factors Lmx1a and Foxa2; these are expressed in the progenitors of dopamine-releasing neurons during midbrain development and are required for the maturation of these progenitors into neurons[9]. PTB depletion further increased the expression of these factors in midbrain astrocytes. By contrast, in cortical astrocytes, the treatment led to increased levels of transcription factors associated with cortical neurons, such as Ctip2 and Cux. In addition, reprogramming of astrocytes in the substantia nigra, or in the neighbouring ventral tegmental area, produced different subtypes of iDA neuron that express subtype-specific transcription factors and proteins: Sox6 and Aldh1a1 in the substantia nigra, Otx2 in the ventral tegmental area.

Qian and colleagues' results indicate that brain-region-specific transcription factors contribute to the astrocyte-to-iDA conversion. However, such a mechanism cannot explain why Zhou *et al.* were able to convert striatal astrocytes to iDA neurons, given that striatal astrocytes express a different set of region-specific transcription factors. What might be the mechanism leading to iDA conversion in the striatum?

Zhou and colleagues show an almost threefold increase in iDA conversion efficiency in the mouse model of Parkinson's disease compared with control mice one month after treatment. These results suggest that astrocytes themselves, or cells in their environment, respond to the loss of endogenous dopamine-releasing neurons by expressing factors that promote the conversion of astrocytes to iDA neurons. And Qian *et al.* found higher conversion efficiency in the mouse midbrain than in isolated midbrain astrocytes, indicating a role for local brain-derived factors in iDA conversion. Identifying local and damage- or disease-specific factors, intrinsic or extrinsic to cells, holds the key to further improving the efficiency of astrocyte-to-neuron conversion.

One intriguing question to arise from these studies is why astrocytes are constantly repressing neuronal genes. One explanation might lie in the cells' developmental origin. Astrocytes and neurons have common ancestors called radial-glia progenitors — stem-cell-like cells that first give rise to neurons and then differentiate into astrocytes and other neuron-supporting glial cells[10]. In the developing mouse midbrain, all radial-glia cell types express *Ptbp1*, whereas differentiating neuron precursors and neurons do not[11]. Perhaps midbrain astrocytes — as descendants of radial glia — have inherited a program to generate neurons that lies dormant unless PTB is depleted (Fig. 1). *Ptbp1* is also expressed in other midbrain cell types[11], including endothelial and pericyte cells in the blood vessels, ependymal cells lining the ventricular cavity and immune cells called microglia. Future studies should examine whether PTB depletion can also convert these cells to iDA neurons in animal models of Parkinson's disease.

For this strategy to be useful in the clinic, its efficiency might need to be improved. For instance, 60–65% of the infected astrocytes do not become iDA neurons. This percentage must decrease, either through more-focused targeting of astrocytes in the substantia nigra, or by introducing factors that enable non-nigral astrocytes to convert to iDA neurons. It will also be important to determine the quality and authenticity of the converted iDA cells at single-cell level, and to investigate whether unwanted cells are generated. Both Qian *et al.* and Zhou *et al.* provide evidence that astrocytes are converted to other neuron types, besides iDA cells. Moreover, Qian *et al.* show that converted iDA neurons mainly project to the septum, rather than the striatum, and that only 8% of the fibres that project to the septum come from iDA neurons. However, on a positive note, more than half of the fibres reaching the striatum were contributed by iDA neurons. This finding — together with the demonstration that the conversion process restored striatal dopamine levels and motor activity — provides evidence for a remarkable functional reconstitution of the nigrostriatal pathway by iDA neurons.

In a final set of experiments, Qian *et al.* explore a way in which their approach might be used in the clinic: using short nucleic acids called antisense oligonucleotides that bind to an mRNA and prevent its translation into protein. The authors show that local transient delivery of antisense oligonucleotides against PTB led to the generation of iDA-like neurons and to motor recovery in the mouse model of Parkinson's disease, demonstrating the validity of the approach.

Future experiments will need to examine whether human midbrain or striatal astrocytes can also be converted to iDAs, and whether the converted cell types and their targets are correct and stable over long periods. The safety of PTB depletion and the strategies used to deliver the treatment will also have to be carefully assessed, to rule out any collateral damage to bystander host brain cells or to the converted cells, or any damage resulting from the strategy's depletion of astrocytes. Although many questions remain to be answered, the simplicity and efficiency of this gene-therapy approach to cell replacement makes it very attractive. The current studies promise to open a new chapter in the development of regenerative medicine for neurological disorders such as Parkinson's disease.

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Archaeology

Large-scale early Maya sites revealed by lidar

Patricia A. McAnany

Archaeology is transforming our view of how ancient Maya societies developed. Use of lidar technology has now led to the discovery that large, monumental structures that aid naked-eye astronomy were built unexpectedly early. **See p.530**

In archaeology, there are few watershed moments, when a technological breakthrough changes everything. But the invention of radiocarbon dating in the 1940s brought one such revolution, by providing a consistent, worldwide system for placing archaeological material in chronological order. A more-recent transformative innovation is the airborne application of a remote-sensing technique called light detection and ranging (lidar) to create a model (also known as a digital-elevation model) of the bare-surface terrain that is hidden by trees in forested areas[1]. Lidar is changing archaeological study of the ancient Maya in Mexico and Central America. It is increasing the speed and scale

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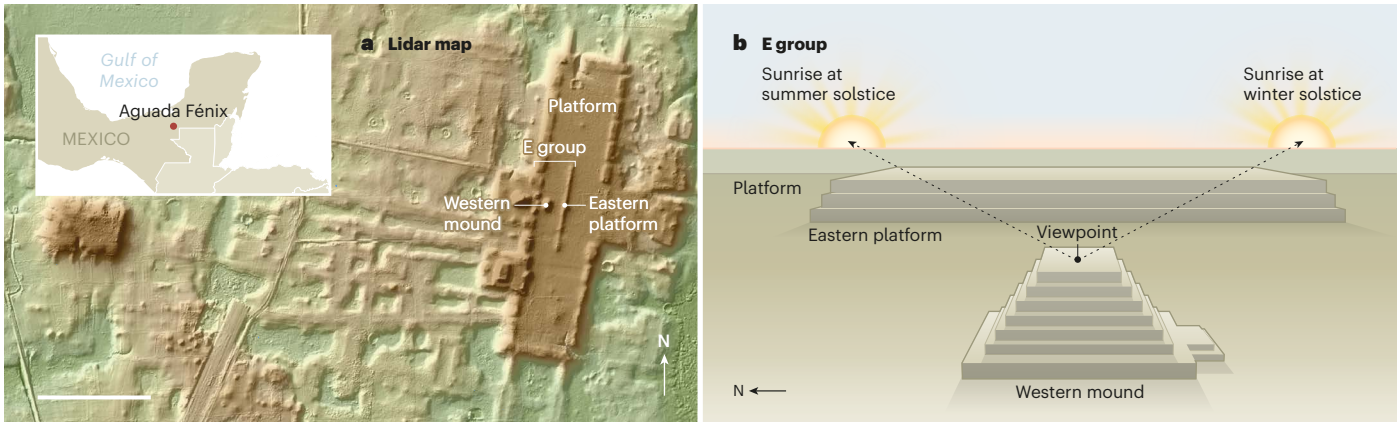

A. IMAGE, TAKESHI INOMATA

Figure 1 | An early Maya site. a, Inomata *et al.*[2] report the discovery of a site in Mexico at Aguada Fénix that is associated with the ancient Maya. Using surface-mapping technology called lidar, followed by excavations, the authors reveal a huge platform built from clay and earth that dates to 1000–800 BC. It contains a type of structure called an E Group (comprising a western mound and eastern platform) that is associated with astronomical observations. Inomata and colleagues' finding reveals surprisingly early large-scale landscape alterations pre-dating the emergence of Maya royal courts and providing insight into how Maya societies developed. Scale bar, 500 metres. **b**, In a typical E-Group arrangement, a western mound or pyramid provides a viewing site that aids the observation of sunrise on the horizon at the summer and winter solstices. These events are viewed by looking towards the corners of an elongated platform to the east.

of discovery, and reshaping our understanding of the antiquity of monumental-scale landscape alteration. On page 530, Inomata *et al.*[2] provide a prime example of this in their study of the region of Tabasco in Mexico that borders the Usumacinta River.

Lidar requires an aeroplane or drone to fly over the area of interest. Laser pulses are emitted and signals bouncing back generate what is termed a point cloud of data points. Expert image processing and prodigious computer capacity can then yield models of bare terrain from which the vegetation has been digitally removed. In areas where dwellings, platforms, pyramids and even palaces can be obscured by high-canopy vegetation, a bare-terrain model yields something close to a topographic map of the surface. Straight lines and corners in a bare-terrain model suggest elements that have human rather than geological origins.

Generating such models might not sound impressive for arid landscapes, but it is a game changer where high-canopy trees obscure the view. Lidar images from one plane flight can provide more information than can be generated by decades of conventional archaeological surveys. As a veteran of pre-lidar survey techniques and an archaeologist who works in the humid tropics that are associated with ancient Maya civilizations, I have spent thousands of hours of fieldwork walking behind a local machete-wielding man who would cut straight lines through the forest. This process creates a grid within which we archaeologists proceed on foot to locate any structures present. Then, after more machete-cutting to reveal the corners, shape and height of ancient constructions, the structures could finally be mapped.

This time-consuming process has required years, often decades, of fieldwork to map a large ancient Maya city such as Tikal in Guatemala and Caracol in Belize. At Caracol, laborious clearing and mapping were under way for decades before lidar quickly revealed the full extent of the agricultural terraces and settlement[1]. Bare-terrain models produced by lidar imagery include coordinate information (such as latitude and longitude) that can be used to 'ground-truth' the results by examining the specific physical site. Machete-cutters are still needed during this ground-truthing step.

Airborne lidar has been of benefit for the study of other archaeological sites in tropical forests, such as those at Angkor Wat in Cambodia[3]. Lidar data have revealed artificial reservoirs built around the temples there, yielding subtle hints about the limits to the resilience of this complex hydraulic system. This research has also underlined the vastness of the landscape modifications undertaken by people of the Khmer Empire[4].

Back in the tropical forests of Petén in Guatemala – the heartland of Maya 'divine' rulers during the Classic period (AD 250–800) – is a region called the Maya lowlands that archaeologists have studied nearly continuously since the mid-twentieth century. Intriguing because of its hieroglyphic writing system, naturalistic sculpture and painting style, and adroitness in maize (corn) farming, Classic-period Maya society was organized politically around dozens of royal courts. Archaeologists have lavished much attention on these courts, but only a small fraction of the landscape beyond and between them has been mapped using conventional methods.

To remedy this, a large lidar programme was initiated[5]. The resultant bare-terrain models show a landscape that was intensively and deliberately modified by humans in a way that would easily have escaped detection by even the most seasoned conventional field mappers. The spatial continuity of landscape modifications can be more obvious when viewed from above rather than at ground level. Inomata and colleagues echo this point in reference to their key finding: the discovery of massive, ancient platforms made of clay and earth, measuring about 400 metres across and 1,400 metres in length, at Aguada Fénix in the Usumacinta region of Tabasco, which lies at the western boundary of the Maya lowlands. These platforms date to between 1000 and 800 BC. In the northern part of the Maya lowlands, where the forest is more scrubby but no less impenetrable than the Tabasco forest, a similar lidar 'reveal' is happening with equally profound results[6–9].

In comparison with the Maya region farther east and the region to the west associated with Olmec societies (known for colossal stone heads from the second to first millennium BC), Tabasco has taken a back seat in terms of archaeological investigations during the past century, despite its position between those two regions. That changed when Inomata and colleagues decided to conduct a survey in twenty-first-century style using lidar. This was not a random 'fishing expedition' to discover whatever they could find. Instead, their search focused on a type of construction called an E Group (Fig. 1). Known as the earliest form of non-residential architecture in the Maya lowlands, E Groups were used for naked-eye astronomy[10]. Some, such as those found by Inomata and colleagues, were built up to 3,000 years ago and, interestingly, they pre-date even a clear footprint of settlement in the form of dwellings and villages.

Archaeologists seek to understand which came first in the development of community life – sedentary life in a fixed dwelling, or periodic gatherings for group-based ritual activities, such as religious or astronomical observances. The former was generally

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thought to have paved the way for the latter, but newer evidence is emerging to suggest it was the other way around.

Human ancestors might first have come together to mark the change of seasons observable in the movement of the Sun or other celestial bodies across the sky or along the horizon. E Groups (Fig. 1) contain a low mound or pyramid on the western side of an architectural complex with an elongated platform on the eastern side. Looking from the western structure aids the viewer to witness sunrise during the winter and summer solstices, which are visible along the northern and southern corners, respectively, of the eastern platform (which is elongated from north to south). Brilliantly simple in design, this type of construction was built, over and over again, up and down the Usumacinta region and throughout the Maya lowlands to the east.

Using the revealing 'eyes' of lidar, Inomata and colleagues document 16 instances of E-Group constructions during the first millennium BC. These were built on top of massive rectangular platforms. The platform at Aguada Fénix is the largest of any such platform discovered from this early time period, and Inomata and colleagues suggest that it might be the largest Maya construction built before Spanish invaders arrived. On the basis of the site's absence of excavated stone sculpture depicting rulers — such as the colossal heads found from the same time period in the Olmec region — the authors argue that these constructions were truly public architecture and not built at the behest of rulers. If so, then why were they built so large, and abandoned only hundreds of years later (as indicated by radiocarbon-dating information from the authors' excavations)? And how far to the east and west of Aguada Fénix can such arrangements of a huge platform with an E Group be found? Strictly speaking, this architectural pattern is not a strong characteristic of the central Maya lowlands to the east nor of the Olmec region to the west.

Many questions remain for further research, but there is no doubt that lidar is continuing to transform archaeological research in forested regions. At Aguada Fénix, in particular, the lidar data coupled with Inomata and colleagues' excavations substantially deepen our understanding of the social transformations that occurred there, and strengthen the argument that public architecture on a monumental scale pre-dated village life in eastern Mesoamerica. These findings will lead some to cast a critical eye on the proposed link between public architecture and hierarchical rulership, given that the latter seems to have commenced in the Maya lowlands hundreds of years after the construction of the Aguada Fénix site. The fact that Inomata and colleagues' research took three years, rather than three decades, also demonstrates the powerful way in which lidar is facilitating the rapid detection and investigation of the past by offering a way of peering through the veils of the forest canopy.

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Cancer

Tumour metabolites hinder DNA repair

Lei-Lei Chen & Yue Xiong

Altered metabolism and genome instability are hallmarks of cancer. A mechanism now explains how three small molecules that accumulate in tumours connect abnormal metabolism to genomic problems by hindering DNA repair. **See p.586**

Towards the end of the nineteenth century, chromosomal abnormalities detected under the light microscope revealed that a type of massive genome instability resulting in an abnormal number of chromosomes occurs in certain types of cancer. Not long after, the biochemist Otto Warburg observed that tumour cells tend to use pathways of glucose and energy metabolism that are distinct from those used by normal cells. We now know that genome instability and altered metabolism are two common characteristics of most tumour cells. Genome instability has been investigated continuously since its discovery; altered metabolism was rediscovered as a research area only recently. But not much crosstalk between these two processes in cancer has been reported so far. Sulkowski *et al.*[1] reveal on page 586 how several metabolites that accumulate to high levels in tumour cells suppress DNA repair, thus revealing a direct link between altered metabolism and genome instability caused by DNA damage.

Mutations targeting the genes encoding the enzymes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) result in cells accumulating high levels of the metabolite 2-hydroxyglutarate (2-HG). Mutations in the genes encoding the enzymes fumarate hydratase and succinate dehydrogenase cause cells to accumulate high levels of the molecules fumarate and succinate, respectively. These three small molecules are often referred to as oncometabolites because their accumulation boosts tumour development[2,3], and they are structurally similar to the molecule α-ketoglutarate (α-KG). This is an intermediate in the Krebs-cycle pathway that also serves as a component, called a co-substrate, needed for the function of a family of enzymes called α-KG/Fe(II)-dependent dioxygenases.

This enzyme family, which comprises 65 members in humans[4], catalyses a diverse range of oxidation reactions in proteins, DNA, RNA and lipids. In these reactions, α-KG binds to the active site of the enzyme to aid catalysis. However, 2-HG, succinate and fumarate can compete with α-KG for binding to this catalytic site and thus inhibit these enzymes. One such enzyme is lysine histone demethylase (KDM), which modifies chromatin — the complex of DNA and proteins of which chromosomes are made[5–7].

Two closely related KDMs, called KDM4A and KDM4B, catalyse the removal of a methyl group (demethylation) from a lysine amino-acid residue (termed K9) in the DNA-binding histone 3 (H3) proteins in chromatin. The methylation of H3K9 is linked to a pathway called the homology-dependent repair (HDR) pathway, which mends double-strand breaks (DSBs) in DNA[8]. DSBs are the most dangerous type of DNA damage. If left unrepaired, they can cause chromosome breakage and genomic instability that might promote tumour growth or lead to cell death.

Sulkowski and colleagues investigated HDR in human cancer cells grown *in vitro*. They found that, at a DSB site, the local addition of three methyl groups to H3K9 to generate

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