathways that lead to the upregulation of genes involved in an immune response called the interferon response (dashed lines indicate an indirect effect). In addition, the transcription factor STAT1 is phosphorylated (P), and moves to the nucleus, where it might have a role in activating interferon-response genes.

generate double-strand breaks (DSBs) in mtDNA. They used RNA sequencing to analyse changes in gene expression in cells treated with mTLNs, and found increased transcription of nuclear genes involved in the innate immune response; these included interferon-response genes, which are typically involved in combating viral infections. The authors also found that the transcription factor STAT1 was modified by phosphate groups and relocated to the nucleus — a key part of the interferon response[8].

Breaks in mtDNA that occur through other means, such as treatment with toxic, DNA-damaging agents or errors in replication, often lead to compromised organelle function[9]. But Tigano and colleagues found that the mTLN treatment reduced the number of mtDNAs by only around 60%, which did not seem to have an immediate impact on mitochondrial function. The group observed no changes in key indicators of normal mitochondrial function, such as morphology, the gradient of protons (H^+ ions) across the membrane, and the generation of reactive oxygen species. These data indicate that mtDNA cleavage is a key trigger of antiviral responses.

Next, Tigano *et al.* set out to identify the signalling molecules that relay the message of mtDNA instability to the nucleus. Although the mTLN-treated cells had intact mitochondrial function and were not apoptotic, the group showed that BAK–BAX pores did form on the membrane, consistent with mitochondrial herniation. The authors found that mtRNA — but not mtDNA — accumulated in the cytosol of these cells. The mtRNA molecules were detected by an RNA-sensing protein called RIG-I, which is better known as a sensor of viral RNA in the cytosol[10]. Working with its adaptor protein on the mitochondrial outer membrane, dubbed mitochondrial antiviral signalling (MAVS), RIG-I triggers a signalling pathway that activates interferon-response genes in the nucleus[10]. These findings point to a framework by which cells engage mitochondrial signalling molecules in immune-surveillance mechanisms (Fig. 1).

DNA-damaging agents such as radiation, which is used to treat cancer, elicit a systemic immune response that is thought to be driven by DNA damage in the nucleus. Tigano and colleagues found that radiation depleted mtDNA numbers by 40% and elicited the same immune response as mTLNs, suggesting that DSBs occur in mtDNA as well as in nuclear DNA following irradiation. Strikingly, induction of the interferon response during irradiation was nearly completely abrogated in cells lacking mtDNA. This observation indicates that mtDNA damage caused by radiation can be a driver of interferon responses. Of note, the induction of several other innate immune responses still occurred in cells lacking mtDNA, suggesting that depletion of mtDNA specifically impairs the interferon response.

The study highlights an immunostimulatory role for mtRNA. However, questions remain. For instance, mtRNA molecules are highly unstable in nature[11] — how are mtRNAs stabilized so that they accumulate in the cytosol, as was observed in the current study? Another avenue for further investigation is the factors that stimulate the formation of BAK–BAX pores following mtDNA breaks. It would be of broad interest to study whether drugs that inhibit this pore formation can suppress an inflammatory immune response. The discovery of a mechanism by which cells recognize self-RNAs from mitochondria to initiate an immune response also raises the question of whether this pathway might be involved in autoimmune disease. Finally, it would be exciting to explore whether artificially induced mtDNA damage could be used to increase the efficacy of targeted immunotherapies for cancer.

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Artificial intelligence

Argument technology for debating with humans

Chris Reed

A fully autonomous computer system has been developed that can take part in live debates with people. The findings hint at a future in which artificial intelligence can help humans to formulate and make sense of complex arguments. **See p.379**

The study of arguments has an academic pedigree stretching back to the ancient Greeks, and spans disciplines from theoretical philosophy to computational engineering. Developing computer systems that can recognize arguments in natural human language is one of the most demanding challenges in the field of artificial intelligence (AI). On page 379, Slonim *et al.*[1] report an impressive development in this field: Project Debater, an AI system that can engage with humans in debating competitions. The findings showcase how far research in this area has come, and emphasize the importance of robust engineering that combines different components, each of which handles a particular task, in the development of technology that can recognize, generate and critique arguments in debates.

Less than a decade ago, the analysis of human discourse to identify the ways in which evidence is adduced to support conclusions — a process now known as argument mining[2] — was firmly beyond the capabilities of state-of-the-art AI. Since then, a combination of technical advances in AI and increasing maturity in the engineering of argument technology, coupled with intense commercial demand, has led to rapid expansion of the field. More than 50 laboratories worldwide are working on the problem, including teams at all the large software corporations.

One of the reasons for the explosion of work in this area is that direct application of AI systems that can recognize the statistical regularities of language use in large bodies of text has been transformative in many applications of AI (see ref. 3, for example), but has not, on its own, been as successful in argument mining. This is because argument structure is too varied, too complex, too nuanced and often too veiled to be recognized as easily as, say, sentence structure. Slonim *et al.* therefore decided to initiate a grand challenge: to develop a fully autonomous system that can take part in live debates with humans. Project Debater is the culmination of this work.

Project Debater is, first and foremost, a tremendous engineering feat. It brings together new approaches for harvesting and interpreting argumentatively relevant