of older continental crust were deposited[9]. Finally, between 2.5 billion and 2.9 billion years ago, depending on the craton, high-temperature metamorphism — transformation of the minerals and textures of rock under conditions different from those of their original formation — in the lower crust occurred at the same time as the intrusion into the upper crust of granites characterized by high concentrations of heat-producing elements.

This last event is the one modelled by Reimink and Smye: the amalgamation of the Archaean cores of cratons, which resulted in a cool, strong lower crust and an upper crust cemented together by late-Archaean granites. Putting the authors' findings into context with the geological history of cratons, the story that emerges is that the earliest continental masses ensured their own survival by rising above the oceans, shedding the detritus of atmospheric weathering to sedimentary basins and then reincorporating those sediments into the crust (Fig. 1). In essence, this is the first clear evidence for a full circuit of the rock cycle — the continual sequence of transitions in which rock is converted from igneous to sedimentary to metamorphic rock, and back to igneous.

Reimink and Smye's model opens up questions for future discussion. For example, why did the concentrations of heat-producing elements in sedimentary rocks increase in the late Archaean and peak between 2.5 billion and 2.0 billion years ago? Notably, Earth was dynamic during this period: not only were the continents stabilizing, but also the first major increase in the levels of atmospheric oxygen occurred, which would certainly have influenced how rocks were weathered. Among the heat-producing elements, uranium is especially sensitive to atmospheric oxygen levels, and becomes mobile in fluids when it is oxidized. The onset of oxidative rock weathering by the atmosphere would therefore have released uranium to marine sedimentary basins[10].

Moreover, the redistribution of heat-producing elements during melt extraction is controlled by the behaviour of an array of minerals during melting[5]. Further detailed studies of late-Archaean high-temperature metamorphic rocks and their derivative granites are required to understand the details of how heat-producing elements were distributed between these rocks[11].

In the meantime, these findings add considerably to Earth scientists' understanding of continent formation. More broadly, they contribute to an ever increasing, transdisciplinary dialogue that aims to construct a holistic understanding of our planet, thereby revealing how changes at the surface affect the dynamics of deep Earth, and vice versa.

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The author declares no competing interests.
This article was published online on 8 May 2024.

Cell biology

Donated mitochondria help to build blood vessels

Chantell S. Evans

Organelles called mitochondria are transferred to blood-vessel-forming cells by support cells. Unexpectedly, these mitochondria are degraded, kick-starting the production of new ones and boosting vessel formation. **See p.660**

Blood vessels deliver oxygen and nutrients to tissues and remove waste products from them. When these vessels become narrow or blocked, the blood supply and waste clearance are prevented, resulting in what is called ischaemia, which in turn leads to conditions such as coronary heart disease and heart attack[1]. On page 660, Lin *et al*.[2] report an innovative transplantation strategy to aid the repair of ischaemic tissue; it relies on energy-generating organelles called mitochondria being transferred from one cell to another.

Blood vessels are lined with endothelial cells, which are essential for the formation of vessels and the flow of blood. To treat ischaemic conditions, endothelial cells are transplanted near the site of a vessel blockage to promote the formation of blood vessels and restore blood flow to the tissue[3]. However, a considerable limitation of this therapy is that endothelial cells must be co-transplanted with undifferentiated stem cells called mesenchymal stromal cells, which support tissue repair and regeneration[4]. Until now, the mechanism by which stromal cells promote endothelial-cell engraftment was poorly understood.

> **"The mechanisms that stabilize and destabilize nanotubes remain to be established."**

Lin and colleagues reveal that stromal cells transfer mitochondria to endothelial cells. Unexpectedly, these mitochondria are degraded after transfer, prompting endothelial cells to produce new mitochondria of their own. The authors show that artificially transplanting mitochondria into endothelial cells to mimic this natural transfer can stimulate blood-vessel formation by transplanted endothelial cells, paving the way for a treatment for ischaemic disease that requires only one cell type to be transplanted (Fig. 1).

First, Lin *et al*. transplanted human endothelial cells beneath the skin of mice in the presence or absence of supporting stromal cells, and confirmed that only co-transplanted grafts had viable endothelial cells that formed functional blood vessels. In the past decade, stromal cells have been shown to naturally transfer mitochondria to other cell types, and mitochondrial transfer has been shown to promote the regeneration of tissue that has been damaged by ischaemia[5]. To investigate whether this is how stromal cells enable successful endothelial-cell engraftment, the authors labelled mitochondria in stromal cells with a fluorescent protein called DsRed.

The authors observed DsRed-labelled mitochondria in long protrusions, called nanotubes, that extended from stromal cells and made direct contact with endothelial cells. After 24 hours, DsRed-labelled mitochondria could be seen inside the endothelial cells that lined new blood vessels. However, the mitochondrial transfer was surprisingly temporary:

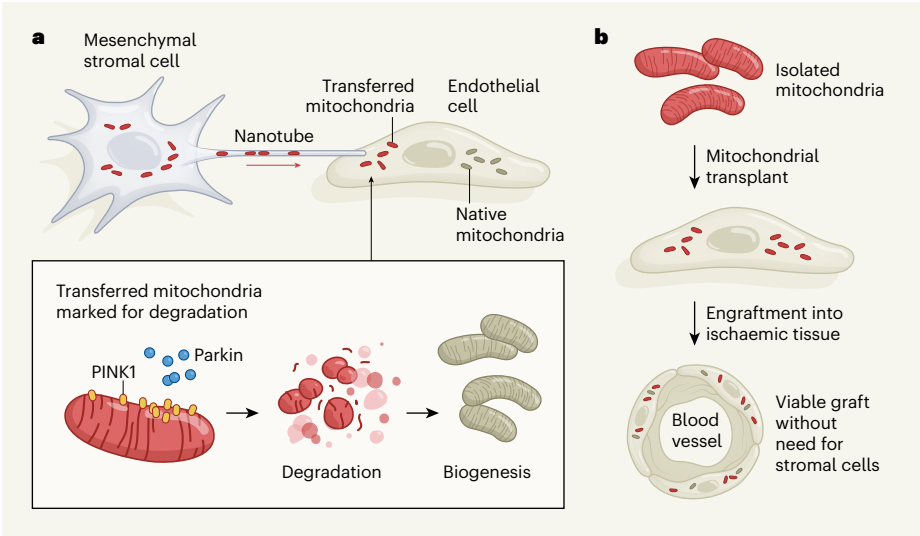

Figure 1 | Transfer of mitochondria organelles enhances the formation of blood vessels. To grow new blood vessels in tissue that has been damaged by a lack of blood supply (ischaemia), endothelial cells, which line the vessel wall, can be transplanted into the damaged tissue. However, these cells form new vessels successfully only if they are co-transplanted with stem cells called mesenchymal stromal cells – a considerable complication to this therapy. **a**, Lin *et al.*[2] found that stromal cells transfer some of their mitochondria to endothelial cells through cellular protrusions called nanotubes. The transferred mitochondria are quickly marked for degradation by the proteins PINK1 and Parkin, which stimulates the production of new mitochondria (biogenesis), boosting endothelial-cell function. **b**, To mimic natural mitochondrial transfer, the authors artificially transplanted mitochondria isolated from stromal cells into endothelial cells, and found that these mitochondria-boosted endothelial-cell grafts were viable and stimulated the formation of blood vessels without the need for stromal cells.

it began immediately after co-transplantation and stopped after blood vessels stabilized. Moreover, selectively blocking nanotube formation disrupted mitochondrial transfer and impaired blood-vessel formation. These findings suggest that the transient transfer of mitochondria through nanotubes is how stromal cells support the viability of endothelial-cell grafts.

Motivated by the limitations of current approaches to treat ischaemia, the authors asked whether artificially priming endothelial cells with mitochondria could mimic the effects of co-transplantation. To do this, the authors incubated mitochondria, isolated from stromal cells, with endothelial cells so that the mitochondria could be taken up through a process called endocytosis. This artificial mitochondrial transplantation replicated the natural transfer process, evident in the enhanced metabolic activity of recipient endothelial cells. Grafting these mitochondria-primed endothelial cells into ischaemic mouse tissue prevented tissue death, because new blood vessels formed and blood flow improved.

Interestingly, the mitochondria that were transferred from stromal cells did not need to be functional to enhance endothelial-cell grafts because, rather than fusing with the existing pool of mitochondria, transferred mitochondria were quickly degraded in a process called mitophagy. During mitophagy, damaged mitochondria are marked for destruction by the proteins PINK1 and Parkin, resulting in their engulfment by intracellular vesicles called autophagosomes and their degradation by organelles called lysosomes[6]. The authors observed artificially transplanted mitochondria in autophagosomes in endothelial cells, but when they impaired mitophagy by silencing expression of the genes that encode PINK1 or Parkin, this prevented mitochondria from being engulfed by these vesicles and reduced the formation of blood vessels in endothelial-cell grafts. Notably, mitophagy induced the production of new mitochondria (mitochondrial biogenesis) in recipient endothelial cells, which enhanced cell function and stimulated blood-vessel formation.

Many details of cell-to-cell mitochondrial transfer are not well understood[7,8]. Lin and colleagues found that increasing the ratio of stromal cells to endothelial cells or growing cells in low-oxygen conditions increased mitochondrial transfer. Furthermore, blocking the action of TNF-α (a protein that mediates inflammation), or of one of the proteins that regulates TNF-α activity, diminished nanotube formation. However, the mechanisms that stabilize and destabilize nanotubes remain to be established. The stromal cell and endothelial cell co-culture system used by the authors could provide a way to begin addressing these fundamental mechanisms.

By contrast, the interplay between mitochondrial biogenesis and mitophagy is well established[9]. The authors found that just one transferred mitochondrion could substantially increase mitochondrial energy production in the form of ATP molecules in cultured endothelial cells. In the co-transplant in mice, around 20% of transferred mitochondria were observed in autophagosomes, implying that modest mitophagy triggers robust mitochondrial biogenesis.

Surprisingly, depleting PINK1 in stromal cells or Parkin in endothelial cells prevented mitochondria from being degraded. This suggests that PINK1 must accumulate on the outer mitochondrial membrane in stromal cells before mitochondria are transferred to endothelial cells, where PINK1 recruits Parkin. This finding is important because it demonstrates that this process is specific: only transferred mitochondria trigger mitophagy in endothelial cells. But if PINK1 accumulates on mitochondria before they are transferred, how do the mitochondria avoid being degraded in stromal cells? Also, what happens to mitochondria that have been transferred to endothelial cells if these organelles have not accumulated PINK1?

Lin and colleagues' approach has the potential to overcome the limitations of existing transplantation therapies for ischaemia that are complicated by the need to co-transplant endothelial cells with stromal cells. Notably, mitochondria from different mammalian species and cell types were successfully implanted into endothelial cells, suggesting that the presence of mitochondria matters more than their origin. However, whether mitochondrial transfer could trigger an immune response in the recipient cell is unclear. If, for example, the donor and recipient cells are incompatible, the recipient cell could initiate inflammatory signalling to protect against potentially harmful foreign mitochondria.

Furthermore, mitochondria are thought to be mainly energy producers, but they also trigger cell death and contain their own DNA, which is prone to mutations. Lin and colleagues suggest that the donated mitochondria are degraded, but there is a possibility that undegraded mitochondria could trigger unwanted responses in recipient cells. Finally, it is unclear at the moment how feasible it will be to generate and transplant the artificially primed endothelial cells. Even with these uncertainties, it is tempting to speculate how therapies that are based on mitochondrial transfer could be used to treat more than just ischaemic diseases.

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The author declares no competing interests.
This article was published online on 1 May 2024.

Biomedical engineering

Microbubbles map hidden signs of heart disease

Elisa E. Konofagou

Cardiovascular disease claims more lives each year than do the two next-deadliest diseases combined. An ultrasound technique that tracks tiny gas-filled bubbles could pave the way towards improved early detection.

Roughly every 34 seconds in the United States, someone has a coronary event — an attack brought on by a disease affecting the coronary arteries, which supply blood to the heart muscle. Around every 83 seconds, such an event results in death. One of the main reasons for this death toll is the poor performance of tools that are used to detect a narrowing of the arteries at a time when pharmacological interventions can still reverse it. If people survive a coronary event, this deficiency also makes it challenging to work out the severity of the injury and the potential future outcomes, which could be determined by mapping blood flowing through the part of the heart muscle that remains viable. Writing in *Nature Biomedical Engineering*, Yan *et al.*[1] report the efficacy of a real-time, quantitative method that could overcome these problems — using machinery that can be wheeled into any emergency department.

Yan and colleagues' breakthrough means that a cardiologist or physician can quickly determine the status of different areas of a person's heart muscle (myocardium), and without subjecting the person to stress testing[2]. The method the authors used is based on ultrasound localization microscopy[3–5], which is a super-resolution imaging technique that surpasses the resolution limit of conventional ultrasound imaging with the help of gas-filled bubbles that are just a micrometre in diameter. These microbubbles are injected into a person's bloodstream, and then tracked as they move through the small blood vessels that perfuse the myocardium with oxygenated blood (Fig. 1). This technique is especially useful in the heart, because the thick muscle walls can be penetrated by ultrasound only with low-frequency signals that otherwise offer very low spatial resolution.

Although ultrasound localization microscopy has been reported previously, and its application to the myocardium is not new[3–5], Yan *et al.* have now shown its clinical applicability unambiguously. By using it for people who are diagnosed with heart disease, and in a clinical environment, the team confirmed that the results of the method are consistent with those of other, more-invasive clinical-imaging methods, such as coronary angiography, which is based on computed tomography.

This task is not trivial. The required resolution is on the order of tens of micrometres, and the imaging must be undertaken while the myocardium moves and stretches by centimetres over the course of a heartbeat. This can result in artefacts that make tracking small vessels extremely challenging — and quantifying the flow through them even more so. However, Yan *et al.* found that they were able to circumvent these difficulties by tracking the microbubbles with hundreds of images per second, which made the method extremely sensitive, thereby reducing the number of tracking errors.

The endeavour is made even more challenging by the fact that it uses the most conventional form of cardiac ultrasound imaging, known as transthoracic echocardiography. Transthoracic echocardiography is safer than some other forms of cardiac imaging used in the clinic, but it has drawbacks. Perhaps the biggest problem is that the probe is placed between a person's ribs to obtain an 'acoustic window' — a way for ultrasound to penetrate the myocardium unhindered. But this can produce artefacts that compromise the image quality so much that the ultrasound probe might need to be inserted into the person's throat instead.

These artefacts typically result from the ultrasound signal reflecting off the cardiac muscle, and then bouncing off the ribs before returning to the probe. This creates imaging noise that motion-tracking algorithms can mistake for direct reflections from the myocardium, resulting in inaccurate information about the underlying structure. Yan *et al.* successfully reduced these artefacts, achieving a spatial resolution of 13–16 micrometres in a controlled environment, and hundreds of micrometres in a moving heart. This resolution enabled the authors to distinguish blood vessels that were hundreds of micrometres apart

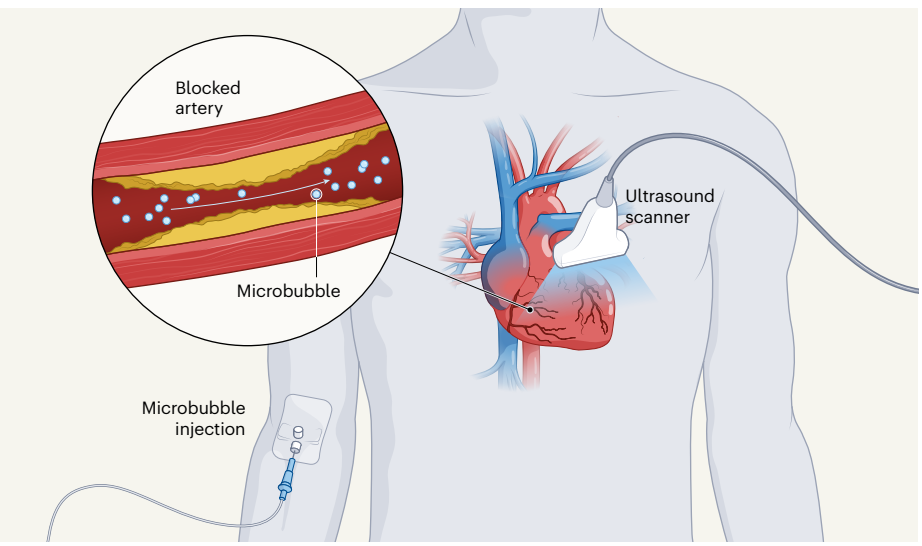

Figure 1 | Super-resolution imaging of blood flow through the heart muscle. Yan *et al.*[1] showed that ultrasound can be used to determine the health of a person's heart muscle (myocardium) by tracking the flow of gas-filled microbubbles through the small blood vessels that perfuse the myocardium with oxygenated blood. The authors developed a way of distinguishing mobile structures from static structures, which increased the sensitivity of the method enough to enable them to verify its efficacy in clinical tests on people diagnosed with heart disease.