

Surprisingly, the nucleomorph¹ contains only 30 genes encoding proteins needed to operate the chloroplast, with most such proteins being encoded in the host nucleus. Why are these 30 genes still found in the nucleomorph? Perhaps gene transfer is incomplete, or perhaps (more likely) it is blocked in some way. There is insufficient evidence either way, but again the sequence of the chlorarachniophyte nucleomorph, which also encodes a mere handful of chloroplast proteins¹¹, might be informative. By determining the extent of overlap between these subsets of stranded genes, we will be able to formulate hypotheses about gene transfer from nucleomorphs, just as we have for mitochondria and simple chloroplasts^{12–14}.

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Earth science

Shaken, not stirred

Michael Manga

It is difficult to obtain a dynamic picture of the Earth's mantle. A study involving geophysical observations with geochemical implications shows that compositionally distinct megablobs contribute to the ebb and flow.

The slow and continual deformation of the Earth's mantle is seen in the motion of tectonic plates at the surface. Flow in the mantle is driven by density variations, which are caused by changes in temperature and composition. Unfortunately, the velocity, pattern and driving forces of flow cannot be observed directly in the mantle, as they can in other dynamic parts of Earth such as the oceans and atmosphere. Rather, studies of the Earth's deep interior rely on indirect geochemical and geophysical measurements that are sensitive to the Earth's structure and dynamics.

On page 1049 of this issue, Forte and Mitrovia¹ combine a wide range of geophysical observations with mineral physics data — such as density and sound speed in minerals — to develop a model of global mantle flow and structure (Fig. 1a). They show that large-scale heterogeneity in the composition of the deep mantle may provide clues about the long-term evolution of the Earth.

The most tantalizing images of the Earth's interior have been obtained by studying the propagation of seismic waves generated by large earthquakes. Using a technique called seismic tomography — the geophysical analogue of a medical CAT scan — various properties of seismic waves, such as their travel times, can be used to infer the three-dimensional pattern of seismic-wave velocity in the Earth. It is tempting to translate wave propagation speeds into tempera-

ture variations in the mantle, and then to infer a model of flow. For example, waves will propagate slowly through regions that are hot, implying that such regions are less dense and will rise buoyantly. Conversely, faster waves imply a colder, denser region that will sink. Indeed, in the lower mantle the correlation of regions of fast waves with the expected locations of cold, subducted (sunken) oceanic plates (Fig. 1b) is usually used to argue that convection involves the entire depth of the mantle². That is, the mantle cannot consist of distinct, isolated layers that do not mix by convection.

Deducing flow patterns from wave speeds can sometimes be perilous, however. For example, the large, fast anomalies of seismic velocity in the upper mantle below many continents are probably due to differences in composition — the 'tectosphere' in Fig. 1b — rather than regions of sinking mantle³. Recent models based on seismic tomography⁴ also suggest that both compositional and thermal structures exist in the deep mantle⁵.

Forte and Mitrovia¹ develop a global convection model based on mineral physics data — specifically, the dependence of density and seismic wave speeds on temperature and composition. Their model incorporates a large number of global geophysics observations, including gravity measurements, the motion of tectonic plates, and deformations at the Earth's surface and core–mantle boundary that are caused by flow. In short, it

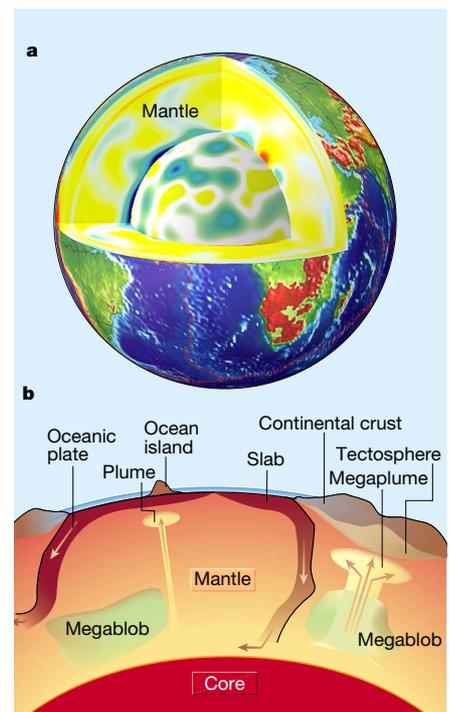


Figure 1 The interior structure of the Earth. a, A cutaway of the Earth, showing temperature variations in the mantle and changes in composition at the core–mantle boundary. (Courtesy of Forte and Mitrovia.) b, The structure of the mantle, showing subducted slabs, the tectosphere and megablobs (discovered by Forte and Mitrovia¹), which all influence temperature and flow (not to scale).

is the most comprehensive integrated study so far of mantle flow.

Forte and Mitrovia verify that the whole mantle appears to act as a single convective system that is driven primarily by thermal anomalies. They also find evidence of large-scale compositional heterogeneity — megablobs — within the lower mantle. The magnitude of the density variations is sufficient to lead to the 'doming' mode of convection, in which large blobs of compositionally distinct mantle 'shake' — that is, the blobs move up and down every so often⁶. This finding is at odds with recent proposals that the deep mantle is convectively isolated from the rest of the mantle⁷.

The results are not definitive, because geodynamic models are limited by the reliability and availability of data. The models of Forte and Mitrovia are even further limited by their use of simple assumptions about the composition of the lower mantle. But the new approach does provide a framework for incorporating improved seismic models and mineral physics data. In particular, much of the mineral physics data is extrapolated from measurements made at low pressures and temperatures, and will undoubtedly be refined.

The compositional variations and temperature anomalies mapped by Forte and

Mitrovica, along with the mantle flow, are snapshots of a dynamic Earth. Such snapshots do not tell us how the megablobs developed, or how they will evolve. Are these blobs 'unstirred' regions that have persisted throughout most of the Earth's history? If so, can they be the physical manifestation of the mantle reservoir that still contains elements that usually tend to be concentrated in the crust? This mantle reservoir is thought to provide the distinctive isotopic characteristics of ocean island basalts formed by mantle plumes originating in the deep mantle⁸ (Fig. 1b). The high viscosity of the lower mantle, inferred from the dominance of long-wavelength seismic structure⁹, slows the rate of mixing. But numerical models of convection have shown that high viscosity in the lower mantle is not sufficient to prevent significant stirring of heterogeneities¹⁰. So, if the blobs are old, they must be much more viscous than the rest of the mantle¹¹. Alternatively, the megablobs could be actively forming and growing, perhaps through the segregation and accumulation of subducted materials¹².

Solving these puzzles will require integrating fluid-dynamic models of thermochemical

convection with an even wider range of observations, in particular those that depend on changes to the mantle. Because this evolution of the mantle is coupled to that of the core and the continental crust, determining the nature and origin of deep mantle structures may ultimately provide new insights into the coupled chemical and dynamic evolution of the entire Earth. ■

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Cancer

Improved mouse models

Anton Berns

Mice that have been genetically modified to be prone to tumours are thought to be poor models of sporadic cancer. This problem can be tackled with a new generation of modified mice.

Cells tend to become cancerous only after they have suffered mutations in several genes, including those that control the mechanisms by which cells multiply, die or migrate to other parts of the body¹. This requirement for several specific genetic alterations poses a barrier to cancer, not least because mutations occur more-or-less at random throughout the genome. Nevertheless, a single, widespread cancer-promoting mutation can dramatically increase the occurrence of tumours. Such a situation occurs for hereditary tumours², as well as in mice that have been genetically engineered to provide models for studying cancer³. This is one of the reasons why such mice are generally poor representations of randomly arising (sporadic) tumours. By using a cunning genetic technique, however, Johnson and colleagues have produced a much more convincing mouse model of sporadic human lung cancers, as they report on page 1111 of this issue⁴.

Given that the accumulation of mutations is thought to be required for tumour formation, it seems strange that, in current mouse models or in hereditary cancers, one widespread genetic alteration can confer

such a strong predisposition to cancer. A fundamental difference between inherited and sporadic cancers may lie at the heart of this conundrum. A cell that is accumulating sporadic tumour-promoting mutations is, at least at first, surrounded by normal cells. These can suppress the propensity of the mutant cell to proliferate. By contrast, when someone has inherited a cancer-promoting mutation, that mutation would be present in many of their cells — a group of such mutant cells would enhance its own proliferation.

According to this concept, a group or 'field' of mutant cells is a tumour-promoting condition in its own right. The observation of 'field cancerization' in cancer patients provides support for this idea⁵. *In vitro*, meanwhile, adding the *Ras* oncogene (a generic name given to three mutant genes that can accelerate cell proliferation) can cause cells to become cancerous, but only in the absence of normal cells⁶. So one of the steps towards sporadic cancer might be the development of a field of mutant cells⁷. Classical mouse models do not incorporate this transition from a single mutant cell to a field of cells, because fields already exist. New models are therefore urgently needed,

and Johnson *et al.*'s genetically modified mice⁴ may meet this demand.

Using intricate genetic techniques, the authors have produced a strain of mice in which an active, mutant *K-ras* gene is generated at random in some cells by means of spontaneous recombination — the shuffling of segments of DNA — between or within chromosomes (Fig. 1, overleaf). This randomness echoes the sporadic occurrence of *K-ras* mutations in many human cancers.

The model has several unique features. First, *in vivo* recombination creates a low but substantial incidence of the active *K-ras* oncogene (the authors estimate that it arises once every 10³ to 10⁷ cell divisions). This gives rise to scattered cells that express that gene. Second, recombination yields an active *K-ras* oncogene within the authentic genetic locus on the correct chromosome. So, at least initially, expression of the mutant gene is under normal physiological control. Third, as the switch occurs randomly, all types of tissue, throughout development, can theoretically experience the effects of the mutant gene. Finally, the mutant gene can be traced easily in fields of cells by standard molecular biological techniques.

The mice showed a high incidence of lung cancers — including adenocarcinomas, which are predominant in humans and have a particularly poor prognosis — as well as some lymphomas (cancers of the blood) and skin papillomas. Metastasis, the migration of tumour cells to other parts of the body, occurred infrequently. The authors then produced mice that also had a deficiency in p53 — a protein that normally inhibits cancer development. These doubly mutant mice had a greater number of malignant tumours.

Analysis of groups of cells from mice with only the *K-ras* oncogene showed that this gene was activated in small foci (fields) of tumour cells — an early feature of cancer — but not in flanking regions (T. Jacks, personal communication). However, it is not clear whether the foci arose from a single cell with mutant *K-ras*, in other words, whether mutant *K-ras* drives the formation of a focus from a single mutant cell that is surrounded by normal cells. It is possible that the recombination event occurred in a single cell before birth, when *K-ras* (whether mutant or normal) is not yet switched on⁸. Such a cell would multiply as usual during development, forming a field of cells with a silent *K-ras* oncogene. After birth, that field of cells would suddenly start to express *K-ras*, and this might drive the formation of foci. Moreover, given that several distinct stages of lung cancer, for example, were seen in the mutant mice⁴, further genetic alterations are no doubt involved in tumour progression. It will be interesting to identify these changes.

Although mutations in the human *K-ras* gene are common in pancreatic and colon cancers, the mutant mice did not have these