unconstrained by physical proximity, and in which the number of contacts per node are widely spread[14]. Models based on human travel data occupy an intermediate position in this spectrum of spatial constraints. The different network structures lead in turn to qualitative differences in the way epidemics spread: whereas epidemics can persist at arbitrarily low levels of virulence in scale-free networks[14,15], epidemics in simple two-dimensional models need a minimum level of virulence to prevent them from dying out quickly[9].

Very roughly, then, one could view models of biological epidemics as rooted in spatial networks, and expanding into less spatial realms to model the technologies that have accelerated human travel. Meanwhile, research on cyber-epidemics has occupied the non-spatial end of the spectrum, with its diverse and far-flung connections, when modelling global communication technologies such as the Internet.

But the spread of short-range wireless communication technologies such as Bluetooth, and the emergence of worms that exploit these systems[2–4], is disrupting this dichotomy by making possible computer-virus outbreaks whose progress closely tracks human mobility patterns. These types of wireless worm are designed to infect mobile devices such as cell phones, and then to continuously scan for other devices within a few tens of metres or less, looking for new targets. A computer virus thus becomes something you catch not necessarily from a compromised computer halfway around the world, but possibly from the person sitting next to you on a bus, or at a nearby table in a restaurant.

Wireless worms can also be used to attack 'mobile ad-hoc networks' (MANETs), which are designed to connect devices such as cheap, low-powered sensors using short-range wireless communication[5]. These networks have applications in environmental monitoring, disaster relief and military operations; when the nodes of such a system are placed in relatively fixed positions, there is a close analogy to some of the oldest and best-studied models of disease epidemics, based on short-range spatial contacts in two dimensions[9].

Although these types of worm have not yet achieved widespread penetration, prototypes have successfully exploited vulnerabilities in wireless protocols including Bluetooth, and it is to be expected that mobile devices will be increasingly targeted by malicious code. In assessing the risks of such attacks, and developing countermeasures against them, it is intriguing to contemplate how we might draw on expertise from the field of human epidemiology in understanding how contagion spreads.

These analogies will, of course, always be incomplete. In particular, the timescales over which highly successful mobile worms operate will probably be shorter than those of their biological counterparts. The initial outbreak, and the opportunities for recovery, will potentially progress much more quickly. Mobile worms are also restricted in a way that has no obvious biological analogy by the limited communication rates of the devices they infect. Particularly aggressive worms will also be confronted with the 'self-throttling' effects of many infected devices competing for limited wireless bandwidth[5,6].

Analogies to biological epidemics can also be exploited for beneficial purposes, in the design of computer-network protocols[16]. For mobile devices, epidemiology helps in dealing with the problem of intermittent connectivity: that the routing of traffic must conform to a dynamic and unpredictable network structure as the owners of mobile devices move around. The result is a growing interest in opportunistic routing, in which messages are passed between devices that come into physical proximity, with the goal of eventually reaching a specified recipient[7]. The development of such protocols has drawn on detailed data concerning human mobility and contact patterns[8].

These lines of work reinforce how the evolution of computer viruses and worms has always been closely linked with the legitimate concerns of computer networking. As that relationship extends into the domain of mobile devices, we are taking further steps towards a world where digital traffic flows not just over the wired backbone of the Internet, but also in small leaps through physical space as people pass one another on the street. ■

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AGEING

From stem to stern

Anne Brunet and Thomas A. Rando

Immortality is the stuff of myth and legend, but lifespan extension is the subject of serious scientific inquiry. Exploring the causes and effects of ageing in stem cells should aid this quest.

The explosion of research on stem cells has given the promise of treatments for degenerative diseases of ageing, enhancement of the repair of damaged tissues and possibly even slowing of decline-in-function that occurs with advancing age. But how stem cells are affected by the ageing process, and whether such changes are a cause or a consequence of organismal ageing, remain unclear[1]. Three research teams[2–4] have recently reported their findings on how age-related accumulation of DNA damage and changes in global patterns of gene expression might lead to the decline of stem-cell function.

In mammals, stem cells reside in many adult tissues and either continually produce new cells for tissues with a high turnover (blood, skin and gut) or serve as a reservoir for gradual cellular replacement or repair in the more stable tissues (liver, muscle and brain)[1]. Stem-cell function, just like that of other cells, declines with age. However, to what extent age-related changes in stem-cell function are due to intrinsic ageing of the cells or due to changes in the environment in which they reside[5] is still unclear.

Many theories have been put forth to explain the decline of cell and tissue function with age, but a main challenge for researchers who study ageing is to distinguish among potential causal influences, virtually all of which interact with one another and lead to organismal ageing (Fig. 1). The free-radical theory of ageing proposes that reactive oxygen species, which are by-products of normal metabolism, are responsible for damage to many cellular components, including DNA[6].

Several mechanisms of DNA repair that are essential for healthy tissues and long life[7] have evolved in cells of higher organisms. In humans or mice, mutations in genes encoding DNA-repair enzymes may lead to dramatic increases in the incidence of cancer and the shortening of lifespan. What has remained unclear is how susceptible adult stem cells are to the age-

related accumulation of DNA damage, how effective DNA-repair activities are in these cells, and to what extent this balance contributes to the characteristics of tissue ageing.

Nijnik *et al.*[2] and Rossi *et al.*[3] tested the hypothesis that accumulation of DNA damage is an essential mechanism underlying age-related decline in the function of haematopoietic stem cells (HSCs). These cells reside in the bone marrow and give rise to all cellular components of blood — from red blood cells to cells of the immune system[8]. For this, Rossi *et al.* studied mice that carry mutations in various DNA-repair pathways and show signs of accelerated ageing, whereas Nijnik *et al.* discovered and studied a mouse strain with a mutation in a gene encoding a DNA-repair enzyme, which models a human syndrome characterized by immunodeficiency and developmental abnormalities.

Both teams found that HSC function was severely impaired in rapidly ageing mutant mice. Moreover, HSCs from the mutant mice had compromised ability to generate blood cells even when they were transplanted into normal mice, indicating that the defects were intrinsic to the stem cells. Intriguingly, although the types of DNA defects that would be expected to accumulate in the various mouse mutants studied are different, the altered HSC functions observed in all of these mutants were similar. This suggests that HSCs have a limited repertoire of potential responses to intrinsic damage.

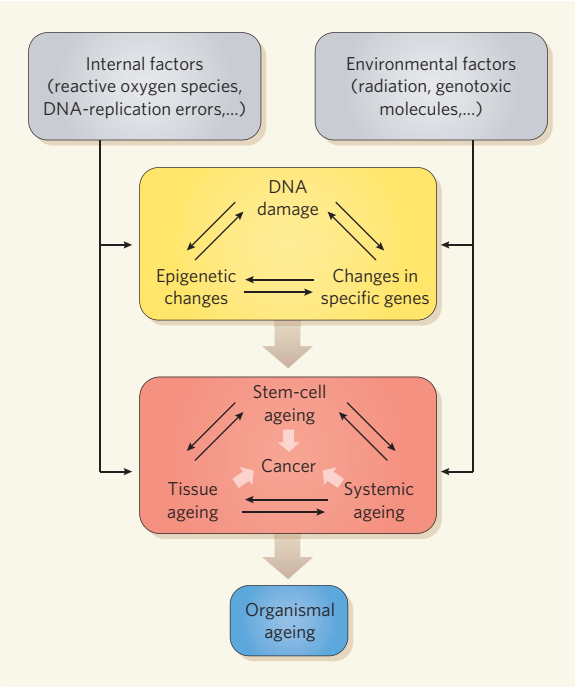

Figure 1 | Interplay between factors and networks influencing ageing. As stem cells are essential for tissue homeostasis and repair throughout life, three groups[2–4] have explored what factors influence alterations in their function with age. These studies, together with previous work, suggest that the story is complex, involving interactions between different networks and at several levels. At the genomic level, both internal and environmental factors cause alterations in individual genes, groups of genes through epigenetic changes, and chromosomes, at least some of which arise from direct damage to DNA. At the levels of cells and tissues, functional changes in stem cells and other cells in the tissue influence each other and are, in turn, influenced by systemic changes that may be conveyed from one tissue to another via the circulation. All of these may contribute to the possible development of cancer in tissues throughout the body. The ultimate outcome is organismal ageing.

Do these results pertain to HSC ageing and the age-related decline of immune responses in normal mice? That partially depends on how accurately biological processes in the genetic mutants studied reflect those of normal ageing. Clearly, there are limitations in extrapolating results from a mouse or human with a single gene mutation, even if the outcome of the mutation resembles normal ageing. Thus, it is crucial to investigate the relationship between accumulation of DNA damage and ageing in genetically normal HSCs and their progeny.

Rossi *et al.*[3] did find that HSCs from normal old mice have more DNA damage than those from younger animals, hinting that increased DNA damage may be responsible for limited stem-cell function in aged organisms. However, these authors also found that, in old mice, the DNA of HSC progeny was less damaged than HSCs themselves. This could be either because the progeny with high levels of DNA damage are selectively eliminated, because only HSCs without DNA damage successfully divide, or because the committed progenitors that are derived from HSCs can repair the lesions more efficiently than can HSCs themselves.

Can mechanisms other than accumulation of damaged DNA underlie stem-cell ageing? Chambers *et al.*[4] asked whether the overall pattern of cellular gene expression was altered in aged HSCs. Looking for changes across the whole genome, they found that, indeed, old HSCs show high-order changes in gene expression: groups of genes, or entire chromosomal regions, which were normally silenced in young HSCs, were now turned on, whereas other genes and genomic regions were expressed at lower levels than in young cells.

Among the genes with reduced expression were those involved in modulating chromatin, which is the complex formed by DNA and histone proteins. Epigenetic changes — changes in chromatin structure without mutations in the DNA sequence — influence gene expression. The authors[4] suggest that such epigenetic changes may underlie altered HSC function in aged animals. In agreement with the observations of Nijnik *et al.*[2] and Rossi *et al.*[3], Chambers and colleagues also found that the expression of genes involved in DNA repair was reduced in aged HSCs. Intriguingly, studying a mutant mouse strain with features of premature ageing, they found that HSCs had a 'molecular signature', defined as a distinct pattern of gene expression, that was similar to that of HSCs from young animals[4], even though there is a marked decline in HSC regenerative potential in this strain[9]. Although this finding is interesting as a possible example of how a molecular signature of ageing may be uncoupled from cellular function, it may also highlight how a rapidly ageing mouse mutant might not mimic the characteristics of normal ageing.

The work of Chambers *et al.*[4] brings into perspective the complexities of the ageing process and how single-gene mutations or single biological processes are unlikely to account for the myriad of cellular, tissue and organismal changes associated with ageing. Even if epigenetic changes are a hallmark of ageing, what are the processes that initially lead to them in old cells? The juxtaposition of these studies raises a conundrum similar to that of 'chicken or egg': do age-related epigenetic changes render DNA more susceptible to damage, or does DNA damage underlie epigenetic changes? And how do general epigenetic modifications fit in with specific genes that have been shown to limit HSC function[10] or maintain HSC potential[11] during ageing? More importantly for regenerative medicine, are these epigenetic changes (and thus possibly ageing) reversible?

The authors[2–4] converge in their general conclusions that, with age, adult HSCs decline in function but not number, and that DNA damage and epigenetic modifications may limit the regenerative potential of these cells. They also agree that HSCs are not protected from age-induced damage and, in fact, ageing may result in an accumulation of DNA mutations in these cells, thereby increasing the risk of cancer.

Their findings also raise further questions. Are these observations true for adult stem cells in other tissues, particularly tissues with much lower cellular turnover than the blood? Would stem-cell 'enhancement', whether genetic or epigenetic, delay the ageing characteristics of a particular tissue or even lead to an extension of lifespan? Understanding what limits stem-cell function during ageing will be essential for the field of regenerative therapeutics, which proffers the hope that the remarkable potential of stem cells will be harnessed for the repair of injury and the treatment of diseases. ■

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PALAEOANTHROPOLOGY

Homing in on early *Homo*

Daniel E. Lieberman

Newly described fossils from Georgia in Eurasia and from Kenya shed more light on the earliest members of the genus *Homo*. These finds indicate that there was considerable variability in their size and shape.

The fossil record of human evolution is like a pointillist painting: one sees a different picture close up from when one stands back. For years, students of human evolution have tended to prefer standing back when considering the evolution of the genus *Homo* from the genus *Australopithecus*, by contrasting what came before with what came after. Two sets of discoveries now help us to look more closely at the complex transition from *Australopithecus* to *Homo*. One of the papers concerned is by Lordkipanidze and colleagues (page 305 of this issue)[1], and deals with postcranial bones (those other than the cranium) from Georgia, Eurasia. The other, by Spoor and colleagues[2], was published in *Nature* on 9 August and describes cranial material from Kenya.

In terms of the big picture, the transition to *Homo* was one of the most substantial in human evolution. The time before then was the era of the australopiths. This diverse group of species had brains 400–550 cm^3 in volume (only slightly larger than that of a chimpanzee), big cheek teeth, and massive faces adapted to generate and withstand large chewing forces. Australopiths also had many adaptations for upright bipedalism. But they were chimpanzee-sized (100–150 cm tall, weighing 30–50 kg), and retained some features useful for climbing trees, such as relatively long arms, upwardly oriented shoulders and long, curved digits.

Sometime after the transition came *Homo erectus*. This species first appeared in Africa about 1.9 million years ago, and quickly moved out of Africa by 1.8 million years ago. It had a bigger brain, a less snout-like, vertical face, and small, nearly human-sized teeth. A spectacular skeleton, of a juvenile male from Nariokotome, Kenya, dating to 1.5 million years ago, came to epitomize our view of the species as having a very modern body: tall (160–185 cm), large (50–70 kg), with long legs, and otherwise only subtly different from your body or mine[3]. *Homo erectus* also seems to have resembled modern humans in having low levels of sexual dimorphism, with males being about 10–20% larger than females.

When viewed up close, however, the *Australopithecus–Homo* transition has always been murky. One problem is that we don't know enough about *Homo habilis*, the putative ancestor of *H. erectus*. In addition, early *H. erectus* fossils are quite variable, and the more we look, the more we find contrasts with later hominins (the formal term for a species in the human lineage). For example, their rate of development was rapid and chimp-like, rather than slow and extended as in modern humans[4]. Also, brain size relative to body size in the earliest *H. erectus* fossils is not much different from that of many australopiths or *H. habilis*[5]. Finally, the earliest non-African fossils of *Homo* from Dmanisi, Georgia, which are dated to 1.77 million years ago, resemble *H. erectus* in many respects. But they are highly variable, and more in the size range of *H. habilis* than of *H. erectus*[6,7].

The new discoveries[1,2] further highlight the transitional and variable nature of early *Homo*. Lordkipanidze and colleagues[1] describe several postcranial fossils from Dmanisi, including partial skeletons of an adolescent associated with a previously reported cranium (D 2700), some limb bones from an adult associated with a massive, previously reported jaw (D 2600), and some foot bones from two smaller adults. In many respects, the fossils resemble modern humans and the Nariokotome *H. erectus* skeleton. The adult's limb proportions are quite modern, with a relatively long femur compared with the humerus, and a tibia/femur ratio similar to that of modern humans from Europe. The feet have a well-developed arch and are at least as modern as those of another early *Homo* foot, OH 8, from Olduvai Gorge in Tanzania[8].

Other details, however, are less human-like. Most importantly, the Dmanisi individuals' stature and body mass are smaller than those of the Nariokotome boy. The larger adult would have weighed 48–50 kg and stood 147–166 cm tall. The adolescent would have weighed 40–43 kg and been 145–161 cm tall, so its adult weight and stature would have been even greater. Estimates of relative brain size are in the range of *Australopithecus*, well below those of later *H. erectus* and modern humans.

Other differences are also apparent. In modern humans, the elbow joint is typically rotated relative to the shoulder joint, so that the forearm naturally hangs with the palms facing inwards; but the new Dmanisi humeri lack torsion, so their palms would have been oriented more forwards. Lack of humeral torsion, a highly plastic and variable feature, suggests something different about the shoulder in these specimens. In addition, although the adolescent's collar-bone is of normal length for a 15–16-year-old human[9], and the shoulder joint faces sideways (though at the more vertical end of human variation), other aspects of shoulder-blade shape seem to be primitive. New analyses of the Nariokotome boy also suggest a lack of humeral torsion[10].

Evidence that early *Homo* was less modern and more variable than sometimes supposed is also bolstered by Spoor and colleagues' finds from Lake Turkana, Kenya[2]. One of the fossils, KNM-ER 42700, is a beautiful

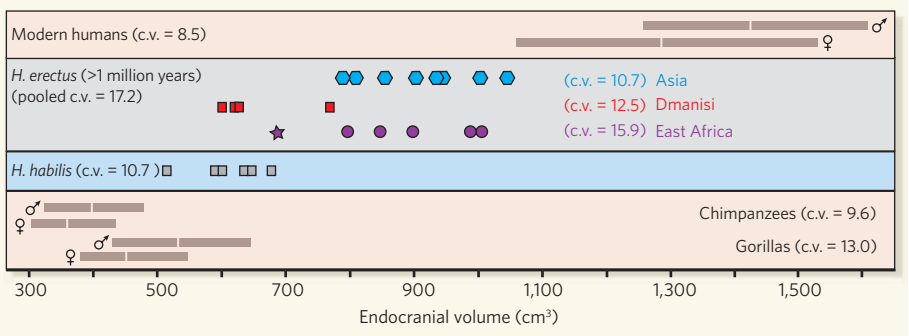

Figure 1 | The wide range of brain sizes in early *Homo*. Brain sizes (as endocranial volume) of *Homo habilis*, and of *Homo erectus* fossils more than 1 million years old, compared with those of modern humans and extant great apes (chimpanzees and gorillas). Data are from refs 1, 13 and 14. The Dmanisi crania and the new KNM-ER 42700 *H. erectus* cranium from Kenya (star)[2] have smaller brains than most other *H. erectus* specimens. Furthermore, including them in the same species as other fossils attributed to *H. erectus* yields a coefficient of variation (c.v.) of 17.2, much higher than those of modern humans and great apes, even in highly sexually dimorphic species such as gorillas. Grey bars indicate the 95% confidence interval around the means for each sex in the modern human and great ape samples. Values for c.v. are standard deviations as a percentage of the mean, and are corrected for sample size.