extreme densities of white dwarfs, and even into neutron stars or black holes. B68 seems to be hovering near the brink of gravitational contraction and will most likely collapse to form a star (Fig. 1), unless stabilized by other forces. Despite its low temperature of 16 K, the primary stabilizing force is thermal pressure. In addition, it is likely that the globule possesses a weak magnetic field, which could help stabilize it further[7]. Nonetheless, B68 appears to be only marginally stable, and so could easily be destabilized by physical processes, such as further cooling or a drop in the internal magnetic pressure, or by being hit by a travelling blast wave from a supernova explosion. So Alves and co-workers predict that the exquisite dark silhouette of B68 may well, sometime in the future, be converted into yet another little shining star in the Milky Way. ■

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1. Alves, J., Lada, C. J. & Lada, E. A. *Nature* **409,** 159–161 (2001).
2. Bok, B. J. *Pub. Astron. Soc. Pacif.* **89,** 597–611 (1977).
3. Reipurth, B. *Astron. Astrophys.* **117,** 183–198 (1983).
4. Benson, P. J. & Myers, P. C. *Astrophys. J.* (suppl.) **71,** 89–108 (1989).
5. Williams, J. P. & Myers, P. C. *Astrophys. J.* **518,** L37–L40 (1999).
6. Chandrasekhar, S. *An Introduction to the Study of Stellar Structure* (Univ. Chicago Press, 1939).
7. Nakano, T. *Pub. Astron. Soc. Jpn* **31,** 697–712 (1979).
8. Heathcote S. *et al. Astron. J.* **112,** 1141–1168 (1996).

Cancer

Death and methylation

Peter A. Jones

Malignant melanoma cells can resist committing suicide when attacked by chemotherapy. The explanation lies in the discovery that a key gene in the cell-death pathway is switched off in this cancer.

An ability to avoid committing suicide is one of the keys to a cancer cell's survival, whether it is spreading from one part of the body to another by metastasis or facing attack from chemotherapy. Malignant melanoma is a particularly nasty form of cancer in this respect. It is both highly metastatic and resistant to chemotherapy, implying that it has mastered the art of avoiding suicide by not implementing the biochemical pathway that leads to cell death (apoptosis). How melanomas do this was a mystery until now, because — unlike other cancer cells — melanoma cells usually have fully functional *p53* genes, which are important in triggering apoptosis.

Writing on page 207 of this issue[1], Soengas and colleagues go a long way to solving the riddle. They show that malignant melanoma cells can avoid suicide by inactivating a gene at a step further on from p53 in the apoptosis pathway. This means that they can survive during chemotherapy and metastasis even though their *p53* genes are functioning normally. But what makes this study doubly interesting is that the inactivated gene — *Apaf-1* — is merely switched off, instead of being completely lost or mutated. The implication is that the suicide pathway could potentially be reactivated in melanomas, making them less dangerous.

The p53 protein is a key player in the cell-suicide pathway[2,3] (Fig. 1, over). When a cell suffers DNA damage or certain types of stress, its p53 proteins are activated and send a death signal to the cell. p53 is kept in check by a protein called MDM2, which causes the destruction of p53. MDM2 itself is under the control of the $p14^{ARF}$ protein, which confines MDM2 to a subsection of the nucleus (the nucleolus). This prevents p53 breakdown. Stress signals are transmitted to $p14^{ARF}$ in part through a death-associated protein kinase, DAPK[4]. This apoptosis pathway is disrupted in most human cancers[2,3] by downregulation or loss of $p14^{ARF}$, upregulation of MDM2, or mutation (and therefore inactivation) of p53.

The exact mechanisms by which p53 promotes apoptosis are not known, but probably involve Bax, a molecule that stimulates the release of cytochrome *c* from mitochondria. Cytochrome *c* activates the Apaf-1 protein, which in turn activates the enzyme procaspase-9, resulting ultimately in cell death. Several proteins can interrupt this death cascade and thus keep the cell alive. The existence of such a complex pathway (with many feedback loops not shown in Fig. 1) certainly gives plenty of places at

Molecular physiology

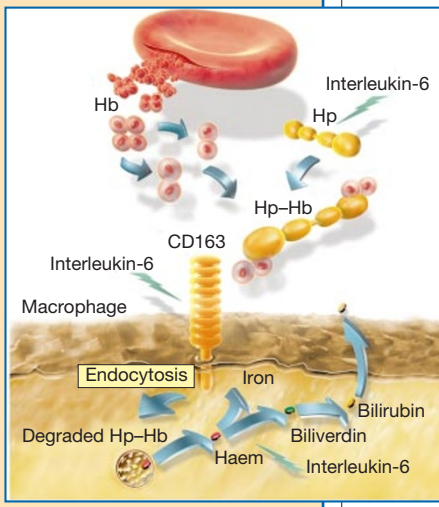
Haemoglobin scavenger

Normally, ageing red blood cells approaching the end of their 120-day lifespan are degraded in the bone marrow, liver or spleen. In some circumstances, however — such as during infection with malaria or in some autoimmune disorders — red cells may burst within blood vessels. Haemoglobin (Hb) released from ruptured red cells can be toxic unless cleared rapidly from the circulation. Haptoglobin (Hp), a protein found in blood plasma, binds free Hb, but the events that lead to removal of the Hp–Hb complex from the blood have been elusive — until now.

Elsewhere in this issue (*Nature* **409,** 198–201; 2001), Søren K. Moestrup and colleagues describe how they detected a receptor protein that clears the Hp–Hb complex from blood. They identify the protein as CD163, known to be expressed only on the surface of tissue macrophages and monocytes — white blood cells — and to be involved in inflammation. It seems that the Hp–Hb complex acts as a 'come hither' signal to patrolling macrophages, detected through their CD163 antennae. The Hp–Hb complex is then engulfed by the macrophage and digested to release haem (see graphic).

These findings reveal an intriguing link between iron metabolism and the immune system. The authors speculate that the Hp–Hb complex, like antibodies, may crosslink several CD163 molecules on the surface of macrophages, triggering an internal signalling cascade that results in increased secretion of anti-inflammatory cytokine molecules. Moestrup and colleagues also propose that different inherited human variants of Hp in complex with Hb may have different anti-inflammatory potency. But it is also feasible that the Hp–Hb complex responds to immune processes. CD163 and Hp are upregulated in response to factors such as interleukin-6, seen in the early, acute phase of inflammation, suggesting that this may be a means of enhancing Hb clearance during inflammatory conditions.

Further evidence is needed. But it is tempting to speculate that variations in Hp and CD163, or pertubations of their function, may be involved in autoimmune disorders such as systemic lupus erythematosus, and in abnormal iron metabolism. **Carina Dennis**



S. K. MOESTRUP

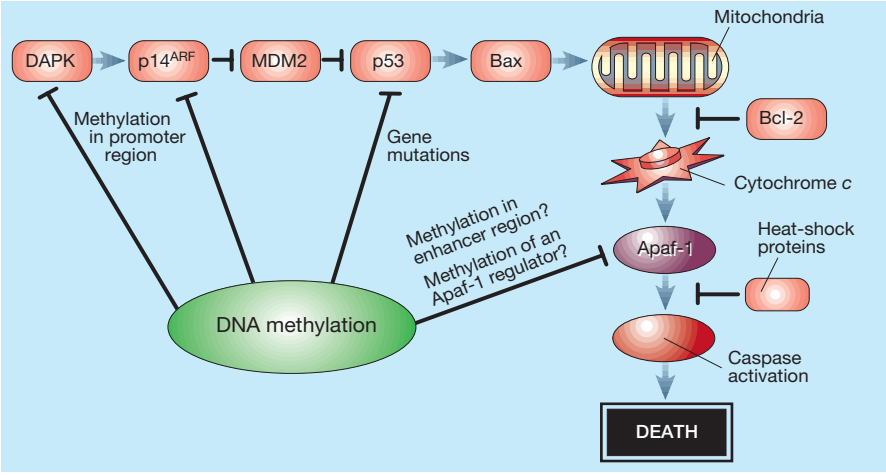


Figure 1 **The p53-mediated death pathway, and how it can be subverted by DNA methylation. Increased levels of p53 can lead to the initiation of a cascade of events that results in cell death by apoptosis. p53 is kept in check by a pathway involving DAPK, p14^{ARF} and MDM2. This pathway is disabled in some way in most human cancers, often by inactivation of p53. Malignant melanomas, however, often have intact *p53* genes. As shown by Soengas *et al.*[1], these cancers do not express one of the downstream members of the cascade — *Apaf-1* — and thus escape apoptosis in response to stresses such as chemotherapy. The *Apaf-1* gene seems to be disabled by abnormal methylation. This has also been observed for the *DAPK* and *p14*^{ARF} genes, and DNA methylation is involved in generating mutations in the coding region of the *p53* gene in other cancers. So DNA methylation can contribute in several ways to inactivating the apoptosis pathway.**

which death can be subverted, to which we can now add the inactivation of Apaf-1.

What makes the results of Soengas *et al.*[1] so interesting is that they reveal a reversible switching off — rather than a permanent deactivation — of the *Apaf-1* gene. The switch may involve the addition of methyl groups to cytosine nucleotides in DNA, and the removal of acetyl groups from the histone proteins that bundle up DNA into the compressed form seen in the nucleus. Soengas *et al.* show that the *Apaf-1* gene can be turned back on by treating cultured melanoma cells with inhibitors of DNA methylation or histone deacetylation.

This 'epigenetic' gene silencing is increasingly being recognized as a common way in which cancer cells inactivate cancer-related genes[5,6]. Attention has focused on the methylation of cytosines in genes with a high proportion of cytosine–guanosine dinucleotides (the methyl-acceptor sequence) in their promoter regions. After these 'CpG islands' are methylated, and after changes associated with histone deacetylation have occurred, the relevant genes become silent. One example is the abnormal methylation of the promoter of the *p14*^{ARF} gene. This results in the downregulation of the gene and the degradation of p53, disabling the suicide pathway[7]. The promoter of the *DAPK* gene is also subject to silencing by methylation[8].

But unusually Soengas *et al.* find that, although the *Apaf-1* promoter is a CpG island (and therefore a potential target for methylation), there were no changes in the methylation of this region before and after melanoma cells were treated with the methylation inhibitor. So the exact mechanism by which methylation switches off this gene remains in doubt. Perhaps the methylation inhibitor reactivates an unknown gene that controls *Apaf-1*, or perhaps it demethylates another control region of the *Apaf-1* gene, such as an enhancer or insulator.

In any case, it seems that the methylation of cytosine nucleotides in human cancer cells can help to inactivate the apoptosis pathway at several points — either upstream (at p14^{ARF} or DAPK) or downstream (at Apaf-1) of p53. And, as well as contributing to gene silencing, methylation can also substantially increase the occurrence of harmful single-nucleotide mutations when it takes place in the coding regions of genes such as *p53* (ref. 9). We clearly pay a price for having methylated cytosine residues in our genomes. Methylation is essential in controlling gene expression under normal circumstances. But it also has several ways in which it can disable the pathways that protect us from cancer.

On the other hand, the fact that the *Apaf-1* gene can be silenced by epigenetic changes yet reactivated by drug treatment may have clinical benefits. It might be possible to make melanoma cells sensitive to chemotherapy. Moreover, other important pathways — such as those involving retinoic-acid receptor β2 (ref. 10), needed for cellular differentiation, or the DNA-repair protein MLH1 (ref. 11) — can be abnormally silenced by DNA methylation. In fact, the list of genes subject to abnormal epigenetic downregulation is growing rapidly. The search for ways to reactivate them will, no doubt, be a major area of research — perhaps involving high-throughput screens such as gene-expression chips — over the next few years. But it may

100 YEARS AGO

In investigating the causes of directions of various spirals, I discovered a certain law and order in the arrangement of the direction of the spiral in horns which will interest many of your readers. (1) That in the antelopes the right-hand spiral is on the left of the head, and the left-hand spiral on the right of the head (crossed). (2) That in sheep the right-hand spiral is on the right of the head, and the left spiral on the left side of head (homonymous, or same name). The *wild* goats agree with the antelopes in regard to the spiral direction of their horns (crossed), and the oxen agree with the sheep in cases where the spiral can be noted (homonymous). Exceptions are not numerous and not difficult to remember, but this letter is not intended to do more than record the usual rules for spiral directions in horns. If these observations be of value in clearness of description of a difficult point, it will be a gain; and they may also prove useful in classification. By taking a corkscrew (or a right-handed spiral) in the hand, it is easy to verify on the horns themselves the direction of their spiral curves.

From *Nature* 10 January 1901.

50 YEARS AGO

The Société helvétique des Sciences naturelles held its 130th meeting at Davos during August 26–28. The Society has met there twice before—in 1890, when Davos was becoming one of the great health resorts of Europe, and in 1929, when it was also one of the great sport centres… In the afternoon, all sections joined up for the funicular railway ascent of the Weissfluhjoch. The very complex geological panorama was elucidated by Prof. J. Cadisch, of Berne. The Federal Institute for Research on Snow and Avalanches was inspected, with its low-temperature rooms, its thermically tested snowball of about a foot diameter and its stereoscopic microscope showing, in all its perfection, the scintillating branched symmetry of a crystal of snow. Afterwards, a film lecture on "Die Metamorphose des Schneekristalls", by Dr. M. de Quervain, added the dynamic to the static picture, a striking feature being the spontaneous passage to a less symmetrical form with the effect of reducing the surface area. Avalanche research was also illustrated by a film, which by a tragic coincidence had caught a skier being engulfed.

From *Nature* 13 January 1951.

come as a surprise to many scientists that little of our detailed molecular knowledge of how cells function is actually being used at present in treating human cancers. ■

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1. Soengas, M. S. *et al. Nature* **409,** 207–211 (2001).
2. Soengas, M. S. *et al. Science* **284,** 156–159 (1999).
3. Vousden, K. H. *Cell* **103,** 691–694 (2000).
4. Raveh, T. *et al. Nature Cell Biol.* **3,** 1–7 (2001).
5. Jones, P. A. & Laird, P. W. *Nature Genet.* **21,** 163–167 (1999).
6. Baylin, S. B. *et al. Adv. Cancer Res.* **72,** 141–196 (1998).
7. Robertson, K. D. & Jones, P. A. *Mol. Cell. Biol.* **18,** 6457–6473 (1998).
8. Kissil, J. L. *et al. Oncogene* **15,** 403–407 (1997).
9. Rideout, W. M. III, Coetzee, G. A., Olumi, A. F. & Jones, P. A. *Science* **249,** 1288–1290 (1990).
10. Widschwendter, M. *et al. J. Natl Cancer Inst.* **92,** 826–832 (2000).
11. Herman, J. G. *et al. Proc. Natl Acad. Sci. USA* **95,** 6870–6875 (1998).

Earth science

In the beginning…

Alex N. Halliday

Grains of the mineral zircon have survived from way back in Earth's history. Analysis of these grains provides information on the state of our planet as long as 4.4 billion years ago.

When did the Earth's continents and oceans first form? On pages 175 and 178 of this issue, Wilde *et al.*[1] and Mojzsis *et al.*[2] address the question with reports of uranium–lead (U–Pb) ages and oxygen isotopic compositions of extremely old zircon grains. Their results provide evidence that continents and liquid water were surface features of the earliest Earth. Part of one grain appears to have formed 4.4 billion years ago: this is the oldest terrestrial solid yet identified. Although it is unclear how general a picture a few tiny zircon grains can provide, the results represent a significant advance in reconstructing Earth's Dark Ages (Fig. 1).

The U–Pb dating technique depends on the two main isotopes of uranium, ^{235}U and ^{238}U, which undergo spontaneous chain decay until they form stable ^{207}Pb and ^{206}Pb, respectively. The probabilities of decay of ^{235}U and ^{238}U are extremely small, so their half-lives are long — 700 million and over 4 billion years, respectively. The unique feature that you can simply use the ratio of ^{207}Pb to ^{206}Pb to determine an age, even if the U/Pb ratio has been recently perturbed, makes U–Pb dating the most powerful way of determining the absolute age of material from the early Solar System[3]. The technique has been used to date the origin of the Solar System at 4.566 ± 0.002 billion years ago[4].

However, the method is inadequate for defining the rates of formation of planets and their component parts, such as the core and atmosphere. In the 1950s came the first convincing evidence of a now-extinct isotope, ^{129}I, that was present at the birth of the Solar System[5]. This discovery sparked the beginning of the use of extinct nuclides, such as ^{53}Mn, ^{107}Pd, ^{129}I and ^{182}Hf, which have half-lives that are two orders of magnitude shorter than that of ^{235}U. Although the parent isotope is extinct, its former abundance can be estimated from a correlation between the isotopic abundance of the daughter and the parent/daughter element ratio in an object of independently known age. One can then use the isotopic abundance of the daughter in other objects to determine their precise age relative to that of the original object.

From these studies, we know that the accretion (aggregation) of small bodies in the solar nebula occurred within about ten million years of the birth of the Solar System[6]. Similarly, we can show that Earth's growth was protracted, and dominated by impacts and planetary collisions[7]. By 4.51 billion to 4.45 billion years ago the Earth had reached its present mass, with a metal core and primitive atmosphere[7–9]. These timescales are consistent with computer models of planetary accretion[10]. In its early stages Earth probably had a magma ocean, sustained by heat from impacts and the blanketing effects of a dense atmosphere, but much of that atmosphere would have been lost with the dispersion of the solar nebula and during planetary collisions[8,9,11]. The Earth would then have cooled quickly, the outer portions would have solidified, and the first primitive crust would have developed.

There was, however, no direct evidence of what such a crust might have looked like. Unlike on the Moon and Mars, no rock older than 4 billion years old seems to have been preserved on Earth. An intense bombardment of the Moon occurred up until roughly 3.9 billion years ago[12]. So Earth's earlier crust may have been destroyed by impacts at around the same time, or it could be that a hotter Earth had an inherently unstable surface. Some argued that the earliest crust was like the Lunar Highlands — made from a welded mush of crystals that had previously floated on the magma ocean. Others suggested that it was made of denser rocks like

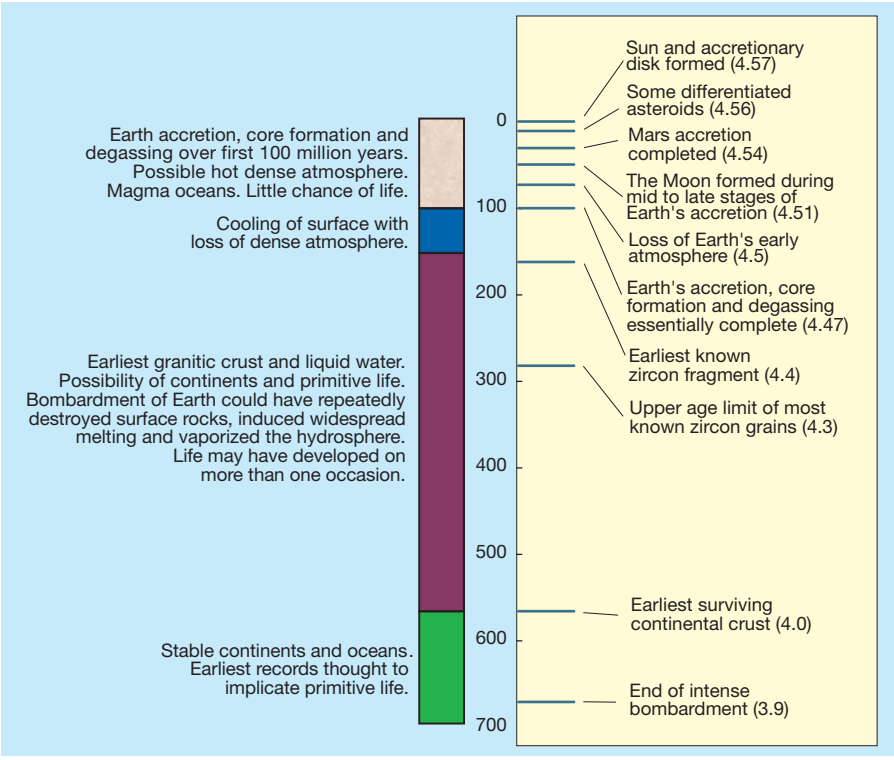

Figure 1 **Earth's earliest history, in millions of years, starting from the origin of the Solar System; numbers on the right show absolute ages in billions of years. Dynamic modelling, U–Pb dating of meteorites, and the use of short-lived nuclides all provide evidence for how the Earth formed over the first 100 million years of the Solar System's existence. The Dark Ages of before 4 billion years ago, strictly termed the Hadean, is a period from which no rocks seem to have survived. All we have from this time are a few zircon grains. Wilde *et al.*[1] and Mojzsis *et al.*[2] are the latest to show that zircons nonetheless represent a wonderful archive of information about the early Earth.**