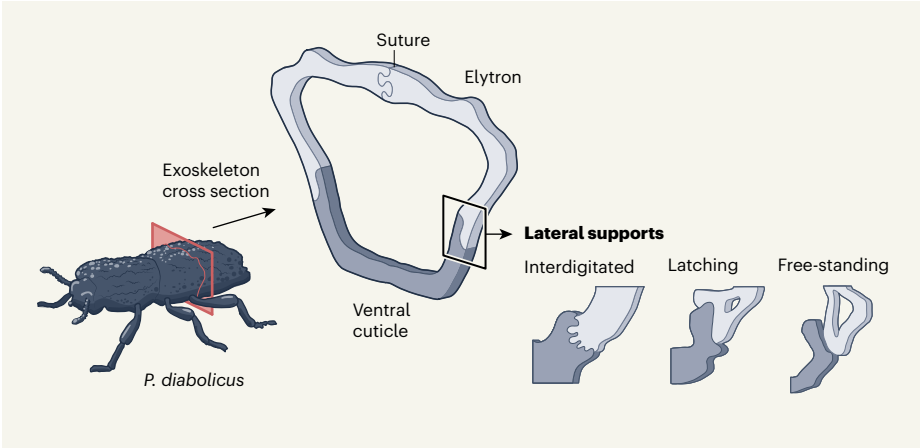

Figure 2 | Tough joints and interfaces. Rivera *et al.*[1] report that joints and supports in the exoskeleton of *Phloeodes diabolicus* help to account for the insect's remarkable crush resistance. A joint known as a suture locks together the beetle's hardened forewings (the elytra). The suture consists of interlocked, ellipsoidal structures called blades. This interlocked structure, combined with the layered microstructure of the blades (not shown), enhances the suture's toughness. Three types of lateral support connect the ventral cuticle to the elytra: interdigitated, latching and free-standing. The interdigitated joints are the stiffest and strongest under compression, whereas the latching and free-standing supports allow the exoskeleton to undergo some deformation when compressed.

laminated blades were significantly tougher than were the other two types, and absorbed more energy.

In engineering applications, commonly used joints between materials often fracture at their thinnest regions, where tensile stress is concentrated, leading to unpredictable and catastrophic failure[11]. By contrast, in Rivera and colleagues' bio-inspired blades, tensile stress results in localized delamination (separation of the layers); this causes the neck region of the blade to expand laterally, so that the interlocked blades grip each other even more tightly.

The laminated blades also fracture in a more predictable and gradual manner than do joints used in engineering, initially producing non-propagating, circumferential cracks. If the bio-inspired blades were used as jointing materials in practical applications, these cracks could be regularly inspected to pre-empt their final fracture, and would therefore be safer and more reliable than currently used jointing materials. However, further evaluation of Rivera and colleagues' laminated blades will be needed — for example, to characterize their properties under compression, bending and torsion, and to discover how they become fatigued over time — before applications can be considered.

The authors' work mainly focuses on mechanical performance at the submillimetre and the macroscopic scale, taking into account the behaviour of the interfacial structures and laminated microstructures of *P. diabolicus*'s elytra. However, the effects of structural features at lower hierarchical levels (smaller scales) in the elytra still need to be explored, using multi-scale modelling and experiments. Emerging methods[12] that use artificial intelligence and machine learning might accelerate the search for hierarchically structured materials, based on these elytra, that have superior mechanical properties for engineering compared with currently available materials.

In the meantime, Rivera and co-workers' approach — integrating advanced characterization methods with mechanical testing, simulations and 3D printing — provides a template for investigations of other remarkable natural materials that have complex architectures. And the authors' work demonstrates that you should never underestimate the capabilities of insects.

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1. Rivera, J. *et al. Nature* **586**, 543–548 (2020).
2. Meyers, M. A., McKittrick, J. & Chen, P.-Y. *Science* **339**, 773–779 (2013).
3. Chen, P.-Y., McKittrick, J. & Meyers, M. A. *Prog. Mater. Sci.* **57**, 1492–1704 (2012).
4. Naleway, S. E., Porter, M. M., McKittrick, J. & Meyers, M. A. *Adv. Mater.* **27**, 5455–5476 (2015).
5. Dunlop, J. W. C., Weinkamer, R. & Fratzl, P. *Mater. Today* **14**, 70–78 (2011).
6. Barthelat, F., Yin, Z. & Buehler, M. J. *Nature Rev. Mater.* **1**, 16007 (2016).
7. Huang, W. *et al. Adv. Mater.* **31**, 1901561 (2019).
8. Yaraghi, N. A. & Kisailus, D. *Annu. Rev. Phys. Chem.* **69**, 23–57 (2018).
9. Jayaram, K. & Full, R. J. *Proc. Natl Acad. Sci. USA* **113**, E950–E957 (2016).
10. Sun, J. & Bhushan, B. *RSC Adv.* **2**, 12606–12623 (2012).
11. Malik, I. A., Mirkhalaf, M. & Barthelat, F. *J. Mech. Phys. Solids* **102**, 224–238 (2017).
12. Gu, G. X., Chen, C.-T., Richmond, D. J. & Buehler, M. J. *Mater. Horiz.* **5**, 939–945 (2018).

Tumour biology

Seeds of cancer in normal skin

Inigo Martincorena

Sequencing the genomes of individual skin cells called melanocytes has revealed a rich landscape of DNA changes. These insights shed light on the origins of melanoma, an aggressive type of cancer. **See p.600**

Mutations occur in our cells throughout life. Although most mutations are harmless, they accumulate in number in our tissues as we age, and if they arise in key genes, they can alter cellular behaviour and set cells on a path towards cancer. There is also speculation that somatic mutations (those in non-reproductive tissues) might contribute to ageing and to diseases unrelated to cancer. However, technical difficulties in detecting the mutations present in a small number of cells, or even in single cells, have hampered research and limited progress in understanding the first steps in cancer development and the impact of somatic mutation on ageing and disease. Tang *et al.*[1] report work on page 600 that overcame some of these experimental limitations to explore somatic mutations and selection in individual melanocytes — the type of skin cell that can give rise to the cancer melanoma.

The epidermis is the skin's outermost layer. Just 0.1 millimetres thick, the epidermis is battered by mutation-promoting ultraviolet rays over a person's lifetime, and is the origin of the vast majority of skin cancers.

To understand the extent of somatic mutation in a human tissue, and the origin of skin cancers, a previous study[2] used DNA sequencing of small biopsies of normal epidermis. This revealed not only that mutations are common in normal cells, but also that mutations in cancer-promoting genes favour the growth

of small groups of mutant cells (clones) that progressively colonize our skin as we age. However, the sequencing of biopsies of epidermis made up of thousands of cells mostly detected mutations in cells called keratinocytes, which comprise around 90% of all cells in the epidermis[3]. These are the cells from which the common, but typically treatable, non-melanoma skin cancers develop. The origins of melanoma, a rarer but more lethal form of skin cancer, lie in single cells scattered throughout the skin, called melanocytes (Fig. 1). These cells produce a pigment called melanin that gives skin its colour and protects it from the onslaught of sun damage.

To detect mutations in melanocytes, Tang *et al.* had to devise reliable ways to sequence the DNA of single cells. Two main approaches have been used for other cell types: single-cell sequencing, which relies on error-prone, whole-genome amplification[4]; and growing single cells into colonies of thousands of cells in a dish, which enables the use of more-reliable sequencing methods[5,6]. The former approach introduces many errors per cell that can be mistaken for genuine mutations, whereas the latter method is restricted in use to cells that grow well *in vitro*. Melanocytes are difficult to grow into large colonies of cells *in vitro*, so Tang *et al.* combined the two approaches, growing single melanocytes *in vitro* into colonies of tens to hundreds of cells; only then did they undertake the whole-genome amplification step, thus minimizing DNA sequencing errors.

Through a series of clever analyses and controls, which included sequencing DNA and RNA from each colony to confirm certain mutations, the authors could reliably detect somatic mutations found in single melanocytes. The accuracy of the results was also helped by the fact that skin cells, including melanocytes, have much higher mutation rates than the rates of other cells in the body[6], minimizing the confounding effect of sequencing errors arising from the amplification approach.

Tang *et al.* sequenced key parts of the genomes of cellular colonies derived from 133 individual melanocytes, collected from 19 body sites in 6 deceased donors. The donors included two people with skin cancer, as well as cancer-free individuals. They were all of European ancestry, and their ages ranged from 63 to 85 years. Although the modest sample size is a limitation of the study, the biological insights from this technical tour de force are remarkable.

Reassuringly, the vast majority of mutations detected had the expected characteristic signature of DNA alterations associated with ultraviolet damage. The number of mutations per melanocyte varied widely across donors and body sites, with an average of around 20,000 mutations per cell in sun-exposed areas, which is approximately similar to the number of mutations found in melanomas[2]. An unexpected observation is that chronically sun-exposed skin (on the face, for example) had lower numbers of mutations than did intermittently sun-exposed skin (in areas such as the thigh or back). The authors speculate that this finding could explain why most melanomas occur in intermittently sun-exposed areas, although further analysis, using more donors, will be needed to confirm this observation.

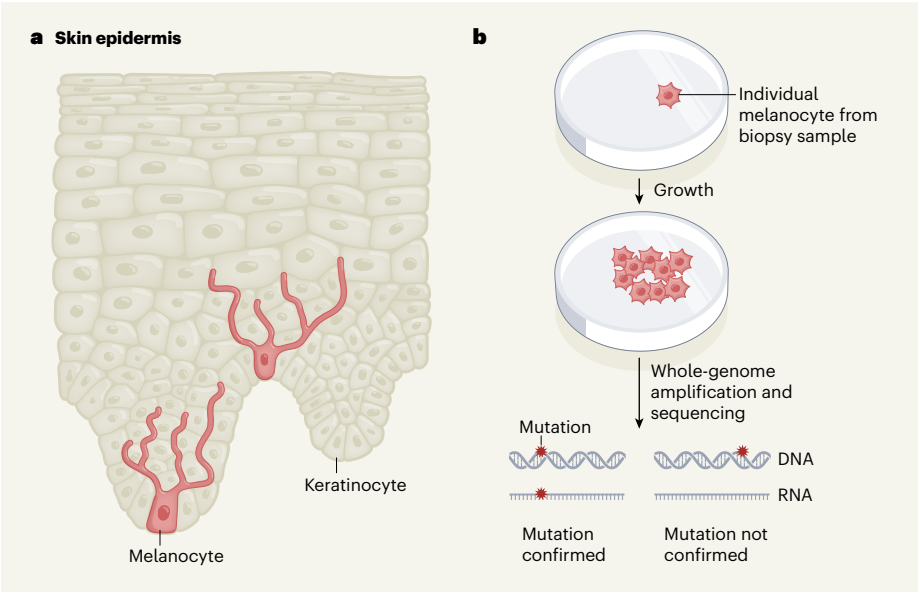

Figure 1 | Identifying mutations in human skin cells. a, Tang *et al.*[1] analysed a type of cell called a melanocyte, which is present at the base of the skin's outer layer (termed the epidermis). Cancer-promoting mutations in melanocytes can lead to the formation of a lethal cancer known as melanoma. Studying mutations in these cells is difficult because the cells are rare compared with another type of epidermal cell, called a keratinocyte. **b**, The authors obtained biopsied samples of human skin, and isolated individual melanocyte cells from healthy individuals and from people with skin cancer. After growing individual cells *in vitro* to obtain colonies of cells, Tang and colleagues used the method of whole-genome amplification, and sequenced DNA. To determine whether the possible mutations identified were genuine or the result of sequencing errors, the authors compared DNA and RNA sequencing results corresponding to the same genetic region to check whether the results matched.

A second finding, which was even more unexpected, is that some melanocytes in sun-exposed tissues had many fewer mutations than did other melanocytes in the same biopsy sample. The origin of these cells is unclear. One possibility is that they previously resided in a site safe from sun damage, such as a hair follicle, that provided a protected niche. Tang and colleagues' observation of a population of seemingly 'protected' cells among highly mutated cells is reminiscent of the discovery[7] that some lung cells in ex-smokers do not have characteristic tobacco-induced mutations, and that these cells might even slowly replace the lung cells damaged by years of smoking. Future studies to investigate melanocytes with surprisingly low numbers of mutations will be of interest to understand the origin and function of such cells.

By analysing genes involved in the development of melanoma, Tang *et al.* found that around 20% of melanocytes had one melanoma-driving mutation (occasionally, some cells had two such driver mutations). Interestingly, the authors observed that these mutations can lead to melanocyte growth that results in 'scattered fields' of mutant melanocytes, as suggested by evidence that some melanocytes obtained from the same biopsy shared the same driver mutations. In the past few years, studies of several tissues[2,8,9] have reported similar observations of mutations in cancer-driving genes promoting the growth of cells to form mutant clones. This previously unknown phenomenon is emerging as a common feature of ageing across multiple tissues.

The cancer-promoting mutations in melanocytes found by Tang and colleagues occurred mainly in well-documented melanoma-promoting genes that activate the MAPK signalling pathway, such as *BRAF* and *NRAS*. Remarkably, the two most-common mutations in melanoma (a mutation termed $BRAF^{V600E}$ and mutation of the regulatory promoter region of the *TERT* gene)[10] are absent from the list. To explain this conundrum, the authors propose that melanomas emerge from two main routes. Either they arise from existing moles in the skin, which often have the $BRAF^{V600E}$ mutation, or they form *de novo* without a pre-existing mole. The cancer-driving mutations found by the authors in scattered melanocytes might therefore represent the origins of some *de novo* melanomas.

This carefully conducted study offers an unprecedented view of the landscape of somatic mutations in normal melanocytes, providing new clues about the origins of melanoma and presenting many intriguing observations that should motivate further research. Together with similar efforts in other tissues, studies such as this one by Tang and colleagues are rapidly changing our understanding of somatic mutations in normal tissues and the relevance of these mutations for health and disease.

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1. Tang, J. *et al. Nature* **586**, 600–605 (2020).
2. Martincorena, I. *et al. Science* **348**, 880–886 (2015).
3. McGrath, J. A., Eady, R. A. J. & Pope, F. M. in *Rook's Textbook of Dermatology* (eds Burns, T., Breathnach, S., Cox, N. & Griffiths, C.) Ch. 3 (Blackwell, 2004).
4. Lodato, M. A. *et al. Science* **348**, 880–886 (2015).
5. Welch, J. S. *et al. Cell* **150**, 264–278 (2012).
6. Blokzijl, F. *et al. Nature* **538**, 260–264 (2016).
7. Yoshida, K. *et al. Nature* **578**, 266–272 (2020).
8. Jaiswal, S. *et al. N. Eng. J. Med.* **371**, 2488–2498 (2014).
9. Kennedy, S. R., Zhang, Y. & Risques, R. A. *Trends Cancer* **5**, 531–540 (2019).
10. Huang, F. W. *et al. Science* **339**, 957–959 (2013).

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Geoscience

Melt mapped inside Earth's mantle

Laura Cobden

An analysis of seismic data reveals the location and quantity of melted rock, known as melt, in Earth's upper mantle. The results show how these factors are correlated with the movement of the planet's tectonic plates. **See p.555**

Throughout most of Earth, seismic waves speed up as they travel deeper. A notable exception is the boundary between the rocky mantle and the liquid outer core, at a depth of about 2,900 kilometres. A second slow region, commonly referred to as the low-velocity zone (LVZ), lies directly beneath the tectonic plates. The origin of this region, where wave speeds can suddenly drop by up to 10% (ref. 1), has been debated because reductions in wave speed can be caused by many factors. By combining measurements of wave speed with those of a second observable quantity, the attenuation (energy dissipation) of seismic waves, Debayle *et al.*[2] (page 555) demonstrate that partial melting of the mantle is the most probable explanation for the LVZ.

Earth's tectonic plates represent both a thermal and a mechanical boundary layer to the vigorous convection that takes place inside the mantle. Although other rocky planets also have a rigid outer layer (lithosphere), Earth is unusual in having moving plates. It is thought that plate mobility is aided by the presence of a low-viscosity layer, called the asthenosphere, over which the plates can readily slide (Fig. 1). The fact that the LVZ is seen at depths coincident with the asthenosphere (about 60–300 km) suggests a causal relationship. However, the LVZ might not be present at all locations around the globe, and has mostly been found beneath oceanic plates.

Observations of the LVZ date back as far as the 1950s[3]. Originally, the presence of melted rock (melt) was used to explain both the low wave speeds and the mechanical weakness of the LVZ. In the past 15 years, this interpretation has been questioned[1] because the amounts of melt required to give the observed wave-speed reductions are potentially too large to be dynamically stable, given estimated rates of melt production and extraction[4]. This discrepancy might be reconciled if the melt is concentrated into thin layers embedded in melt-free mantle regions[5]. Alternatively, the LVZ could be generated by the release of water from subducting plates[6] (whereby an oceanic plate sinks into the mantle) or by thermally activated deformation along grain boundaries[1] (the interfaces between mineral grains).

As seismic waves travel through Earth, they continually lose energy. Part of this attenuation is caused by geometric spreading of the waves and their scattering off large lateral or vertical structural changes in the mantle. However, a sizeable component is the result of the wave-propagating medium having intrinsic anelasticity — a delay in the deformation of a material in response to applied stress. Such anelasticity is mostly caused by internal friction (for example, along grain boundaries), and it leads to decreases in both wave speed and amplitude. At the temperatures and pressures of the upper mantle, the wave-speed reductions become substantial, and some studies suggest that anelasticity effects alone might be sufficient to generate the LVZ (see ref. 7, for example).

Seismic attenuation is defined in terms of the quality factor, Q, where Q^{-1} represents the fractional loss in energy per wave cycle. Combining measurements of wave speed and Q provides a powerful tool[8] for discriminating between the different hypotheses for the LVZ. This is because wave speed is sensitive to variations in temperature, chemical composition and melt fraction, whereas Q is predominantly controlled by temperature, at a given depth and seismic frequency, assuming that there is limited contribution from scattering. For a fixed chemical composition, one can vary the

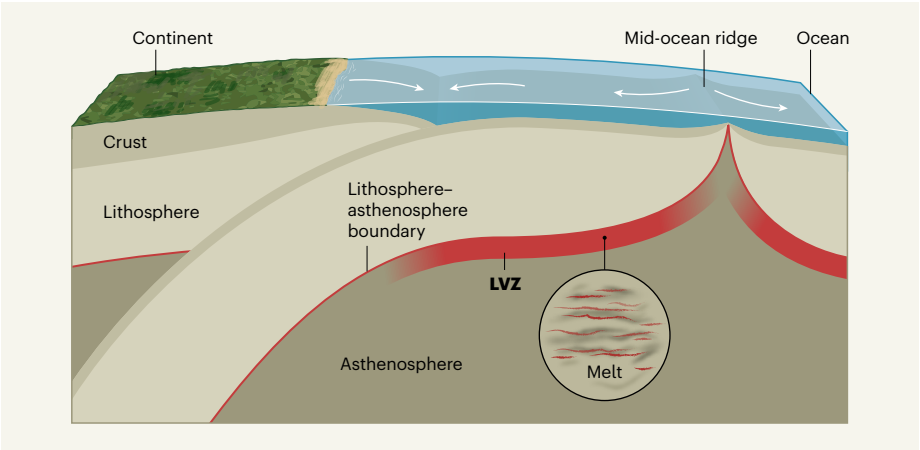

Figure 1 | Location and possible origin of the low-velocity zone (LVZ). The movement of Earth's tectonic plates (white arrows) is thought to be aided by a low-viscosity layer known as the asthenosphere. Shown here is an oceanic plate being pushed beneath a continental plate, and the separation of two oceanic plates at a mid-ocean ridge; each of these plates consists of a lithosphere (rigid outer layer) and crust. The LVZ is a region in which the velocity of seismic waves is lower than that in the layers above and below. This region is situated close to the boundary between the lithosphere and asthenosphere, mostly beneath oceanic plates. Debayle *et al.*[2] show that the most probable explanation for the LVZ is the presence of melted rock (melt). Such melt is probably concentrated into thin layers embedded in melt-free regions[5].