our knowledge of such systems to limited examples of well-documented case studies[9]. Conventionally in archaeology, a four-tiered decision-making hierarchy is generally associated with a highly complex 'state' level of organization and a socially stratified class system — a level of social complexity not often associated with early Amazonia, until now. This is also yet another example of what has been termed low-density urbanism, which is often associated with the tropics and is quite distinct from the more spatially concentrated patterns found elsewhere.

The Casarabe might have mapped this settlement hierarchy of their world onto the landscape through the roadways that were documented in this study, thanks to the totality of coverage possible with lidar. Large sites are marked by a bullseye arrangement of concentric ditch and bank features that then connect to smaller settlements, lacking monumental features, through a series of straight causeways that extend for several kilometres.

Cotoca and Landívar exhibit the characteristics of large centres that typically anchor complex settlement systems. Each is associated with differential access to space and services denoted by monumental civic-ceremonial architecture. In this part of the world, monumental buildings were constructed not of stone but of earth, which erodes easily over time, especially in the tropics. The scale of the architectural remnants at these sites, which include earthen pyramids that once towered more than 20 metres over the surrounding savannah, cannot be overstated and is on a par with that of any ancient society. Cotoca and Landívar are truly examples of a new class of Amazonian urbanism, and the debate over where they fit into anthropological definitions of ancient cities is now open.

All these settlements are embedded in a human-engineered landscape with a massive water-control system designed to maximize food surpluses to support the large Casarabe population. This system both stored and diverted water, depending on the season and the needs of farmers. The reservoirs might have served as fish ponds, providing a crucial resource for subsistence.

As with other tropical regions, the application of archaeological lidar to the Amazon has launched a transformative process of discovery, documentation and reworking of assumptions held for decades regarding the nature of ancient societies. Prümers and colleagues' work is the opening salvo of an Amazonian new orthodoxy that challenges current understanding of Amazonian prehistory and fundamentally enriches our knowledge of tropical civilizations. Continuing this work will require extraordinary partnerships with Indigenous communities and other stakeholders to formulate unique collaborations and tackle issues of data sovereignty concerning issues of access and privacy[10]. Acceptance of the new orthodoxy for the Maya was a decades-long 'slow-burn', but because of lidar it will be more like an explosion for Amazonia.

Unfortunately, given the rapid rate of ecological change that threatens not only ecosystems but also cultural resources, we are running out of time[11,12]. If the Amazonian new orthodoxy is to be suitably documented before the archaeology vanishes forever, we must see many more large-scale lidar scans and studies like the one presented by Prümers and colleagues.

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Genetics

Blood's life history traced through genomic scars

Aswin Sekar & Benjamin L. Ebert

Two studies of the mutations acquired by blood-forming cells over time provide insights into the dynamics of blood production in humans and its relationship to ageing. **See p.335 & p.343**

Humans produce roughly two million blood cells each second, derived from a relatively small pool of haematopoietic stem cells (HSCs). Over a lifetime, each HSC accumulates mutations in its DNA, some of which confer a competitive advantage on the cell and its descendants. The result is a phenomenon known as clonal haematopoiesis, which leads to an expanded pool of blood cells descended from the same HSC. Two studies[1,2] in *Nature* now transform our understanding of the dynamics that underpin clonal haematopoiesis in ageing and cancer development.

Whereas some HSCs accrue mutations that drive their clonal expansion (known as driver mutations), all HSCs steadily accumulate mutations that do not provide a selective advantage (passenger mutations). Each HSC and its progeny share a unique set of passenger mutations, and these can be used as barcodes to trace the shared lineages between cells derived from the same HSC. Because HSCs accumulate these mutations linearly over time, they can also be used to estimate when a driver mutation arose during an individual's life.

On page 343, Mitchell *et al.*[1] made use of this type of approach to assess clonal dynamics during ageing. The authors isolated individual HSCs from 10 people between 0 and 81 years of age with normal haematopoietic characteristics. They first grew the single cells in culture, generating colonies of clonal cells, and then performed whole-genome sequencing on between 224 and 453 colonies per individual.

The authors next generated phylogenetic trees for each person's clones, inferred from patterns of shared passenger mutations. Strikingly, the trees revealed an abrupt reduction in the diversity of clones around 70 years of age (Fig. 1). On the basis of the frequency of branch points in the phylogenetic trees, the researchers estimated that 20,000 to 200,000 unique HSCs contributed to blood production in the 4 people younger than 65. By contrast, most blood cells were derived from 10 to 20 HSC clones in the 4 people older than 70.

These findings indicate that clonal haematopoiesis in older people is the norm, not the exception. Although clonal haematopoiesis is more common in older individuals, these trees also reveal that the clones typically arose decades earlier. The seemingly ubiquitous presence of small clones (those that make up less than 10% of circulating blood cells) in people over 70 does not herald the development of leukaemia to the extent seen with larger clones[3]. But these results raise the intriguing possibility that reduced

clonal diversity might underlie other blood- and immune-related signs of ageing, such as anaemia or an increased infection risk.

Only about 20% of the clones found in people over 70 had mutations that were previously shown to drive clonal haematopoiesis or leukaemia. So how did these clones without known drivers become dominant? The authors found that non-synonymous mutations in HSCs (those that lead to a change in the amino-acid sequence of the protein encoded by the mutated gene) arose at a faster rate than did mutations that did not alter the sequence — this indicates that non-synonymous mutations give HSCs a selective advantage. Indeed, the comparison revealed that more than 5% of possible non-synonymous mutations could drive clonal haematopoiesis. This result implies that a vast number of genetic variants that HSCs acquire might influence blood production. The finding converges with studies of inherited genetic variation, which have described thousands of variants that influence blood-cell traits[4,5].

Finally, the authors used modelling to confirm that the steady accumulation of mutations that confer a modest fitness advantage over a lifetime can indeed account for an abrupt reduction in clonal diversity in older people.

Large-scale studies of clonal haematopoiesis, which survey mutations in blood samples collected at a single time point across tens of thousands of individuals[6], have enabled precise estimates of the prevalence of mutations that drive clonal haematopoiesis. But direct observations of the rate at which clones grow over time have been lacking. On page 335, Fabre *et al.*[2] made a valuable advance in this regard, through serial blood sampling.

Fabre and colleagues analysed the blood of 385 people aged 54 to 93. They took up to 5 samples from each person over a median period of 13 years. The authors found that the vast majority of clones in these blood samples from older people initially grew at a stable exponential rate, which levelled off over time. However, this rate varied substantially depending on the genes in which mutations arose. In addition, Fabre and co-workers discovered that the rate of growth varied owing to what they call the unknown-cause effect — that is, for a reason or reasons that could not be systematically explained by age or sex.

Like Mitchell *et al.*, Fabre and colleagues next grew clonal colonies from single isolated HSCs from three people, then performed whole-genome sequencing and used these data to construct phylogenetic trees, mapping the relationships between clones (Fig. 1). Combining the phylogenetic and longitudinal analyses revealed that some clones arose relatively early in life and their growth slowed with age, whereas others arose later and their growth did not slow appreciably. The authors also identified clones that expanded despite lacking mutations known to drive clonal haematopoiesis or leukaemia. The growth trajectories of these clones were similar to those with known drivers. Finally, Fabre *et al.* showed that there is a strong correlation between a faster growth rate and the risk of a clone becoming cancerous.

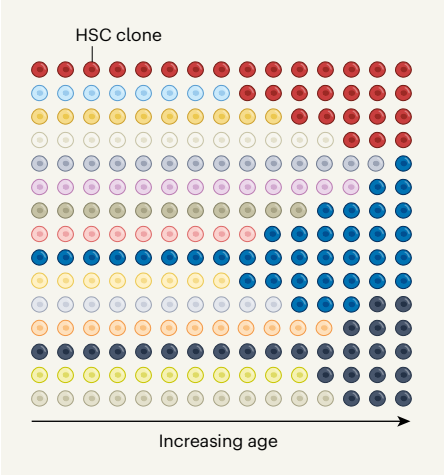

Figure 1 | Clonal dynamics of blood production change with age. Haematopoietic stem cells (HSCs) give rise to blood cells. Mutations in HSCs that make their descendants fitter than other blood cells lead to the production of expanded pools of identical HSC clones — a process called clonal haematopoiesis. Two studies[1,2] analysing the dynamics of clonal haematopoiesis during ageing show that blood cells are produced from many different HSCs in young people, but that this diversity reduces abruptly with age, with a few clonal populations becoming dominant. The age at which clones typically arise and the rate at which they expand can vary on the basis of the mutations that drive them. Cells derived from the same HSC are indicated in the same colour in this graph; cell numbers are much reduced for simplicity.

These two studies raise several avenues for future investigation. First, research has thus far focused mostly on clones that carry known drivers — the causes and consequences of clonal haematopoiesis without known drivers clearly warrant more study. In particular, are these clones merely markers of increased cancer risk, or do they have a causal role in blood cancers (with which they are associated when they account for a substantial portion of blood)?

"These two landmark studies help to explain well-established and fundamental findings about ageing."

Second, the mechanisms by which genetic changes in HSCs confer a selective advantage, the reasons that mutations in different genes cause differing rates of clonal expansion and their impact on differentiated, mature blood cells are still unclear. These issues could be investigated by linking the mutations to gene-expression profiles at a single-cell level[7] to reveal the key molecular and cellular events affected.

Third, beyond gene- and mutation-intrinsic effects, other factors (the unknown-cause effect) that influence clonal growth rate remain to be explored. Fabre *et al.* found that inherited genetic variation did not underlie this effect in the case of clones driven by one specific mutation, but inherited variation might nonetheless influence the growth rate of other clones[6,8]. Furthermore, competition within the unique complement of clones in an individual could contribute to variation in how fast a given clone expands.

Finally, understanding the extent to which the dynamics of clonal haematopoiesis contributes to ageing and its manifestations (and vice versa) will require much larger sample sizes than were feasible using the approaches of these two papers. To that end, the development of a technique to infer such dynamics from single-time-point blood samples, reported last year[9], might prove valuable.

These two landmark studies help to explain well-established and fundamental findings about ageing. Mitchell and colleagues' discovery that many genetic variants might be able to trigger clonal haematopoiesis probably extends to other tissues. The phenomenon of somatic mosaicism, in which a tissue is made up of multiple genetically distinct cell populations, could conceivably underlie manifestations of ageing. Fabre and co-workers' observation that some genetic influences are stronger than others might underlie variation in the rate of ageing and age-associated disorders. Together, both papers show how the life story of haematopoiesis is permanently etched into individual blood cells, through the genomic scars they bear.

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