experiments, two parties (called Alice and Bob, following a convention often used in cryptography) use pairs of entangled particles instead of single photons to exchange the key (Fig. 1b). Alice and Bob measure their particles independently under a strict set of experimental conditions. Some of the measurements are used to create a key, whereas others are used to perform a test that has been shown to rigorously detect entanglement[7–11]. Passing the test guarantees that a hacker has not tampered with the entangled particles in any way that would allow them to predict or control Alice's and Bob's measurements. In our courier example, the hacker could provide the briefcase used to transport the keys, and any tampering would still be detected.

This method eliminates one of the biggest security risks from the system. Because there is no need to trust the devices that create and distribute the entangled particles, these schemes are said to be device independent. Alice and Bob need worry only about protecting the devices that choose their measurements from being tampered with, and isolating their labs to keep information about their results or the key from leaking out.

Nadlinger and co-workers performed measurements on entangled ions that were trapped by an oscillating electromagnetic field. Their measurements were taken over a period of nearly 8 hours, creating a shared key that was 95,884 bits long. This is the first complete implementation of a device-independent protocol for generating a key. But in this case, the stations were separated by only 2 metres — about the minimum distance needed for Alice and Bob to carry out a secure conversation while practising social distancing during a pandemic. Moving the stations farther apart, to more realistic distances, is not trivial.

In Zhang and colleagues' experiment, measurements were made on entangled atoms, trapped by laser beams, and the two systems were much farther apart, at a separation of 400 m. The researchers were able to prove that the system met the rigorous requirements for device-independent key distribution. But this increased distance reduced the rate at which entangled particles could be generated — so much so that a key could not be created in a reasonable amount of time.

In both experiments, the rate at which particles at the two stations can be entangled decreases markedly as the distance between them increases. For device-independent quantum-key distribution to become practical, the obstacle of low rates at long distances must be overcome. Still, both demonstrations represent major advances in quantum-communications technology.

Several efforts are under way around the world to build the kinds of entangled quantum network that will eventually support these device-independent cryptographic protocols[12]. Because the requirements for these protocols are so demanding, they serve as a useful benchmark — any quantum network that can meet them is able to exceed a crucial operational threshold. Consequently, I expect that our most advanced future quantum networks will have these device-independent cryptographic capabilities built in, enabling widespread adoption of innovative ways of keeping our most sensitive secrets safe.

Krister Shalm is in the Department of Physics, University of Colorado at Boulder, Boulder, Colorado 80309, USA.
e-mail: lynden.shalm@colorado.edu

1. Nadlinger, D. P. *et al. Nature* **607**, 682–686 (2022).
2. Zhang, W. *et al. Nature* **607**, 687–691 (2022).
3. Singh, S. *The Code Book: The Evolution of Secrecy from Mary, Queen of Scots to Quantum Cryptography* (Doubleday, 1999).
4. Bennett, C. H. & Brassard, G. *Theor. Comput. Sci.* **560**, 7–11 (2014).
5. Gerhardt, I. *et al. Nature Commun.* **2**, 349 (2011).
6. Acín, A. *et al. Phys. Rev. Lett.* **98**, 230501 (2007).
7. Hensen, B. *et al. Nature* **526**, 682–686 (2015).
8. Shalm, L. K. *et al. Phys. Rev. Lett.* **115**, 250402 (2015).
9. Giustina, M. *et al. Phys. Rev. Lett.* **115**, 250401 (2015).
10. Rosenfeld, W. *et al. Phys. Rev. Lett.* **119**, 10402 (2017).
11. Li, M.-H. *et al. Phys. Rev. Lett.* **121**, 80404 (2018).
12. Wehner, S., Elkouss, D. & Hanson, R. *Science* **362**, eaam9288 (2018).

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Developmental biology

A self-defence strategy for long-lived eggs

Deepak Adhikari & John Carroll

Egg cells need to stay out of harm's way to keep the next generation healthy and free of unwanted mutations. A mechanism by which eggs avoid the ravages caused by harmful reactive oxygen species has now been discovered. **See p.756**

In what seems to be a high-risk evolutionary strategy, female mammals are born with a finite reserve of immature eggs. These eggs need to be capable of avoiding harm until the end of an organism's reproductive life — for more than 40 years in people — to remain capable of producing healthy offspring. Writing on page 756, Rodríguez-Nuevo *et al.*[1] have now found an adaptation that might explain how eggs stay safe for so long, related to how they produce energy.

Cellular energy is stored in ATP molecules. Most ATP is made in organelles called mitochondria by a process known as oxidative phosphorylation, which involves five protein complexes in the inner mitochondrial membrane. Complexes I to IV comprise an electron transport chain (ETC), which begins with oxidation of the molecule NADH to NAD^+ by complex I. Oxidation releases electrons, which are passed from complex to complex, coupled to the pumping of hydrogen ions that generates an electrical potential across the mitochondrial membrane. This mitochondrial membrane potential (MMP) ultimately drives ATP synthesis by complex V (Fig. 1a). Complexes I–V are highly evolutionarily conserved across most of the animal kingdom, except in a few unicellular organisms[2] and parasitic plants[3].

Unfortunately, oxidative phosphorylation comes with some collateral damage. Inevitably, some electrons leak from the ETC, and are received by oxygen to generate reactive oxygen species (ROS) — highly reactive molecules that wreak havoc in cells by inducing damage to essential biomolecules such as RNA, proteins and lipids. In eggs, this type of damage could prevent proper egg development or embryo formation. Furthermore, ROS-induced damage to nuclear or mitochondrial DNA can lead to genetic mutations that could propagate across generations. It makes sense, then, to take extreme, even unique, measures to protect eggs from ROS. And this is exactly what Rodríguez-Nuevo *et al.* have discovered.

The authors noted that something was different about the mitochondria in eggs compared with those of their neighbouring support cells: the organelles had a much-reduced MMP. They examined early-stage eggs (called primordial oocytes, which remain quiescent in the ovary for most of the lifespan) from humans and the frog species *Xenopus laevis*. This revealed that primordial oocytes lack any detectable ROS signals. Furthermore, when the researchers induced ROS artificially, eggs degenerated rapidly, suggesting that they are particularly prone to ROS-mediated damage — perhaps indicating poorly developed protective mechanisms.

These data point to primordial oocytes having relatively low mitochondrial activity

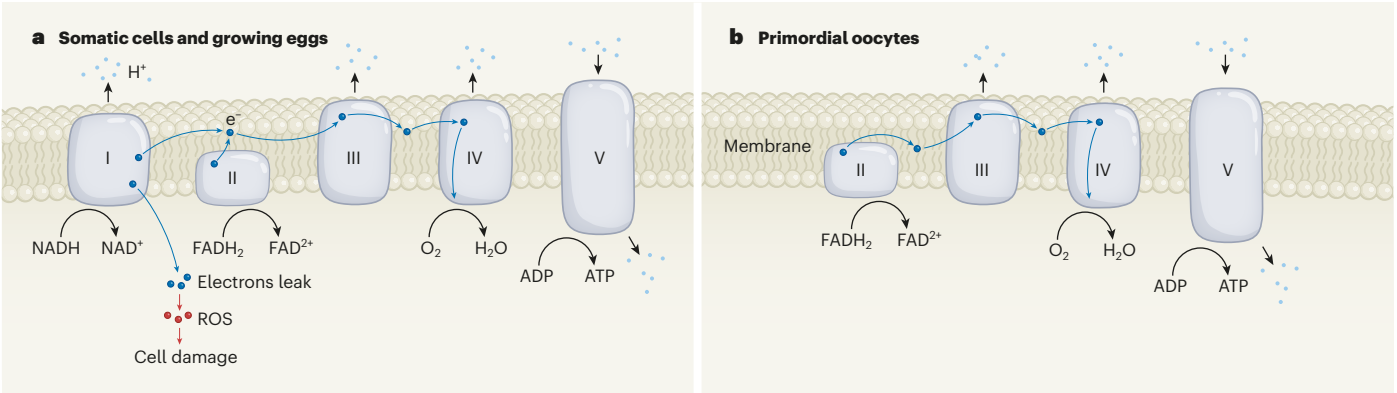

Figure 1 | Energy production in eggs and other cell types. a, In somatic cells (those that are not sperm or eggs) and eggs that are growing, the inner membrane of organelles called mitochondria harbours five protein complexes, called complexes I–V. Complexes I and II release electrons (e^-), through oxidation of NADH molecules to NAD^+ and $FADH_2$ to FAD^{2+}, respectively. The electrons are passed from complex to complex, and used by complex IV to promote conversion of oxygen to water. Electron transport releases energy that results in pumping of hydrogen ions across the inner mitochondrial membrane to generate an electrical potential. This enables complex V to generate the energy-carrying molecule ATP from ADP. Some electrons leak (mainly from complex I), producing reactive oxygen species (ROS) that can damage cells. **b**, Eggs can exist in an early stage as 'primordial oocytes' for decades before their growth, and must avoid accumulating ROS-mediated damage. Rodríguez-Nuevo *et al.*[1] show that early eggs lack complex I — essential ATP production is maintained by the release of electrons from complex II.

and a resultant absence of ROS (Fig. 1b). To find out how this mitochondrial status is achieved, Rodríguez-Nuevo and colleagues treated *Xenopus* primordial oocytes with specific inhibitors of complexes I–V. The authors found that the eggs degenerated in response to inhibitors of complexes II–V, but were mostly insensitive to the complex-I inhibitor rotenone. This demonstrates that primordial oocytes do not need complex I — the complex from which most ROS is generated[4] — for ATP production.

Rodríguez-Nuevo *et al.* then examined the molecular composition and organization of mitochondrial complexes in primordial oocytes. Analysis showed that the relative level of complex I in early *Xenopus* and human eggs was well below that in other cell types. This was accompanied by an increase in levels of mitochondrial protease enzymes and chaperone proteins — components of a quality-control mechanism called the mitochondrial unfolded protein response (UPR^{mt}) that degrades misfolded proteins to protect the organelle from damage. These data suggest that an imbalance in the ratio of ETC subunits triggers the UPR^{mt} to support continued mitochondrial function in the absence of complex I. However, almost nothing is known about the egg's UPR^{mt}, so this will be an avenue for future study.

If primordial oocytes lack complex I and are also incapable of generating energy through glucose metabolism[5], how do they create sufficient ATP to sustain their activity? Fortunately, complex II, which catalyses oxidation of $FADH_2$ molecules to FAD^{2+}, is also an entry point for electrons. Although less efficient, this entry point also generates an MMP sufficient to support ATP production, but without generating large amounts of ROS[6].

The authors found that everything changes once the primordial oocytes begin to develop. Through careful biochemical assays, they demonstrated that, whereas complex I was neither assembled nor active in *Xenopus* primordial oocytes, it became active in larger, growing eggs that are on the path to ovulation. Concomitantly, growing eggs became sensitive to complex-I inhibitors, showed increased expression of complex-I subunits and started generating ROS.

The need to assemble complex I in growing eggs probably reflects an increased energy demand as the cell's volume rapidly expands. Relative to the long period in which primordial oocytes are arrested in the ovary, the growth phase is fast and the time for accruing damage more limited, probably making the pay-off worthwhile. Perhaps growing eggs also activate protective mechanisms against ROS. Going forwards, it will be interesting to investigate the signals that control the induction and assembly of complex-I subunits, whether there is an accompanying upregulation of mechanisms to protect against ROS, and whether disruption of complex-I assembly during the growth phase can lead to infertility in certain contexts.

One such context is older mothers, for whom there is a well-established decline in egg fertility that is, at least in part, thought to be mitochondrial in origin[7]. If complex-I assembly is deficient in these growing eggs, faulty operation of the ETC would lead to a reduced capacity for ATP generation and increased ROS[8]. In support of this, high ROS levels and hampered ATP production are features of eggs from older mothers[9–11]. Furthermore, mitochondria-targeted therapies in ageing female mice improve oocyte quality, along with reduced ROS and improved ATP production[9,10].

Many of the conclusions of Rodríguez-Nuevo and colleagues' study are drawn from *Xenopus* eggs, which have a different life cycle from the eggs of mammals. However, this choice is understandable, because *Xenopus* eggs are large and sufficiently numerous to provide the volume of material needed for biochemical analysis. Remarkably, the authors gathered information from a few isolated human primordial oocytes, and found a similar lack of complex I and induction of the UPR^{mt}. It will be interesting to see whether remodelling of the ETC by eliminating complex I is a universal feature of primordial-oocyte development in mammals, and indeed any organisms that have a long-lived resting pool of eggs.

This study provides the first evidence of a cell existing in its physiological state without complex I — and it does so in a developmentally regulated manner, mitigating its vulnerability to ROS. This finding has implications for understanding how long-lived cells maintain viability over decades. And specific to eggs, the discovery adds to our understanding of how the remarkable primordial oocyte provides a safe haven for both nuclear and mitochondrial DNA between generations.

Deepak Adhikari and **John Carroll** are at the Monash Biomedicine Discovery Institute, Monash University, Melbourne 3800, Australia.
e-mail: j.carroll@monash.edu

1. Rodríguez-Nuevo, A. *et al. Nature* **607**, 756–761 (2022).
2. Raven, J. A. & Beardall, J. *J. Exp. Bot.* **68**, 2683–2692 (2017).
3. Senkler, J., Rugen, N., Eubel, H., Hegermann, J. & Braun, H.-P. *Curr. Biol.* **28**, 1606–1613 (2018).
4. Grivennikova, V. G. & Vinogradov, A. D. *Biochim. Biophys. Acta* **1757**, 553–561 (2006).
5. Eppig, J. J. *J. Exp. Zool.* **198**, 375–381 (1976).
6. Brand, M. D. *Exp. Gerontol.* **45**, 466–472 (2010).
7. Pasquariello, R. *et al. Biol. Reprod.* **100**, 971–981 (2019).
8. Miwa, S. *et al. Nature Commun.* **5**, 3837 (2014).
9. Al-Zubaidi, U. *et al. Hum. Reprod.* **36**, 771–784 (2021).
10. Sasaki, H. *et al. Front. Endocrinol.* **10**, 811 (2019).
11. Ben-Meir, A. *et al. Aging Cell* **14**, 887–895 (2015).

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