

standing basin formation and regolith processes is to fly a sample-return mission to the far side of the Moon, near its largest impact crater, the South Pole–Aitken Basin (Fig. 1). Such a mission was given high priority this summer by the US National Research Council's planetary decadal survey<sup>10</sup>. Of course, it is doubtful that a first, moderate-cost mission could locate and return extra-lunar meteorites, given their rarity, but it would be a step towards that goal.

Although Armstrong *et al.*<sup>4</sup> believe that their theoretical calculations are conservative, they could still be too optimistic about the prevalence of extra-lunar materials on the Moon. Such samples must exist, however, in whatever tiny amounts, and set a marvellous challenge as analytical and sampling techniques improve during future decades. ■

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Ageing

# The old worm turns more slowly

Thomas B. L. Kirkwood and Caleb E. Finch

Detailed studies of cellular changes in ageing nematode worms show that they, like humans, suffer progressive muscle deterioration. Randomness of cell damage is another shared hallmark of the ageing process.

When the nematode worm *Caenorhabditis elegans* was first considered as a model for the study of ageing some 20 years ago, few foresaw how valuable it would prove to be. The past decade, in particular, has seen an explosion of work on the genetics of lifespan in this species. Building on pioneering work by Tom Johnson<sup>1</sup> and others, more than 50 mutations that extend lifespan have now been described, and the metabolic pathways regulated by these genes are being unravelled<sup>2</sup>. Some of these genes regulate a key developmental switch, which directs young worms that find themselves in poor environments to adopt a long-lived stress-resistant form (the dauer larva). Other genes control core processes, such as the overall rate of metabolism. These are exactly the kinds of processes predicted to be important for longevity by the evolutionary theories of ageing, in particular the ‘disposable soma’ theory, which suggests that competition for metabolic resources between processes such as growth, reproduction and cellular maintenance lies at the heart of the ageing process<sup>3</sup>.

But despite its value in studying the genetics of longevity, a major limitation to the use of *C. elegans* as a model of ageing has been the scarcity of data on the pathology of aged worms. We knew how long worms lived, but not how they died. This situation is radically changed by Herndon *et al.*<sup>4</sup>, writing on page 808 of this issue, who give a detailed description of the cellular changes that occur

with ageing in wild-type and long-lived mutant worms.

The adult worm contains just 959 somatic cells (that is, cells not involved in reproduction) and each cell can be identified in terms of its function. Using a combination of fluorescence and electron-microscopic techniques, Herndon *et al.* have characterized the major cellular changes that accompany ageing in a number of important cell types. Intriguingly, they found that worms are perhaps not so very different from humans, at least in the sense that an important aspect of their decline into senescence is the pro-

gressive deterioration of muscle, known as sarcopenia. By contrast, the worm nervous system appears remarkably well preserved. If old worms wriggle less, it is not, it seems, because they have forgotten how to do so.

A dramatic feature of the changes described in the aged worms is the seemingly random nature of the large variations between individuals; in other words, the changes appear to be highly stochastic. This is all the more remarkable in an organism that, in so many other respects, is under strict genetic authority. Nematode strains have exceptional genetic uniformity (arising from the fact that they are self-fertilizing hermaphrodites), they are cultured in highly uniform environmental conditions and they have a developmental process of almost clockwork precision. We know, of course, that in humans one of the hallmarks of the ageing process is an increase in variability. Indeed, it has been said of humans that we are all born copies but die originals. This variability in human populations can readily be attributed to the uniqueness of our individual combinations of nature and nurture, but such an explanation does not work for worms.

In fact, variability in worm ageing has been staring us in the face, but has only recently been noticed<sup>5</sup>. The conventional way to plot data on longevity in worms, as in other organisms, is as a survival curve, where the percentage still alive is plotted against age. If we plot exactly the same data in another way, showing instead the statistical distribution of age at death, we see at once the extraordinary variation in lifespan between individual worms, despite the uniformity of their nature and nurture (Fig. 1). The range of lifespan for a given strain is wide and not so very different, in terms of standard deviation expressed as a percentage of the mean, from that of outbred, free-living humans.

Where does this variability in worm ageing come from? Not, seemingly, from their nature or nurture. The answer may be that,

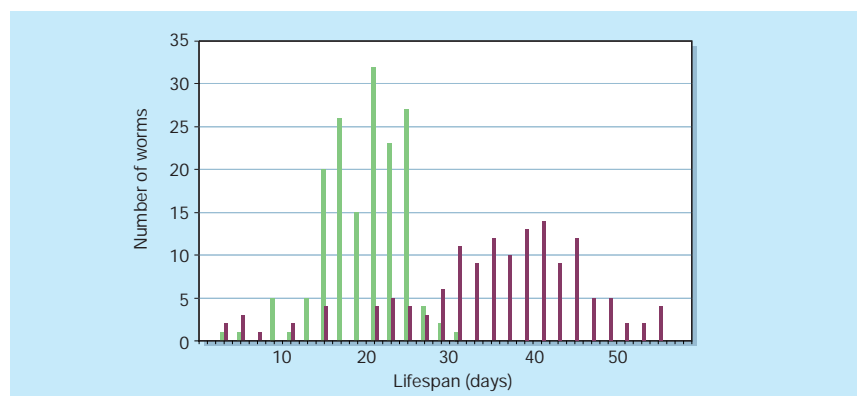


Figure 1 Lifespan distributions for individual *Caenorhabditis elegans* nematodes in isogenic populations of wild-type (green) and long-lived *age-1* (purple) strains. Although the distributions have different mean values, the spread of both (compared to the mean value) is similarly broad. The range of lifespans in nematodes is indicative of the randomness of the ageing process, which Herndon *et al.*<sup>4</sup> have now investigated at the cellular level (data provided by T. E. Johnson<sup>1</sup>).

as predicted by the disposable soma theory, ageing at the cellular level is the result of stochastic damage. Tracking down the molecular changes that underlie the cellular heterogeneity described by Herndon *et al.*<sup>4</sup> will not be easy, but the first forays into this thicket are being made. It will not be surprising if we find that mitochondrial DNA mutations are important<sup>6</sup>. These are commonly seen as a feature in the ageing of post-mitotic cells such as neurons and muscle across a range of species, including humans.

Equally, we are learning that a range of intrinsic biochemical stresses contribute to the progressive build-up in cells of damage that is, in essence, random. The broad reproducibility of the ageing process from individual to individual masks the fact that at the cellular and molecular level the aged organism is enormously heterogeneous. Neighbouring cells may bear very different burdens of molecular lesions. Genetic differences in ageing rate reflect the fact that the average rates at which damage accumulates are controlled by the efficacy of repair and other maintenance processes.

We know that long-lived *C. elegans* mutants commonly gain their longevity through increasing their resistance to stress<sup>7</sup>. This increase in stress resistance, although it modulates the rate at which stress-induced damage accumulates, will not, by itself, alter the variability embedded in the process. As can be seen in Fig. 1, for the long-lived mutant the range in lifespan measured as a fraction of the mean remains the same as in the wild type. But it remains open whether the random damage accumulated during ageing could account for the large differences between individual worms that are seen even early in adult life. Other stochastic processes may be at work during development of cell contacts, for example in neuromuscular junctions<sup>8,9</sup>.

Let us imagine that aged worms can now be taken for a complete model of old people, we must remember that the adult worm is post-mitotic; it has no dividing cells apart from those in its gonads. Thus, *C. elegans* can never be a model for the important contributions to human ageing that come from impaired cell proliferation in the many mammalian tissues and organs that maintain themselves by cell renewal. Nevertheless, the work of Herndon *et al.*<sup>4</sup> marks a milestone in our advance towards understanding the deep secrets of the ageing process. ■

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## Cancer

# Pinning a change on p53

Kevin M. Ryan and Karen H. Vousden

An enzyme-induced conformational change is now implicated in activating the p53 protein, one of a cell's prime movers in preventing tumour development.

One in three of us will succumb to cancer at some point in our lives. So it's not surprising that p53, a protein that helps to prevent the development of malignancies, is the subject of intense scrutiny. In recent years great progress has been made in understanding how p53 is regulated. Two reports in this issue, by Zheng *et al.*<sup>1</sup> and Zacchi *et al.*<sup>2</sup> (pages 849 and 853), now add a new level of complexity to our knowledge of this regulation by showing that, in order to become fully activated, p53 requires the involvement of an enzyme called Pin1. This discovery adds yet another player to an already crowded field. But it also sheds light on a series of previously described, but poorly understood, phosphorylation events — types of protein modification — that are known to affect p53.

Although it is not needed for normal growth and development, p53 occupies the nodal position in a pathway that monitors and responds to cellular stress, and that has tumour-suppressive effects<sup>3</sup>. p53 is considered to function primarily as a gene-transcription factor and, once activated, it can induce the expression of a large number of genes, many of which evoke either cell-cycle arrest or programmed cell death (apoptosis).

The type of response depends on the cellular and genetic context, but ultimately the effect is the same — to restrict the proliferation of cells that might otherwise go on to form a malignant tumour<sup>4</sup>.

Because p53 is such a potent inhibitor of cell growth, efficient regulatory mechanisms are necessary to control it during normal cell proliferation. Intrinsic to this regulation is the control of p53 protein stability, mediated by the HDM2 protein (Mdm2 in the mouse)<sup>5,6</sup>, which keeps p53 levels low in unstressed cells. When p53 function is required, HDM2 activity is blocked, resulting in p53 stabilization and subsequent activation of its tumour-suppressor function.

The correct folding of any protein is fundamental to its ability to function properly. One level at which folding is determined involves the orientation of peptide bonds between adjacent amino acids, which in most cases favours a *trans* configuration — that is, with the two 'central' carbon atoms of the two amino acids lying on opposite sides of the peptide bond, as opposed to the same side (*cis*). Exceptions to this rule are the peptide bonds that link the amino-acid proline with its 'upstream' neighbour (X-Pro), where —

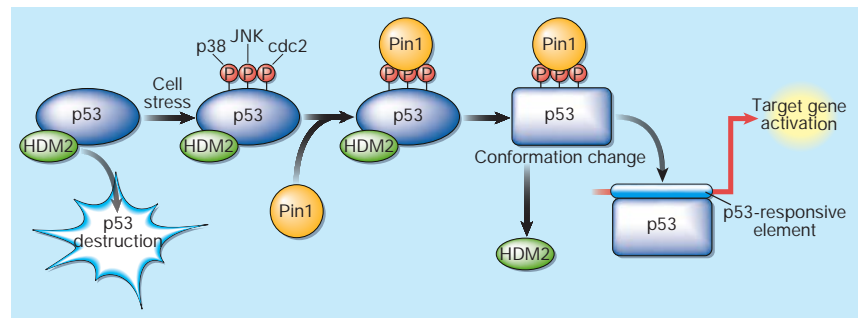


Figure 1 Regulation of p53 protein by Pin1, as suggested by the results of Zheng *et al.*<sup>1</sup> and Zacchi *et al.*<sup>2</sup>. If the cell is not under stress, p53 is not needed and is destroyed by HDM2 (left). Following some cellular insult or other, however, collective phosphorylation of p53 by various kinases — p38, JNK and cdc2 — takes place. The protein is then bound by Pin1, a peptidyl-prolyl isomerase, which changes the conformation of p53, displacing HDM2 and so stabilizing and activating p53. Acting through the p53-responsive element, p53 then functions as a transcription factor for various genes involved in arresting cell growth or inducing programmed cell death. Both processes have the same end, that of preventing tumour formation.

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