perovskites, thereby opening up a versatile strategy for designing new 2D nanomaterials[6]. This approach has already led, for example, to the preparation of materials that emit white light[7], exhibit electrical conduction between layers[8] or take advantage of the chirality (lack of mirror symmetry) of the organic groups[9].

A family of organic cations called organoammonium ions has been widely used to make layered perovskites. These ions contain a positively charged 'head' group that binds to certain octahedrally arranged atoms in the inorganic perovskite layers, together with a hydrocarbon 'tail', which assemble into organic bilayers in the layered-perovskite architecture because of van der Waals interactions. Aubrey and colleagues now report that further chemical groups can be incorporated into the tails to direct the formation of the crystal lattice of a second inorganic compound (Fig. 1c).

The authors find that different chemical groups can act as templates for the formation of various sublattices that have distinct compositions and structures. A key achievement is that the resulting layered perovskites can be synthesized in acidic aqueous solutions — the metal salts that act as precursors of the sublattices are soluble in such environments, thus enabling their use in these reactions. In the resulting crystals, the two types of inorganic sublattice can, for example, either be well separated by large organic cations, and therefore be non-interacting, or can be linked by single atoms, which leads to interactions and mixing of the sublattices' electronic properties.

Aubrey and colleagues' method allowed them to make macroscopic single crystals of layered perovskites containing several hundreds to thousands of stacked layers, with perfect control of the atomic order at the interfaces between layers. The authors highlight the design freedom of their approach by integrating six different sublattices into layered-perovskite structures. For example, the authors report the formation of a material that contains lead chloride layers, in which the two different inorganic sublattices are separated by just one bridging chloride ion. The authors' optical experiments and computational modelling show that the electronic wavefunctions of this material extend over both inorganic layers and exhibit a phenomenon called state mixing — which alters the optical properties of the material, such as its wavelength of emission and bandgap.

One advantage of heterostructures made from graphene and related 2D materials is that they have clean (uncontaminated), well-defined surfaces that enable investigation of their optoelectronic properties, and that aid their integration with other device platforms, such as silicon-based technologies. By contrast, solution-based fabrication methods usually produce surfaces that are contaminated by organic residues. Innovative approaches for cleaning the surfaces of Aubrey and co-workers' triple-decker perovskite crystals are therefore needed — perhaps involving cleavage or exfoliation of the crystals.

Nevertheless, the versatility of Aubrey and colleagues' fabrication strategy raises expectations that a wide variety of single-crystal materials could be produced in the future. The impact of these findings will depend on whether the materials exhibit exciting phenomena, such as quantum effects, 'topological' electronic states that lead to spatially dependent conductivity, or unusual optical behaviour. An even greater range of compositions and optoelectronic properties might become possible using post-fabrication processes such as ion exchange[10] (in which a specific type of inorganic ion in the perovskite layers is replaced by a different type). Future device applications will depend on whether the sublattices can improve key functionalities of layered perovskites — for example, their electrical conductivity, which would make them useful as integrated electrodes in light-emitting diodes and solar cells.

Roman Krahne and **Milena P. Arciniegas** are at the Italian Institute of Technology, Genoa 16163, Italy.
e-mails: roman.krahne@iit.it; milena.arciniegas@iit.it

1. Liu, Y., Huang, Y. & Duan, X. *Nature* **567**, 323–333 (2019).
2. Novoselov, K. S., Mishchenko, A., Carvalho, A. & Castro Neto, A. H. *Science* **353**, aac9439 (2016).
3. Aubrey, M. L. *et al. Nature* **597**, 355–359 (2021).
4. Tartakovskii, A. *Nature Rev. Phys.* **2**, 8–9 (2020).
5. Wang, Z. *et al. Nature Energy* **2**, 17135 (2017).
6. Li, X., Hoffman, J. M. & Kanatzidis, M. G. *Chem. Rev.* **121**, 2230–2291 (2021).
7. Dhanabalan, B. *et al. Adv. Mater.* **33**, 2008004 (2021).
8. Passarelli, J. V. *et al. J. Am. Chem. Soc.* **140**, 7313–7323 (2018).
9. Long, G. *et al. Nature Rev. Mater.* **5**, 423–439 (2020).
10. Roy, C. R. *et al. J. Am. Chem. Soc.* **143**, 5212–5221 (2021).

The authors declare no competing interests.

Genetics

Mutation fingerprints encode cellular histories

Kamila Naxerova

Cells continually acquire mutations and pass them on to their progeny. The mutation profiles of human cells shine a light on the cells' developmental history and their dynamics in adult tissue. **See p.381, p.387, p.393 & p.398**

The human body consists of trillions of cells that perform innumerable tasks as members of different organ systems. They are all descendants of the fertilized egg, which divides again and again to generate large numbers of progeny during embryonic development. Later in life, cells continue dividing to compensate for cell death and to ensure consistent tissue function. The ancestral relationships between the body's cells can inform us about their division and migration histories. Park *et al.*[1] (page 393), Coorens *et al.*[2] (page 387), Li *et al.*[3] (page 398) and Moore *et al.*[4] (page 381) now provide insights into human embryonic development and tissue maintenance by uncovering the lineage relationships between cells that reside in different parts of the body.

The common principle uniting the four studies is that they use mutations in the genome as markers for tracing lineage. Throughout their lives, cells continually acquire random mutations that are passed on to all their descendants as permanent tags. A cell's mutation profile therefore represents a fingerprint that encodes its ancestry back to the fertilized egg. By sequencing the genomes of cells from different parts of the body, ancestral relationships can be determined and a cellular 'family tree' can be constructed, enabling a retrospective view of the cells' provenance and past behaviour.

The four studies showcase several fascinating applications of this principle. Park *et al.*[1] and Coorens *et al.*[2] shed light on the earliest stages of human embryonic development. They inferred the mutation profiles of individual cells from tissues collected from recently deceased adults at autopsy and constructed cell-lineage trees that visualize how the cells relate to each other. The branching points of such trees represent cells that existed in the past and can resolve the first embryonic cell generations in great detail (Fig. 1a).

Consistent with previous work[5–7], Park *et al.* and Coorens *et al.* observed that the first two discernible lineages (which could well be the two cells that arise from the first division of

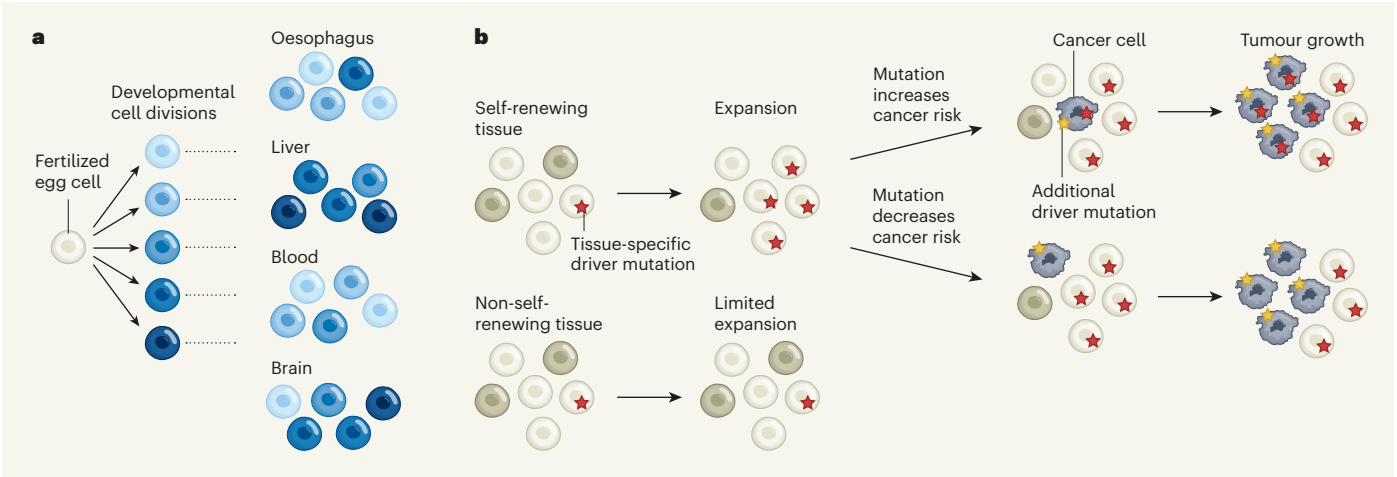

Figure 1 | Tracing cellular ancestry over a human lifetime. a, Mutations permanently label cells arising from the fertilized egg cell. Park *et al.*[1] and Coorens *et al.*[2] used mutations to decode cells' history through embryonic development. They revealed the variable contributions to different adult organs of lineages that emerged early in development (coloured cells). **b**, Li *et al.*[3] and Moore *et al.*[4] examined mutations to investigate the cellular dynamics that take place during normal tissue maintenance later in life. In self-renewing tissues, cells with mutations in specific genes can gain a competitive advantage and give rise to a disproportionately large fraction of the tissue, within the restrictions of its structure. In non-self-renewing tissues (such as the brain), mutations that confer a competitive advantage might occur but would be more limited in their spread unless they drastically change a cell's behaviour. Further genetic alterations might lead to cancer (dark-grey cells), either when combined with, or independently of, the initial mutation, through mechanisms that are incompletely understood.

the fertilized egg) contribute variably to the body's tissues. This finding highlights the stochastic nature of cell-fate decisions that take place during early development. Moreover, of the first eight cells to arise, only approximately three give rise to the embryo, whereas the rest separate from these cells to form other tissues outside the embryo, such as the placenta.

Both Park *et al.* and Coorens *et al.* also observed that the mutation rate is relatively high, approximately 2.4 mutations per cell per generation, during the first few embryonic divisions. It then drops considerably, at about the same time that cells activate more-mature DNA-repair mechanisms.

Cells in the early embryo mix extensively, so that physical proximity does not always suggest relatedness. For example, Park *et al.* observed that adjacent connective-tissue cells can derive from lineages that segregated with the first embryonic division. However, some lineages that arise after the third generation become enriched in organs that derive from a layer of cells in the early embryo called the ectoderm, and mutations that arise after approximately six to nine generations can become enriched in specific organs. Resolution of developmental events beyond the first 15 cell generations or so will require the analysis of more cells from more tissues, but the current analyses already provide a tantalizing taste of what the future holds.

Li *et al.* and Moore *et al.* demonstrated that mutations can also reveal important insights into the biology and evolution of tissues in later life. To achieve this, the authors sequenced the genomes of small groups of cells dissected from different organs, and examined the abundance and diversity of mutations in them.

Moore *et al.* observed that many known tissue structures that are visible under the microscope, such as the folds of the inner lining of the small and large intestines, consist of genetically similar cells that all descended from a recent common ancestor — a tissue-resident stem cell. By contrast, tissues that do not self-renew, such as muscle and brain, typically contain genetically different cells with no recent shared ancestry.

Furthermore, by examining the mutations that accumulate in different tissues, it is possible to pinpoint and quantify the molecular mechanisms that introduce mutations into the genome in different cellular environments. For example, both Li *et al.* and Moore *et al.* showed that, in contrast to other tissues, a high fraction of the total mutations found in gastrointestinal tract cells are attributable to cell division, whereas liver cells are vulnerable to mutations resulting from exposure to toxins originating outside the body. Moore *et al.* observed that precursors of sperm cells in the testes acquire mutations at an unusually low rate, potentially hinting at special DNA-repair mechanisms that protect the genetic material passed on to the next generation.

"Cells continually acquire random mutations that are passed on to all their descendants as permanent tags."

In addition to the ubiquitous neutral mutations, some cells acquire 'driver' mutations that affect their behaviour and that might cause them to contribute to a disproportionately large fraction of a tissue's cell population (Fig. 1b). Li *et al.* found that different genes cause such abnormal cell behaviour in different tissues, and, to some extent, in different individuals. In some tissues, populations carrying a particular driver mutation are constrained in their expansion by microanatomical structures in the tissue, and therefore typically remain small. In tissues with a 'flatter' anatomy, however, a mutant population can expand to encompass large areas, without obviously affecting tissue function adversely.

Together, the four studies provide an impressive demonstration of the power of modern genetics to decode the cellular dynamics that unfold in our bodies over time. Scaled-up versions of these experimental designs will provide insights into how organs are formed and, crucially, deepen our understanding of diseases caused by harmful mutations that sometimes arise during embryonic development.

From the point of view of human health, tissue evolution during later life is probably an even more pressing topic than embryonic development. Already, our conceptual understanding of how cancer develops has been shifted profoundly by the recognition that healthy tissues can contain mutations that were previously thought to be relatively specific to cancers[8]. It is becoming clear that some of these alterations might not drive cancer at all, but might simply be inherited from normal cells by cancer cells. Some

mutations that spread throughout normal tissues might even protect against cancer[9,10].

Li *et al.* report that a notable fraction of tissue samples across different sites, such as the oesophagus and the rectum, contained three or more mutations thought to drive cancer – although it is not clear whether these driver mutations were present together in the same cell. This is consistent with previous work demonstrating the presence of up to three driver mutations in normal airway cells from people who smoke[11]. Three driver mutations is uncomfortably close to the average four or five that are found in cancers[12], particularly given the limited sampling of normal tissue so far. Indeed, if cells with three driver mutations can easily be found in a small tissue sample, cells with four or five drivers probably exist in that tissue as well – without necessarily giving rise to cancer.

These new insights invite us to reconsider how we genetically define cancer. If having multiple driver mutations does not make a cancer, what does? Is a particular, tissue-specific combination of mutations required? Or is the presence of such mutations required in addition to permissive environmental conditions? Chromosomal abnormalities have often been cited as being specific to cancer cells, but both Li *et al.* and Park *et al.* report that normal cells in some tissues contain chromosomal changes as well.

It is likely that full clarification will be possible only with the generation of a 'normal-tissue genome atlas', in which the mutational composition of different tissues is carefully mapped across many individuals as a function of age, medical history and lifestyle. Only then can we hope to answer the foundational question about the genetic definition of cancer with some rigour.

Kamila Naxerova is at the Center for Systems Biology, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114, USA.
e-mail: naxerova.kamila@mgh.harvard.edu

1. Park, S. *et al. Nature* **597**, 393–397 (2021).
2. Coorens, T H. H. *et al. Nature* **597**, 387–392 (2021).
3. Li, R. *et al. Nature* **397**, 398–403 (2021).
4. Moore, L. *et al. Nature* **597**, 381–386 (2021).
5. Bizzotto, S. *et al. Science* **371**, 1249–1253 (2021).
6. Ju, Y. S. *et al. Nature* **543**, 714–718 (2017).
7. Spencer Chapman, M. *et al. Nature* **595**, 85–90 (2021).
8. Martincorena, I. *et al. Science* **348**, 880–886 (2015).
9. Zhu, M., Lu, T., Yopp, A. C., Wang, T. & Zhu, H. *Cell* **177**, 608–621 (2019).
10. Colom, B. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.06.25.449880 (2021).
11. Yoshida, K. *et al. Nature* **578**, 266–272 (2020).
12. Campbell, P. J. *et al. Nature* **578**, 82–93 (2020).

The author declares no competing interests.
This article was published online on 25 August 2021.

Human behaviour

Text-message nudges encourage vaccination

Mitesh S. Patel

A field trial shows that text-message 'nudges' encourage people to get vaccinated against COVID-19. To be effective, nudge approaches such as this must combine three aspects: they must prompt, enable and motivate behaviour. **See p.404**

Nudges are subtle changes to the way in which choices are offered or information is framed that can have an outsize impact on behaviour. As the supply of COVID-19 vaccines increases around the world, many nations are faced with the challenge of how best to encourage people to get vaccinated. Although various campaigns to do this have been implemented, little is known about which types of approach work and which do not. On page 404, Dai *et al.*[1] present findings from a large field experiment that reveal new insights into the three key elements that must be combined in strategies aimed at increasing the likelihood that people will get their vaccination against COVID-19.

Dai and colleagues set out to determine whether a single text message from a person's health-care provider could change COVID-19 vaccination rates. In addition, they tested whether vaccination rates differed when recipients were told the vaccine was already theirs – that is, when they had psychological ownership of the vaccine. These text messages included phrases such as the vaccine has "just been made available to you", and encouraged recipients to "claim your dose". Such an approach has been used successfully to nudge influenza vaccination[2], but has not previously been tested for vaccination against COVID-19.

In the main clinical trial, more than 93,000 individuals in a large health-care system who had not organized an appointment by the first weekday after an initial invitation were randomly placed in a control group or a test group and then followed for 4 weeks. These individuals were among the first wave of people eligible for vaccinations (owing to age or pre-existing medical conditions). Of the control-group individuals who did not receive any text-message reminders, 13.9% got

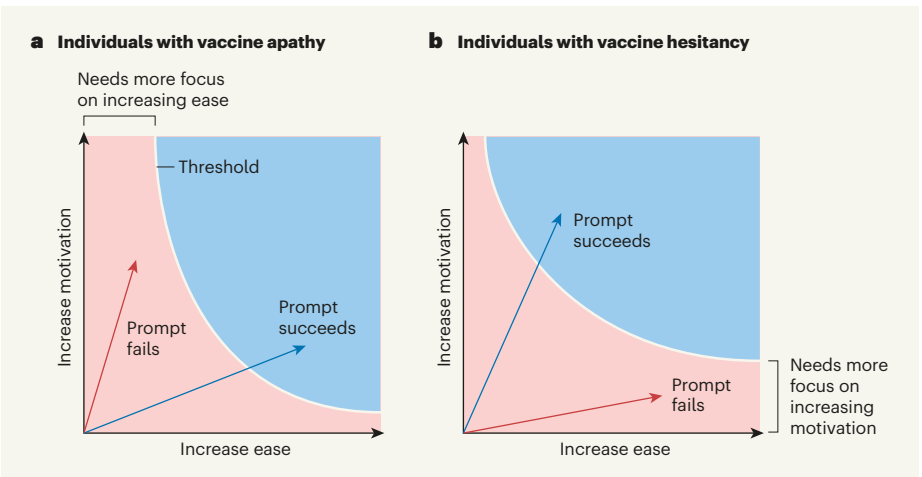

Figure 1 | Nudges to encourage vaccination uptake will depend on individuals' attitudes. Nudges are ways in which information is presented or choices offered that drive behavioural change. Dai *et al.*[1] report the effects of sending individuals text-message reminders to encourage them to book an appointment to receive their vaccine against COVID-19. According to the Fogg Behavior Model, nudges should combine three aspects for success: they should prompt an action, increase motivation and make action easier. But nudges need to be tailored to individuals with different attitudes. **a**, If individuals are apathetic about getting a vaccine, prompting nudges will need to focus more on making it easier to arrange an appointment. Dai *et al.* achieved this by including a link to the booking website in the text messages. **b**, If individuals are more hesitant about getting vaccinated, such nudges will need to focus on increasing motivation.