species (including *S. bayanus*), and failing to find matches for 742 genes, estimated that the gene count should be reduced to 5,651. The crux of their argument was the assumption that if a gene is functional, it should be conserved among closely related species (see Fig. 1). Because the Génolevures project covered only 20–40% of each genome, the possibility remained that those 'missing' genes might be found in the unsequenced regions.

Kellis and colleagues[3] have now closed the door on that possibility: their sequence data cover 98% of two species and 93% of the third. Based on sequence alignments among the species, they largely confirm the results of the earlier study and argue that 503 genes should be deleted from the yeast catalogue, leaving 5,726 genes, of which 43 are newly discovered in their study.

Regulatory sequences, which sit outside genes and turn them on and off, are the key to understanding how a genome fits together. Whether we are comparing human and mouse, or yeast and yeast, we still have to answer the puzzling question of how seemingly huge differences in physical, biochemical or behavioural characteristics can result from sometimes tiny differences in the protein sequences. Regulatory sites occur virtually anywhere in the vast areas between protein-coding regions, and they can be identified because — unlike non-functional regions — they are conserved. The closer two species are, the more regulatory sites they are likely to share. Unfortunately, if the species are close enough, many pieces of non-functional DNA will be conserved merely by chance. A nice solution to this problem is to sequence more than two related species, dramatically increasing the signal-to-noise ratio (Fig. 1). The idea is that functional sequences should be conserved across multiple species, whereas chance conservation will only appear in pairwise comparisons. Using this principle, Kellis and colleagues have identified 42 novel sequence motifs that appear likely to have biological functions in yeast.

The most dynamic parts of the yeast genome are the chromosome ends, called telomeres. Kellis *et al.* aptly describe the rapid change and exchange going on in these regions as "genomic churning". The telomeres contain many genes not found elsewhere in the genome, and it appears that they form a crucible in which genomic change occurs: as the telomeres swap back and forth between chromosomes, they can carry pieces of genes along with them, which may combine with others to create new genes. Similarly rapid changes are evident in the telomeres of the malaria parasite *Plasmodium falciparum*[11]. Given the important events associated with these regions, sequencing of telomeres of the human genome — which, so far, have been neglected — should become a priority.

If 8% of the estimated protein complement of yeast was wrong, how much of the human counterpart might be eliminated by a similar study of mammalian species? How many genes and regulatory regions would be discovered? The human gene count has already dropped from more than 31,000 to just under 25,000 (refs 12, 13) in the two years since the initial genome publication. To understand our own genome better, we should sequence the genomes of several other mammals besides mouse and rat (both are almost done), choosing species that vary in their evolutionary distance from humans. At the chromosome level, only primates have as much structural similarity to human as these four yeast species share, and even those have different chromosome numbers: chimpanzee (*Pan troglodytes*) has 24, gibbon (*Hylobates concolor*) has 25, and macaque (*Macaca fuscata*) has 21. At the sequence level, we might gain more information from studying more distant mammals, such as cat (*Felis catus*), pig (*Sus scrofa*) and dolphin (*Tursiops truncatus*).

This new study of yeast genomes[3] makes it clear that comparative genome sequencing has tremendous analytical power: it offers the prospect of enhancing our knowledge of thousands of genes at once as well as providing fresh clues about the function of the vast amount of genomic DNA that does not encode genes. As it has done before, lowly yeast shows us a path towards a better understanding of our own biology. ■

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Molecular biology

Disruptive influence

Marco Foiani

Recombination is a vital cellular process implicated in DNA metabolism — but it must be tightly controlled. The discovery of a protein that disrupts recombination intermediates sheds light on the control mechanisms.

On pages 305 and 309 of this issue, Krejci and co-workers[1] and Veaute and colleagues[2] describe a biochemical mechanism that controls the genome 'shuffling' occurring in dividing cells and in DNA repair. Their findings have implications for how genome stability is maintained, and hence for the development of cancer.

Genome shuffling is referred to as 'recombination', and is a cellular process by which extensive tracts of DNA are moved from one part of the genome to another. There are several recombination pathways[3], some not yet well characterized, which are routinely used by normal cells to repair damaged chromosomes, to assist in DNA synthesis, and even to regulate gene expression. Recombination also occurs during the production of eggs and sperm, in which its function is to mix the genetic information such that each egg and each sperm is genetically different.

Despite its importance, however, recombination can sometimes be harmful: it can generate damaging genomic rearrangements, as well as intermediate structures that cannot be processed normally. Cells need to coordinate recombination with other responses to DNA damage, with progression through the cell-division cycle, and with chromosome replication. Otherwise, cells invariably become genetically unstable as the proteins that bring about recombination take over the chromosomes. During DNA replication, for instance, the double helix unwinds and separates, and the two strands are used as templates to make another helix. Replication frequently stalls, and a 'checkpoint' ensures that the separated DNA (the replication fork) maintains its integrity during these pauses. Without this checkpoint, abnormal replication intermediates form and are processed by unscheduled recombination[4]. In addition, in some inherited human diseases — Werner, Bloom and Rothmund–Thomson syndromes — mutations in enzymes implicated in DNA metabolism (DNA helicases) cause increased recombination, genome instability and a predisposition to cancer[5].

So cells must have mechanisms to control recombination and to prevent harmful chromosome rearrangements. One possible mechanism in yeast involves the Srs2 protein (a human relative of which has not yet been discovered, but it is surely only a matter of time). Srs2 is another DNA helicase — it can unwind double helices — and it has previously been implicated in DNA replication, in restarting the cell cycle after DNA-damage-

induced arrest, and in recombination[6–9]. For instance, mutations in the gene encoding Srs2 lead to excessive recombination[7]. Krejci *et al.*[1] and Veaute *et al.*[2] now provide biochemical evidence that Srs2 actively inhibits a key step in one particular recombination process — homologous recombination, or genetic exchange between two matching DNA regions.

During homologous recombination, single-stranded DNA must be produced, and the Rad51 protein binds this DNA to form so-called Rad51 nucleofilaments. Rad51 then mediates the exchange of this strand with a complementary tract of DNA. Krejci *et al.* and Veaute *et al.* show that Srs2, as well as acting as a helicase, also has a 'translocase' activity: it dislodges Rad51 from these filaments, thereby preventing recombination.

These findings explain why alterations in Srs2 are associated with hyper-recombination in yeast[7] (which is reminiscent of the excessive recombination seen in cancer cells). The results might also provide an explanation for other previous findings — and they raise new questions.

For instance, single-stranded DNA might signal the presence of DNA damage[4,9], leading to the recruitment of specialized proteins that activate the checkpoint response. The checkpoint then delays the cell cycle, allowing time for the damage to be repaired by various processes, some of which are mediated by Rad51. Srs2 is known to be involved here: it is phosphorylated in response to DNA damage[8] and, in its absence, cells manifest obvious checkpoint alterations[8,9], such as a hyperactive checkpoint that stops the cell cycle from restarting even when the damage has been repaired[9].

Perhaps the newly discovered inability of Srs2 mutants to dislodge Rad51 from nucleofilaments can explain this aberrant checkpoint: it might be necessary to remove Rad51 after recombination-mediated DNA repair so that the proteins that activate the damage-induced checkpoint can also be removed[9]. Veaute *et al.* also suggest that the Rad51 nucleofilaments themselves could be a checkpoint-activating signal, and hence that the removal of Rad51 by Srs2 is necessary to tell the cell that division can begin again. This is plausible, although cells depleted of Rad51 can still promote checkpoint activation. But regardless of whether they signal to the checkpoint, Rad51 nucleofilaments can clearly form during chromosome repair, making it essential that they be dismantled by Srs2 during recovery.

Srs2 also bears a relationship with Sgs1, the yeast counterpart of the human helicases that are defective in Werner, Bloom and Rothmund–Thomson syndromes[10]. When both Sgs1 and Srs2 are mutated, Rad51-mediated recombination causes cell death[10]. Although the functional interaction between these two helicases remains unknown, it is possible that they have a similar role in processing Rad51 filaments. If these proteins do have the same biochemical function, it is not surprising that they can sometimes substitute for each other[11]. But they do not seem to be redundant, hinting that they might act at different cell-cycle stages or different steps in replication. Perhaps Sgs1 is involved during the replication of damaged chromosomes by antagonizing the formation of Rad51 intermediates and hence promoting specialized, replication-specific repair processes. Srs2, by contrast, could preferentially contribute to the processing of Rad51 filaments after the passage of the replication fork, and later on in the cell cycle.

Another question is whether Srs2's translocase activity is implicated in other cellular pathways involving protein–DNA complexes. Support for this idea comes from Veaute and colleagues' finding[2] that Srs2 can also remove RecA, an *Escherichia coli* relative of Rad51, from DNA.

In addition, both genetic and physical approaches have shown that yeast cells with mutant Srs2 are defective in certain types of recombination event[9,12,13]. The implication is that Srs2, as well as preventing an early step in homologous recombination, might actively promote specific recombination subpathways. This apparent paradox could be resolved if this alternative role of Srs2 is more closely related to its helicase activity, or is controlled by its phosphorylation state, or is influenced by the formation of complexes between Srs2 and other proteins or by the type of DNA damage.

Finally, it remains to be seen how Srs2 itself is regulated. Recombination, of course, is often essential, and so must not always be prevented. ■

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Planetary science

Jupiter's moonopoly

Douglas P. Hamilton

A further 23 satellites have been discovered in orbit around Jupiter. With diameters of between two and eight kilometres, the moons are the smallest yet spotted around any planet.

Swinging serenely around the Sun, mighty Jupiter has reason to be pleased: its pre-eminence as the planet with the largest number of natural satellites, or moons, has been dramatically and decisively re-established. Fending off strong challenges from rival Saturn and wild card Uranus, the Solar System's largest planet now has nearly as many known moons as all of its competitors combined. Satellite-seekers Scott Sheppard and David Jewitt are responsible for returning Jupiter to its dominant status — on page 261 of this issue[1], they report the discovery of nearly two dozen new jovian moons.

The search for planetary satellites has a long history, dating back to 1610 and Galileo Galilei's discovery of four star-like objects orbiting Jupiter — Io, Europa, Ganymede and Callisto. Saturn's splendid ring system

Planet	Number of satellites	Number of irregular satellites	Largest irregular satellite and radius (km)	
Earth	1	—		
Mars	2	—		
Jupiter	60	52	Himalia	85
Saturn	31	14	Phoebe	110
Uranus	22	6	Sycorax	80
Neptune	11	5	Triton	1,353
Pluto	1	—		

Figure 1 **Planets and satellites. Irregular, or distant, satellites are found only around the giant planets and are thought to have been captured during the final stages of planetary formation. Total numbers are continually updated at ref. 4 and include this year's findings, up to April 2003: 20 moons at Jupiter, 1 at Saturn and 3 at Neptune. The smallest objects spotted at Jupiter are barely 2 km across[1].**