allow the cocoon to be detected within a day of the stellar explosion.

According to theoretical models[11], the cocoon moves faster than the envelope, but more slowly than the jet. Moreover, the jet is expected to drag material from the core of the exploding star and to deposit it in the cocoon[13,14]. Indeed, Izzo *et al.* find broad absorption features in the supernova spectra that correspond to an outflow that is moving up to one-third the speed of light. These features indicate that the fast-moving material is substantially enriched in 'iron-peak' elements (such as iron, cobalt and nickel), which must have been produced in the stellar core during the explosion. The authors' observations provide direct evidence that material from the stellar core is dragged along by the jet and deposited in the outermost layers of the envelope.

Although the γ-ray burst itself was faint, suggesting a weak jet, the energy deposited in the cocoon revealed that the jet was highly energetic. This finding might imply that the observed faint γ-rays originate from a jet that is pointing slightly away from Earth. Alternatively, a more intriguing possibility, and one that I think is more probable, is that we are seeing the cocoon directly, and that the faint γ-rays are the predicted signal of the cocoon breaking out of the stellar envelope[8–10]. Evidently, Izzo and colleagues' exquisite data set carries a lot of information, and considerable theoretical work will be needed to uncover its full ramifications.

Even after decades of extensive astrophysical study, the processes by which massive stars explode are not fully understood, and the role of jets, if they have one, is unknown. Moreover, although jets are rarely observed in these explosions, it is possible that they are much more common than the observations would suggest. Jets require specific conditions to successfully cross the entire stellar envelope and break out. Most probably, many jets are 'choked' — they dissipate all of their energy while still buried in the envelope[15]. Although such choked jets cannot be seen directly, their cocoons can still break out (Fig. 1c; see also the movies at go.nature.com/2sdoeao), and therefore hold the key to identifying these hidden jets.

Remarkably, choked jets in supernovae might have been identified already. Broad absorption features from fast-moving material were seen in early spectra of several supernovae, and have been interpreted as the signature of jet-driven cocoons[12]. Most intriguingly, these features have been found not only in supernovae that are associated with γ-ray bursts, but also in several that are not[12]. Izzo and colleagues' findings support the interpretation of these observations as the marks of hidden jets.

The future looks promising. Next-generation wide-field optical surveys will detect many supernovae within less than a day of their explosion, enabling an effective search for the telltale cocoons. Izzo and colleagues' results pave the way for these searches, which could resolve the long-standing enigma concerning the role of jets in the explosive deaths of massive stars. ■

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1. Alsabti, A. W. & Murdin, P. *Handbook of Supernovae* (Springer, 2017).
2. Piran, T. *Rev. Mod. Phys.* **76**, 1143–1210 (2005).
3. Izzo, L. *et al. Nature* **565**, 324–327 (2019).
4. Blandford, R. D. & Rees, M. J. *Mon. Not. R. Astron. Soc.* **169**, 395–415 (1974).
5. Mészáros, P. & Rees, M. J. *Astrophys. J.* **556**, L37–L40 (2001).
6. Bromberg, O., Nakar, E., Piran, T. & Sari, R. *Astrophys. J.* **740**, 100 (2011).
7. Ramirez-Ruiz, E., Celotti, A. & Rees, M. J. *Mon. Not. R. Astron. Soc.* **337**, 1349–1356 (2002).
8. Kulkarni, S. R. *et al. Nature* **395**, 663–669 (1998).
9. Campana, S. *et al. Nature* **442**, 1008–1010 (2006).
10. Nakar, E. *Astrophys. J.* **807**, 172 (2015).
11. Nakar, E. & Piran, T. *Astrophys. J.* **834**, 28 (2017).
12. Piran, T., Nakar, E., Mazzali, P. & Pian, E. Preprint at https://arxiv.org/abs/1704.08298 (2017).
13. Maeda, K. *et al. Astrophys. J.* **565**, 405–412 (2002).
14. Maeda, K. & Nomoto, K. *Astrophys. J.* **598**, 1163–1200 (2003).
15. Bromberg, O., Nakar, E., Piran, T. & Sari, R. *Astrophys. J.* **749**, 110 (2012).

MEDICAL RESEARCH

Mutations differ in normal and cancer cells

What determines whether genetic mutations lead to cancer? Analyses of healthy cells in the human oesophagus reveal that a high level of genetic alterations arises as people age, yet this doesn't usually result in cancer. SEE ARTICLE P.312

FRANCESCA D. CICCARELLI

Errors in DNA replication can alter a cell's DNA sequence. If such alterations occur early enough in embryonic development, the changes are inherited by all of an organism's cells. But if the alterations arise later in adult life, it is more difficult to track such changes in a small number of cells in a specific tissue, so the extent of these alterations in normal tissues is poorly understood. It is thought that cancer is initiated when cells acquire a minimum compendium of genetic alterations needed to trigger tumour formation. Understanding when such initiating mutations occur in normal cells is crucial for enabling reconstruction of the early events that lead to cancer. Yokoyama *et al.*[1], on page 312, and Martincorena *et al.*[2], writing in *Science,* have analysed the extent of mutations in human epithelial tissue from the healthy oesophagus, and how this relates to the processes that drive cancer development.

Martincorena and colleagues sequenced 74 cancer-associated genes in 844 tissue samples taken from the upper oesophagus of 9 healthy donors who differed in gender, age and lifestyle. For 21 of these samples, the authors also determined whole-genome sequences. A previous study[3] assessing mutations in healthy skin cells reported between two and six mutations per million nucleotides of DNA. By contrast, Martincorena and colleagues report that the mutations in oesophageal cells arose at a roughly tenfold lower rate than that reported for skin. This difference is unsurprising, because skin cells are exposed to more DNA-damaging agents, such as ultraviolet light, than are oesophageal cells.

Instead, the surprise is that, compared with healthy skin, the healthy oesophagus has more mutations in cancer-associated genes. Moreover, at least a subset of these altered genes was under strong positive selection, meaning that the genetic alterations promoted cell proliferation, leading to the formation of cell clones (Fig. 1). Compared with the samples from younger people, the overall number of mutations, the number of mutations in cancer-associated genes and the size of the clones were all greater in the samples from older people. The authors found that the donors' samples had an average of about 120 different mutations in *NOTCH1*, a known cancer-associated gene, per square centimetre of normal oesophageal tissue. Several of these mutations were of the same type as those seen in a cancer of the upper oesophagus called oesophageal squamous cell carcinoma (OSCC).

Yet despite these similarities, there were striking differences between the expansion of cell clones in the normal oesophageal tissue and in OSCC. Normal and cancerous clones seem to be driven by mutations in different genes. *NOTCH1* was the most frequently mutated gene in healthy oesophageal samples, whereas a previous study[4] reported

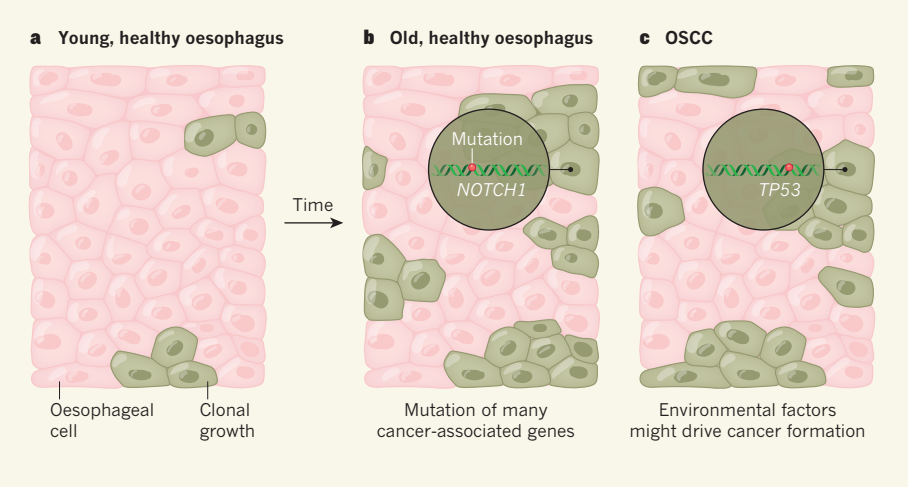

Figure 1 | Mutations in the human oesophagus. Yokoyama *et al.*[1] and Martincorena *et al.*[2] analysed the mutations that arise in oesophageal tissue during healthy ageing, and compared these with changes that occur in a cancer called oesophageal squamous cell carcinoma (OSCC). **a**, The authors report that, in oesophageal samples from young, healthy individuals, only a small percentage of tissue has cells with cancer-associated mutations, and that such cells divide to form cell clones (green). **b**, By comparison, samples from older, healthy individuals contained many more of these mutations and cell clones. The authors report that the most commonly mutated gene in tissue samples from older healthy individuals is *NOTCH1*. **c**, The authors found that a mutation in *TP53* was the most common genetic alteration in OSCC. It is thought that environmental factors might have a role in driving the genetic alterations that cause OSCC[7,8].

that *NOTCH1* was mutated in only around 10% of OSCCs. Mutations in the cancer-promoting gene *TP53* are found in more than 90% of OSCC cases[4], but were present at a much lower frequency in normal oesophageal samples.

In normal cell clones, Martincorena *et al.* found that the prevalent mutational signatures (the type of nucleotide changes and the DNA context in which these occur) were typical of physiological processes, such as the mutational changes that occur over time owing to errors in DNA replication. By contrast, OSCC is dominated mostly by mutational signatures associated with mutation-causing agents, such as cigarette smoking, alcohol intake or an enzyme called APOBEC that can modify DNA[5]. Another hallmark of OSCC is chromosomal instability, which causes frequent gene loss or gain[4]. Martincorena and colleagues observed low levels of chromosomal instability in healthy oesophageal cells.

Yokoyama and colleagues' results were similar to those of Martincorena and colleagues. Yokoyama *et al.* analysed 682 samples of healthy and cancerous oesophageal tissue from 139 individuals, who differed in their ages and risk of developing OSCC. To determine DNA sequences, the authors used a combination of approaches, ranging from the sequencing of whole genomes and whole exomes (protein-coding regions) to the resequencing of specific genes. They found mutations in normal tissue samples from people who had cancer and in samples from healthy individuals. The number of mutations in the normal oesophagus increased with age and exposure to known cancer-risk factors.

Yokoyama *et al.* also observed most of the same differences between normal and cancerous cell clones as those noted by Martincorena and colleagues. Using two computational approaches, they identified 24 genes that were frequently mutated in the healthy and cancerous samples, but only 6 of these were altered in both. Consistent with the study by Martincorena and colleagues, Yokoyama *et al.* found that *TP53* and *NOTCH1* were the most commonly mutated genes in cancerous and healthy clones, respectively. The age-related mutational signature was prevalent in normal oesophageal cells, especially in individuals who were at low risk of developing OSCC. By contrast, mutational signatures associated with APOBEC activity or alcohol intake were prevalent in cancer samples and detectable in normal samples from individuals at higher risk of cancer. The authors detected few chromosomal alterations in normal samples and confirmed the high level of chromosomal instability in OSCC.

Both studies offer insights into the evolution of healthy tissues as people age, and prompt speculation about how this might relate to cancer. The clonal expansion of normal oesophageal cells after cancer-promoting genes have mutated seems to be necessary, but not sufficient, to drive cancer, so something else must happen to the cells for tumours to form. For example, gaining a large-enough number of alterations in cancer-promoting genes might be needed. In both studies, few of the mutations were present in all the cells of the normal clones, and many of the cancer-promoting mutations were often found in spatially distinct subclones. This suggests that none of the normal cells had acquired enough cancer-promoting alterations to start cancer formation.

Other missing factors needed to drive cancer formation might be of environmental origin. The incidence of OSCC is high in Asia and South America, but is low in the Western world[6]. The reasons underlying this geographic distribution are mainly unknown, but it is thought that lifestyle and environmental factors might have key roles[7,8]. All donors providing samples for Martincorena and colleagues' study were from the United Kingdom, and so the mutated cells had probably not been exposed to external factors that can drive the initiation of OSCC. By contrast, the samples analysed by Yokoyama and colleagues were from Japanese individuals, and some of the donors were at high risk of developing OSCC. Yet even in these individuals, several normal clones that seemed to have been present for a long time had not developed into cancer. For example, a clonal expansion in a 70-year-old individual with a high risk of developing OSCC probably started with a mutation in *TP53* that the authors estimated occurred when the individual was 13 years old. Over the many decades, this clone expanded to reach an area of 7 square millimetres, but did not develop into cancer. This indicates that other factors needed for that to happen were lacking.

Another tempting speculation concerns the cancer-driving role of *NOTCH1* and other cancer genes that were more frequently mutated in normal tissue than in cancer tissue. It seems that alterations in these genes are not necessarily early events in cancer progression. Their relatively high mutation frequency in OSCC might simply be because these genes are often mutated in normal tissue. This challenges the idea that common gene alterations in cancer samples indicate genetic changes that are likely to have a cancer-promoting role. Yet this is still the most-common approach used to identify cancer-associated genes[9].

Further investigation is needed into the possible role of non-cancer-associated gene mutations in the clonal expansion of normal tissues. Given the partially independent mechanisms that seem to drive the expansion of normal and cancerous clones, perhaps mutations in genes involved in other processes, such as ageing, might be functionally important in normal clones. Martincorena and colleagues mainly sequenced well-known cancer-promoting genes, and therefore such analysis was not feasible in their study.

Yokoyama and colleagues sequenced all protein-coding regions of the genome, but used only well-established computational approaches to find cancer-promoting mutations in normal samples. Unsurprisingly, they found mostly known cancer-associated genes. Interestingly, they discovered that the gene *PAX9* , which encodes a transcription factor, is commonly mutated in normal oesophageal tissue. Mutations in *PAX9* have not so far been

associated with cancer. This suggests that a less 'cancer-centric' analysis might reveal other genes that can drive the expansion of clones in normal tissue.

We are only starting to map the extent of genetic alterations in normal tissues. The next challenge will be to fully understand their role in healthy tissues and in disease states. ■

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1. Yokoyama, A. *et al. Nature* **565**, 312–317 (2019).
2. Martincorena, I. *et al. Science* **362**, 911–917 (2018).
3. Martincorena, I. *et al. Science* **348**, 880–886 (2015).
4. The Cancer Genome Atlas Research Network. *Nature* **541**, 169–175 (2017).
5. Chang, J. *et al. Nature Commun.* **8**, 15290 (2017).
6. Arnold, M., Soerjomataram, I., Ferlay, J. & Forman, D. *Gut* **64**, 381–387 (2015).
7. Abnet, C. C., Arnold, M. & Wei, W.-Q. *Gastroenterology* **154**, 360–373 (2018).
8. Coleman, H. G., Xie, S.-H. & Lagergren, J. *Gastroenterology* **154**, 390–405 (2018).
9. Repana, D. *et al. Genome Biol.* https://doi.org/10.1186/s13059-018-1612-0 (2018).

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MATERIALS SCIENCE

Hardening mechanisms scaled up

Metals can be strengthened by mechanisms that work on the atomic scale. These same mechanisms used at a much larger scale have been found to also strengthen materials that contain hierarchical, engineered substructures. SEE ARTICLE P.305

GANG SEOB JUNG & MARKUS J. BUEHLER

Atomic-scale mechanisms that affect the structural properties of materials can also inform the design of new materials needed for engineering, such as high-performance alloys. On page 305, Pham *et al.*[1] report their use of 3D printing to translate some atomic-level hardening mechanisms typically found in crystalline materials to a larger scale. The resulting 'architected' materials contain substructures that are designed to mimic atomic arrangements in crystal lattices. Their work provides a fresh approach for developing designer materials and could facilitate the application of hardening mechanisms to different materials and on different scales.

Engineers have a diverse array of tools at their disposal for designing and constructing new materials. Additive manufacturing[2], also known as 3D printing, is one such tool that could revolutionize the field of materials fabrication, in part because it can produce almost any geometric feature. An idea that has received much attention involves using additive manufacturing to make materials that have complex microstructures[3], which are difficult to construct using conventional methods.

Natural materials such as bone, silk and nacre have exceptional properties that many conventional engineering materials lack. These properties arise from the materials' complex hierarchical structures — the macroscopic materials are built up from repeating patterns of smaller building blocks at several different length scales. Additive manufacturing has been used to reconstruct the hierarchical patterns of building blocks found in natural materials, but instead using conventional materials. The products have mechanical properties — such as high toughness, strong impact resistance and the ability to bear heavy loads — that exceed those of the conventional materials[4], and are called architected materials. Many studies have focused on developing approaches that allow hierarchical features of natural materials to be mimicked in completely different classes of material[5]. For example, one could generate a nacre-like material from synthetic polymers, rather than using the exact materials found in nacre.

Structures composed of repeating building blocks are commonly found in crystalline materials such as metals, ceramics and rocks. At the smallest scale, the atoms in crystals form a well-defined lattice in which the packing of atoms in the unit cell (the smallest repeating unit of the lattice) depends on the nature of the atoms' bonds and electronic structures. However, crystals are usually formed from microscopic grains whose lattices are oriented in different directions. If the configurations of atoms at the edges of different grains do not line up with one another, lattice defects form, which are commonly considered to be weak points. In brittle materials, cracks can be initiated from defects such as grain boundaries, and propagate rapidly.

But grain boundaries can have a positive role in ductile materials. Metals under a load typically fail not because bonds between atoms suddenly break, but because atoms slide along a specific plane within a lattice. Such sliding occurs as a result of defects known as

50 Years Ago

The collection of inventions that was on show … last week involved the onlooker in frantic changes of mood, switching his attention one minute to practical mechanical devices and the next to the thrills of psychedelic lighting or the niceties of tea blending … Among the household items was a flower pot designed to maintain a steady trickle of water in the gardener's absence, a new type of safety window for schools and hospitals, and for a wider audience a typewriter with keyboards in Japanese, musical notation or what you will.
From *Nature* 18 January 1969

100 Years Ago

The ex-President of the United States who died in the first week of 1919 was in many ways the most remarkable man … and combined with unusual qualities of intellect and co-ordinated development of bodily skill — for was he not a fine shot, a bold equestrian, an untiring marcher, an adept at most games and sports? — a kindness and sweetness of disposition, and a thoughtfulness for the happiness and well-being of all around him, very rare in great men of the world … Theodore Roosevelt was not only a great naturalist himself, but — what in its ultimate effect was even more important — he set, as President, the fashion in young America for preserving and studying fauna and flora until he had gone far to create a new phase of religion. Under his influence young men whose fathers and grandfathers had only studied the Bible, the sacred writings of the post-exilic Jews and Graeco-Syrian Christians, now realised that they had spread before them a far more wonderful Bible, the book of the earth itself. Geology, palaeontology, zoology, botany, ethnology, were part of Roosevelt's religion.
From *Nature* 16 January 1919