that detachment or delamination of the sub-continental lithosphere has been an important process throughout Earth history; such lithospheres may act as separate long-term source areas or be partly recycled into the convecting mantle. Detachment of lower-crustal to sub-crustal eclogitic residues (Collins) or contaminated mafic–ultramafic cumulates in the lower parts of magmatically thickened crust (N. Arndt and Goldstein, Max Planck Institute, Mainz) have also been proposed as mechanisms for the production of stabilized and broadly tonalitic crust or for buffering the crust–mantle system.

It is important that the significant geochemical and isotope characteristics of detachable crust and lithosphere are identified and their potential for recycling and mixing or retention as separate reservoirs clarified. Clearly, if lower crust (such as the reflective lower crust of western Europe) and lithosphere can detach then our estimates of past growth based on upper-crustal isotope signatures and of average crustal composition will be too low. Models yielding 80 per cent of crustal growth by the end of the Archaean would again be viable if much of the recycled crust was relatively unfractionated and fed into the mantle by processes other than subduction. □

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Cell biology

Ubiquitous cycles of repair

Steve Sedgwick and Lee Johnston

How can one gene in yeast, *RAD6*, affect meiosis, resistance to DNA damage, induced mutability and the cell cycle? Even the cloning of *RAD6* two years ago[1] did not reveal how it plays such a central role in DNA metabolism. However, Jentsch *et al.*, on page 131 of this issue[2], report their quite unexpected finding that RAD6 protein attaches ubiquitin to the histone H2B. This result means that a change in chromatin configuration can lead to complex changes in cell properties. Because ubiquitin is found in all eukaryotic organisms so far examined, the work of Jentsch *et al.* has important implications for many aspects of cell biology.

Ubiquitin is highly conserved, with only 3 of its 76 amino acids differing between yeast and mammals. It can exist free or covalently bound to various proteins, where one of its functions is to promote selective proteolysis of the protein concerned. The ligation of ubiquitin to target proteins occurs in a series of steps: first, ubiquitin joins to an activating enzyme, E1; second, activated ubiquitin is transferred to several conjugating enzymes, E2s; third, E2s donate ubiquitin to specific proteins, which sometimes requires a third enzyme, E3; and finally, isopeptidases remove ubiquitin from some protein–ubiquitin conjugates.

Jentsch *et al.* discovered[2] that the yeast *RAD6* gene encodes an E2-type conjugating protein that ubiquitinates H2B *in vitro*. They began by sequencing a fragment of a yeast E2 protein, and were surprised when the 14 amino acids of this fragment turned out to match the previously published amino-acid sequence of the yeast RAD6 protein[1]. The authors then expressed the entire *RAD6* gene in *Escherichia coli* and showed that cell extracts acquire H2B-conjugating activity.

Jentsch *et al.* speculate that ubiquitination of histones, and perhaps other basic chromosomal proteins, by the *RAD6* gene product *in vivo* induces what they call 'chromatin remodelling', a process that would allow access of repair enzymes to DNA lesions. Such targeting of repair to damaged regions could occur if chromatin which is already ubiquitinated becomes more susceptible to remodelling around DNA damage, or conversely, if DNA lesions trigger localized histone ubiquitination. There are two possibilities for the remodelling step itself. The first invokes the known role of ubiquitin in tagging proteins destined for proteolytic degradation. The second is that the ubiquitinated histones remain in place but with modified properties.

Thus, chromatin remodelling is either the result of proteolytic removal of certain histones or the direct consequence of structural changes produced by ubiquitination. Changes in chromatin structure of this sort could also affect the accessibility of DNA to replication, recombination or even transcription. Indeed, there is a disproportionate amount of ubiquitinated chromatin in fruitfly and mammalian sequences which have the potential to be highly expressed[3]. On expression of such genes, chromatin dissociates, presumably to permit transcription. It is tempting to speculate that the ubiquitination that marks out a transcribable sequence is also involved in bringing about the preferential repair that has been detected in expressed mammalian genes[4]. Until the full range of substrates for *RAD6* ubiquitination is known, there should be some caution in trying to explain all *RAD6* activity in terms of chromatin remodelling. Ironically, the highly acidic tail of RAD6 protein had already led to the suggestion[1] that it remodels chromatin, although by the different mechanism of competitive binding with histones.

A role for *RAD6* in the cell cycle is suggested by the properties of mouse ts85 cells, which have a temperature-sensitive E1-conjugating enzyme and stop dividing at the G_2 phase of the cell cycle at restrictive temperatures[5]. The E2-conjugating activity provided by *RAD6* may also affect cell division because of the slightly protracted *S* and/or G_2 phases of *RAD6* mutants[6]. Expression of *RAD6* seems to be confined to the G_2 phase of the cell cycle[7], suggesting that its usual role is in DNA synthesis or mitosis. It is also possible that other cell-cycle mutants, for instance some in the yeast *cdc* collection, are defective in ubiquitination. It might even turn out that there are oncogenes with defective ubiquitin metabolism.

As far as DNA-repair studies are concerned, ubiquitination is a totally new and exciting factor. Given the apparent conservation of ubiquitin metabolism, it is likely that *RAD6*-like activities exist in mammalian cells. Thus, defects in ubiquitination could account for the pleiotropic phenotypes of some human syndromes. It is a fairly safe bet that many DNA metabolism mutants will soon be taken out, dusted off and assayed for defects in ubiquitin metabolism.

The results described here emphasize the importance of post-translational modification of proteins in the regulation of cellular processes. Jentsch *et al.*[2] had the good fortune to have characterized a mutant in ubiquitin metabolism whose phenotype is already richly detailed. They will now need to find out whether all the functions of *RAD6* are exerted solely through ubiquitination of H2B, or if other undescribed proteins are involved. Whatever the outcome, the unravelling of the complex phenotype of *rad6* mutants in terms of defective ubiquitination should reveal basic rules about how this type of post-translational modification controls the behaviour of cells. □

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