population of the thymus of mice whose haematopoietic stem cells, including those for T cells, have been destroyed by irradiation. For the purposes of reconstitution, Ezine *et al.* supplied the mice with a mixture of a large number of bone-marrow cells from identical mice and a small number from congenic mice that carried a different T-cell surface marker. It was thereby possible in immunohistological studies of frozen thymic sections, prepared several weeks after reconstitution began, to tell which T cells had originated from which stem cells. The results were similar to those that had been previously obtained using a chromosome marker[4]: often thymus lobes contained no cells of congenic type and in other cases discrete foci of congenic-type cells were seen, and occasionally an entire thymus lobe was uniformly of that type. This pattern of distribution indicates that the thymus is recolonized by very few 'stem' cells, and sometimes by only one. As Ezine *et al.* point out, although this model does not tell us the actual number of stem cells colonizing a thymus throughout embryonic development, it does suggest it could be small compared with the size of the T-cell specificity repetoire. That argues in favour of the generation of receptor diversity within the thymus.

The second issue raised by the study is the long-disputed relationship between the thymic cortex and medulla. The medullary region of the thymus contains most of the organ's phenotypically and functionally mature cells (about 10 per cent of the total cell population). The simplest interpretation is that these are the immediate source of cells destined for export, although there could be a similar, but small and transient, pool of such cells in the cortex. The cortex contains the majority of dividing cells and the majority of thymocytes, most of which are both non-functional and phenotypically different from mature T cells. The simplest interpretation would be that these are the immature precursors of the medullary population, but this does not accord with the intrathymic death of most cortical cells. The medullary and cortical populations in fact display a large degree of independence in cell kinetic studies[5,6].

Nevertheless, Ezine *et al.* report cases where both cortex and medulla appear to be repopulated by a single clone, suggesting that a single stem cell has initiated a cell lineage which populates first the cortex and then the medulla. A subpopulation of apparently cortical blast cells, capable of reconstituting both cortical and medullary compartments, was reported by B.-J. Fawlkes and B. Mathieson at the meeting on T-cell differentation at the Basel Institute for Immunology last November. This could be a later intrathymic stage of the type of bone-marrow stem cell suggested by Ezine *et al.* Note, however, that Ezine *et al.* also report instances where only the medulla showed reconstitution with congenic-type cells, suggesting a direct seeding of the medulla without cortical involvement. The studies of Joterau and Le Douarin[7] on colonization of the avian embryonic thymus also suggest independent seeding of the cortex and the medulla.

Why there might be two separate developmental pathways, one cortical to medullary, one medullary alone, is far from clear. It would make more sense if T-cell sublineages of different function were handled in different parts of the thymus. With our present knowledge, it would be more sensible and comprehensible if all T-cell development, from stem-cell immigrants to functional T-cell emigrants, took place in the medulla. It is the involvement of the cortex, with its high level of both cell generation and cell death, and with its non-functional lymphoid cells of peculiar surface composition, that forces us to acknowledge there is something interesting happening in the thymus that we still do not understand. □

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Earth science

Anomalous satellite motion and mantle viscosity

from Kurt Lambeck

FOR many years geodesists have examined evidence for the temporal changes in the Earth's global shape and gravity field. Confirmation that such changes occur on time scales of at least several years has now emerged from the observation of a secular acceleration $\ddot{\Omega}$ of the node Ω of the orbit of the satellite Lageos[1,2], launched by NASA in 1976 and tracked ever since with high-precision laser-ranging equipment. Acceleration of the node implies a secular change in the flattening of the Earth and the most obvious explanation of this — the mass readjustment inside the Earth associated with the rebound of the crust after the melting of the Late Pleistocene ice sheets[1,2] — has recently been analysed in detail by Wu and Peltier[3].

One benefit of the measurement of the anomalous orbital motion is that it will provide an additional estimate of the viscosity of the mantle, a quantity that is central to discussions of mantle convection yet remains uncertain. The information on viscosity contained in the observation of $\ddot{\Omega}$ is the same as that contained in the observation of the Earth's secular acceleration but the latter is contaminated by other physical processes, most notably the secular tidal contributions; as a result no accurate figure for the non-tidal acceleration is available. Furthermore, non-tidal acceleration cannot be uniquely associated with the post-glacial rebound; for example, very long-period contributions could arise from electromagnetic coupling forces acting at the core–mantle interface. The orbital perturbation in the node may therefore reflect a more direct measure of the mantle's effective viscosity.

The power of the analysis of satellite orbits to determine the dynamic flattening, J_2, of the Earth with high precision is well known[4]. Nonetheless, observations of temporaral fluctuations in this quantity have proved elusive. What was missing, until Lageos, was a satellite that could be tracked with great precision and whose orbital motion was almost entirely governed by the Earth's gravity field.

The two studies use nearly the same Lageos data and there are many similarities in the orbital analyses used. Yet their results for the secular accelerations differ significantly: Rubincam[2] obtains $(-10.8\pm2.4)10^{-3}$ arc s yr^{-2} as the value of $\ddot{\Omega}$ while Yoder *et al.*[1] obtain $(-14.7\pm1.3)10^{-3}$ arc s yr^{-2}. Are we in for another long debate on the correct value of a secular variation, matching that of the Earth's non-tidal secular rotation? Why do these differences occur? The problem may be partly one of contamination by long-period tidal contributions because superimposed upon the secular motion of Ω are long-term periodic fluctuations due to the tidal deformations of the Earth, principally the 18.6 year tide. The periods of these tides are well known but the amplitudes are not, primarily because both the ocean response and departures of the solid Earth's response from that of an elastic body remain uncertain[5]. Thus with only 5.5 years of data the Lageos results are still very preliminary. In more leisurely times the authors would have patiently waited until a much longer record had been painstakingly acquired, but one cannot be sure that NASA will still be tracking Lageos a few years from now.

Whatever the exact answer, Wu and Peltier believe it can be explained as the response of the Earth to the new surface load following the removal of the Pleistocene ice from the glaciated continents and the addition of an equal water-mass to the oceans. Locally, sea level and gravity are changing through time; globally the Earth's rotation and the node of satellite

orbits undergo secular changes. Many attempts have been made to deduce mantle viscosities from these direct and indirect observations of the post-glacial rebound but the results have remained conflicting. What can be said is that nearly all observations are accommodated by mantle models of uniform Newtonian viscosity of 10^{21}–10^{22} P. Where controversy arises is in whether there is a significant depth-dependence of viscosity, whether this viscosity is linear and whether there is evidence for lateral variations in viscosity[6]. A principal reason for this state of affairs is that the results are only as good as our inadequate knowledge of the distribution and melting history of the ice loads themselves, partly determined by the rebound observations, particularly by observations of sea-level changes[7-9].

The new J_2 or $\ddot{\Omega}$ observations are largely consistent with the uniform and Newtonian viscosity range of 10^{21}–10^{22} P. Wu and Peltier[3] have attempted to combine this observation with those of the rotational response to deglaciation and conclude that the data imply there to be a thick elastic lithosphere overlying an upper mantle of viscosity 10^{22} P and a lower mantle viscosity of 1–3×10^{22}P. The average thickness of this elastic lithosphere is estimated to be about 120 km with the continental layer being about 200 km thick. This conclusion is reached by assuming a viscosity profile that is determined by local observations of rebound[10] and then determining the lithospheric thickness from the rotation data. The conclusion therefore remains dependent on the assumed ice history. Other recent studies[7-9] have shown that the proposed melting histories remain inadequate to explain sea-level changes in tectonically stable regions far away from the ice loads and point to mantle viscosities that are less than 10^{22} P. As long as the conclusion of a thick average lithosphere is not dependent on the assumed ice load, these observations raise the interesting possibility that there are substantial regional variations in viscosity, for the far-field Holocene sea-level fluctuations are responsive mainly to the mantle flow induced by the added meltwater rather than the flow under the former icesheets. □

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Oncogene activation

Message of *myc* in context

from Miranda Robertson

THERE are two reasons for the exceptional concentration of research on the cellular *myc* proto-oncogene (c-*myc*). The first is historical. The chromosomal translocations characteristic of Burkitt's lymphomas transfer c-*myc* from its normal context into an active immunoglobulin locus[1], where it was quickly identified by a number of research teams whose vigorous investigations on the molecular basis of antibody diversity were immediately deflected to the molecular basis of cancer. The second is the nature of the c-*myc* gene itself. Unlike many other oncogenes, c-*myc* is expressed in a wide variety of both normal[2] and tumour[3] tissues, and can therefore be expected to have some general significance. This expectation is borne out by two recent papers directly implicating c-*myc* in the control of normal and abnormal cell growth[4,5].

The implication of all the recent research, broadly, is that what changes during tumorigenesis is not c-*myc* itself but the regulation of its production. The evidence comes partly from the two recent papers[4,5] on changes in c-*myc* expression during the growth cycle of tumorigenic and non-tumorigenic cells *in vitro*, and partly from the latest investigations on the interaction of c-*myc* with the regulatory mechanisms operating on the immunoglobulin locus in Burkitt's lymphoma cells.

c-*myc* and the cell cycle

The data on the cell-cycle regulation of c-*myc* come from four laboratories: those of Philip Leder and Charles Stiles[4], and those of Gail Sonnenshein and Arthur Pardee[5]. The aim of their experiments was to establish where the product of the c-*myc* gene might act in the successive steps by which cells progress through their growth cycle. There is evidence, cited in both papers, that the progression from quiescence to DNA synthesis (that is, through G_0–G_1)can be divided into roughly three phases, each triggered by different tissue-specific growth factors. The first phase is known as the phase of priming for growth competence; and it is in this phase that c-*myc* is implicated.

Kelly *et al.*[4] have been able to show that a fibroblast mitogen, platelet-derived growth factor (PDGF), and two lymphocyte mitogens, concanavalin A and lipopolysaccharide, stimulate the expression of c-*myc* in those cells that normally respond to them. All three mitogens are believed to act early in the cell cycle to induce competence; and all stimulate transient expression of c-*myc* within 1–2 hours, with a return to baseline well before the onset of DNA synthesis.

The activation of c-*myc* by PDGF is particularly noteworthy, and indeed is particularly noted by Kelly *et al.*, in the light of the very close relationship between the sequence of one chain of PDGF and that of the product of the c-*sis* oncogene[6,7]. This may be the first clear illustration of how the cellular proto-oncogenes encode different components of a single regulatory chain, disruption of any part of which could contribute to tumorigenesis.

The implication of the Campisi *et al.*[5] data is that after a normal cell has been transformed into a tumour cell, regulation of the c-*myc* gene may be disrupted in such a way that its activation is independent of growth factors. They have measured c-*myc* expression during growth and quiescence in three cell lines: the non-tumorigenic mouse fibroblast line A31, and two tumorigenic derivatives, BPA31 and DA31, both transformed by chemical carcinogens. The growth of all three lines can be arrested by starvation (though the tumorigenic cells are slower to respond); but whereas arrested A31 cells cease to express c-*myc*, the transformed cells continue to express the oncogene at the same level after arrest. Apparently, c-*myc* expression, and thus growth competence, is no longer subject to regulation by serum growth factors after transformation.

These observations are, as Campisi *et al.* point out, consistent with the existing evidence that the activation of c-*myc* depends on the disruption of the genetic control of its expression, and not with mutations affecting the function of the product. (This is by contrast, for example, with the c-*ras* family, at least some members of which can be activated by mutations in their coding sequence [8-10].) They are not, as it happens, particularly consistent with the notion, derived from the transfection experiments of Land *et al.*[11], that c-*myc* is one of a class of oncogenes whose activation immortalizes cells (A31 cells are already immortal) and that a second gene (for example one of the *ras* family) is needed to complete transformation. But then, this categorization is in any case operational and indeed Land *et al.* explicitly state that they have no direct evidence that c-*myc* transfection immortalizes. What all this probably means is that tumorigenesis is a function of interactions between different oncogenes (in the Land *et al.* experiments c-*myc* and c-Ki-*ras*) that need not be the same in all tumours. There is, for example, no way of knowing whether the deregulation of c-*myc* in BPA31 and DA31 cells is due to a change in the regulatory region of the gene itself, or to the deregulation of some other component of the pathway in which c-*myc* par-