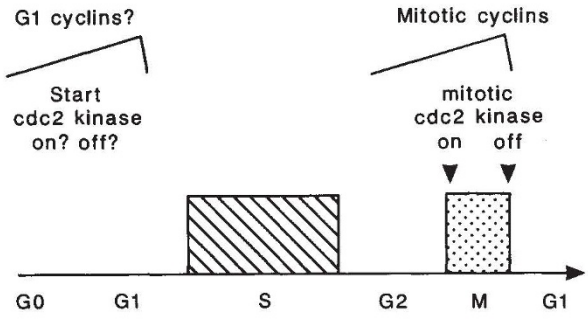

The cell cycle is represented as a time-line, with S phase and M phase represented as shaded boxes. The accumulation and destruction of mitotic cyclins is schematically represented as a graph, with destruction of the cyclin leading into interphase. The timing of accumulation and destruction of the G1 cyclins is largely hypothetical (see ref. 3).

enough degree, the cell enters mitosis. And when these same proteins are subsequently dephosphorylated, the cell leaves mitosis. The proteins remain in their mitotic state of phosphorylation for as long as the mitotic kinase(s) remain active. Simply put, high kinase = mitosis, low kinase = interphase. Cyclin is required, but is not sufficient, to activate the kinase activity of cdc2 for the G2 → M transition, and destruction of cyclin is what shuts off cdc2 kinase, causing the transition from mitosis to interphase.

Entry into S phase is not like this. Hartwell and colleagues showed that the budding yeast equivalent of *cdc2, CDC28*, is required for cells to enter S phase[7]. Cells with temperature-sensitive alleles of the gene responsible arrest at Start, implying that the activity of CDC28 kinase, although required for entry into S phase, is not needed to complete S phase once it is under way. Thus the mitotic model at first sight breaks down. Entry into S phase seems to be controlled in a different way. It is as though there is a period of the cell cycle of ill-defined length and unknown substance during which CDC28 has to be active. The period might be brief, almost a singularity in the cell cycle, or it might be long. Probably, CDC28 kinase, supported by its companion G1 cyclin-like subunits, has to stay active for a finite period, during which time progression of the cell cycle is latched by the synthesis of all kinds of components needed for DNA synthesis. Such a view is consistent with the well-known required period of exposure to growth factors — typically eight hours or so — for cells to perform the transition from resting to growing after a period of quiescence.

The question is, what are the key substrates of the G1 forms of CDC28 kinase? And does the proteolysis of G1 cyclins at any time form a signal in the same way as destruction of the B-type cyclins brings about exit from M phase? Or is it that rapid constitutive turnover of G1 cyclins keeps their levels low and thereby stops the Start-specific form of cdc2 kinase from exceeding the Start threshold?

It was the amino-acid sequences of CLN1, 2 and 3 that initially betrayed their resemblances to cyclins, not their cell-cycle behaviour. Yet the similarity to mitotic cyclins is faint. Of the roughly 400 residues in cyclins, only five widely but conservatively spaced amino acids show complete conservation in all 30 cyclin sequences from yeast to man. These residues probably mark important sites of contact with the cdc2/CDC28 subunits. Another important difference lies in the N termini of G1 cyclins, compared to mitotic cyclins of the A- and B-type family. Mitotic cyclins contain a 'destruction box' with a sequence such as RAALGNISN (single-letter code) that is typically located about 40 residues from the start of the protein and 80–100 residues upstream of the conserved 'cyclin box' (ref. 15). The G1 cyclins have no destruction box and have a shorter N terminus upstream of the cyclin box and a longer C-terminal extension beyond it. Their stability is thought to be determined by PEST sequences[4].

So, where does PRAD1, the new cyclin-like gene from humans, fit into the scheme of things? It contains the five conserved residues, and shows ghostly sequence homology with cyclin A (the resemblance to *CLN* genes is poor). It clearly represents a new class of cyclin, however, if cyclin it be, *sensu stricto*. Like cyclin A, it can bind to and activate cdc2. Its transcript shows striking cell-cycle fluctuations, high in G2, low in S phase, but the protein levels have yet to be measured. If anything, these sparse data suggest the protein has a role in mitosis, but because the control of S phase — if indeed that is what we are talking about — is still so imperfectly understood, we may all yet be on the track of a boojum[16]. □

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RÉSUMÉ

Age and autophage

Is it one of the trials of old age to be eaten from within by one's own proteases? Or is it even a cause? N. Schwartz-Ben Naim *et al. (Biochem. J.* **275**, 47–52, 1991) find that membranes of red blood cells from aged citizens contain proteolytic breakdown products of the main transmembrane protein, band 3. The effect can be reproduced *in vitro* by exposing the membranes to the endogenous protease, calpain I. The attack is on the large cytoplasmic domain of the band 3. Perhaps then the reduced life-span of red cells in old people is caused not by tired enzymes but rather by a change at the outer membrane surface, consequent on the proteolysis.

New for old

If the Universe collapses, might a new universe somehow be born? The inflationary model for cosmology offers apparently such a hope. Immediately after the Big Bang, inflation causes an exponential expansion, blowing up a tiny volume into the Universe observable now. In principle, when the Universe eventually contracts, the same microphysical processes could cause a time-reversed "deflation", abruptly shrinking a large volume of the cosmos to a tiny, dense region from which a new universe could emerge. Sadly, D. Goldwirth shows, in *Physics Letters* (B**256**, 354-358;1991), that this mechanism for cosmic reincarnation is possible but highly unlikely. The virtue of inflation is that, starting from almost any initial conditions, it creates a smooth, uniform, expanding universe. For deflation, the opposite is true: it will start only if the initial conditions are precisely right.

Iron implications

T. A. Rouault *et al. (Cell* **64**, 881–883; 1991) draw attention to an intriguing similarity between an iron-regulated RNA-binding protein (IRE-BP) and the Krebs' cycle enzyme aconitase. IRE-BP binds to sequences in the messenger RNAs for the iron-storage protein ferritin and the transferrin receptor, in the first case inhibiting translation and in the second stabilizing the RNA. With excess iron the affinity for RNA is decreased, and more ferritin and less transferrin receptor is synthesized. Rouault *et al.* point out that the proteins' sequences coincide in regions which the known structure of aconitase implies are functionally important: aconitase is an iron–sulphur protein that can exist in an inactive state with only three iron atoms per molecule and an active state with four iron atoms per molecule. The authors say the proteins may be evolutionarily related and share a structural mechanism for iron-regulated activity.