ing development of quantum computation, quantum cryptography and quantum teleportation. It is entanglement that makes a quantum computer, in principle, so much more powerful than a classical computer; that makes two-photon cryptography 100% safe; and that makes teleportation of quantum states possible. Quantum computation is far from being experimentally realized, but the production of two entangled atoms is a small but important step towards this goal.

In a parallel development, Ed Fry's group in Texas is trying to create entangled states of atoms by dissociating molecules using weak lasers³. And one might speculate about larger objects: there is no reason not to expect entanglement to be observed between molecules, and it is very hard to say what the ultimate size limit will be. The experimental

problem is that the larger an object is, the easier it can be disturbed by minute external influences — the quantum state describing many entangled particles is extremely fragile. But there is no reason in principle not to expect entanglement of macroscopic objects. As we know from the discussion between Albert Einstein and Niels Bohr in the early days of quantum mechanics, the distinction between quantum and classical is not necessarily the distinction between microscopic and macroscopic. □

D. Bouwmeester and A. Zeilinger are at the Institut für Experimentalphysik, Universität Innsbruck, Technikerstrasse 25, A-6020 Innsbruck, Austria.

1. Aspect, A., Grangier, P. & Roger, G. *Phys. Rev. Lett.* **47**, 460–463 (1981).
2. Hagley, E. *et al.* *Phys. Rev. Lett.* **79**, 1–5 (1997).
3. Fry, E. S., Walther, T. & Li, S. *Phys. Rev. A* **52**, 4381–4395 (1995).

Genomic stability

Silencing and DNA repair connect

Stephen P. Jackson

One of the challenges facing molecular biologists is to explain how the huge amount of DNA within the eukaryotic cell nucleus is packaged into chromatin, of which chromosomes are composed, and how this packaging affects processes such as DNA replication, transcription and the maintenance of genomic integrity. On page 900 of this issue¹, Tsukamoto, Kato and Ikeda reveal that three yeast proteins, associated with chromatin and with transcriptional silencing, are also involved in the repair of DNA damage induced by ionizing radiation. These results provide an unexpected dimension to silencing and chromatin organization, and may yield clues to the mechanism

by which DNA double-strand breaks are rejoined.

The fundamental unit of chromatin is the nucleosome, in which DNA is wound around an octamer of the core histones H2A, H2B, H3 and H4. Interactions with linker histones and various non-histone proteins provide further DNA compaction, which, in defined regions of the genome, culminates in the highly condensed state termed heterochromatin. Notable features of heterochromatin are that it is generally transcriptionally silent, is replicated late in S-phase of the cell cycle, is localized to the nuclear periphery, and is relatively inaccessible to DNA-modifying enzymes².

Heterochromatin-mediated transcriptional silencing is most commonly observed in higher eukaryotes, but it also operates in less complex organisms. For example, in the yeast *Saccharomyces cerevisiae*, the factors Sir2, Sir3 and Sir4 function in transcriptional silencing at telomeres and ensure that genetic information in the silent mating cassettes is not inappropriately expressed. All three factors are believed to be targeted to these loci by proteins such as Sir1 and Rap1 (ref. 2). Although the exact mechanism of silencing is unknown, the ability of Sir3 and Sir4 to interact with the amino-terminal tails of histones H3 and H4 (ref. 3), and the requirement of these tails for effective transcriptional silencing, suggest that the Sir proteins help to establish a higher-order, repressed state of chromatin.

The linkage between Sir proteins and DNA repair now reported by Tsukamoto *et al.*¹ came to light through investigations into Ku, a protein that binds to DNA double-strand breaks. This factor functions in the repair of radiation-induced DNA strand breaks by the DNA non-homologous end-joining pathway^{4,5}. It is also required for V(D)J recombination, which helps to generate the virtually limitless antigen-binding repertoire of the vertebrate immune system. The prevailing view is that Ku binds to DNA strand-breaks and recruits other factors involved in DNA repair and DNA damage signalling.

Using the yeast two-hybrid screen, Tsukamoto *et al.* discovered that the *M*, ~70,000 subunit of yeast Ku, named Hdf1 or Yku70, interacts with the carboxy-terminal portion of Sir4. Furthermore, they reveal that inactivation of the *SIR2*, *SIR3* or *SIR4* genes (but not *SIR1*) leads to severe defects in Ku-dependent DNA end-joining, but does not affect the homologous recombination pathway for DNA double-strand break repair. Taken together with radiation sensitivity data, these results show that Sir2, Sir3 and Sir4 are components of the Ku-associated DNA repair apparatus. Given the strong evolutionary conservation of Ku, it is tempting to speculate that functional homologues of the yeast Sir proteins exist in mammalian systems, and that they take part in V(D)J recombination and the repair of DNA damage induced by ionizing radiation.

As well as interacting with yeast Ku70 in the two-hybrid screen, Sir4 also binds to several other factors, including histones H3 and H4, and Rap1 and Sir3 (refs 3, 6). These observations imply that certain interactions with Sir4 could be mutually exclusive, and could mean that the Sir4–Ku70 interaction is indirect. Nevertheless, from the current work it seems reasonable to suppose that Ku recruits the Sir protein complex to sites of DNA damage, and that this might lead to the establishment of a heterochromatin-like state. ►

Figure 1 The work by Tsukamoto *et al.*¹ shows that, together with the DNA end-binding factor Ku, yeast Sir2, Sir3 and Sir4 proteins operate in rejoining breaks in double-stranded DNA. Shown here is a hypothetical mechanism for Ku-mediated assembly of Sir2, Sir3 and Sir4 (red) at the site of a DNA break. Both Ku subunits are shown; dashed lines represent protein–protein interactions that might tether the two DNA ends together and recruit the non-homologous DNA end-joining apparatus. The DNA is depicted as a thick black line, and the histone octamer as a single orange oval for simplicity. As indicated, this model for DNA repair involves the prevention of transcription and of DNA degradation by nucleases.

There are several ways in which such a process could potentiate DNA repair (Fig. 1). First, because silenced chromatin is generally inaccessible to DNA-modifying enzymes, it may prevent nuclease-mediated degradation of damaged DNA ends. Second, heterochromatin-associated silencing could stop processes such as transcription from interfering with DNA repair. Third, heterochromatin-mediated condensation of the damaged DNA might facilitate the juxtaposition and subsequent ligation of the two broken DNA molecules, and could prevent these DNA ends from engaging in other recombination reactions. This third function could be particularly important *in vivo*, where damaged DNA ends might otherwise easily become irrevocably separated, and where recombination with other loci is generally undesirable.

The new data also raise the possibility that the Sir proteins target Ku to certain heterochromatic regions in the absence of DNA damage. Consistent with this idea, as is the case for inactivation of *SIR3* or *SIR4* (ref. 7), loss of yeast Ku function leads to telomeric shortening^{8,9}. Thus, it will be of interest to determine whether Ku affects other Sir-dependent functions, such as tethering

telomeres to the nuclear periphery and transcriptional silencing (in this regard, it is noteworthy that mammalian Ku has been shown to suppress transcription⁵). Finally, the relative inaccessibility of heterochromatin may mean that it is inherently difficult to repair DNA damage in these regions of the genome — in such chromosomal contexts, Sir-mediated targeting of Ku could be a mechanism for potentiating the DNA non-homologous end-joining system to resolve potentially lethal DNA damage. □

Stephen P. Jackson is at the Wellcome/CRC Institute, and the Department of Zoology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QR, UK.

e-mail: spj13@mole.bio.cam.ac.uk

1. Tsukamoto, Y., Kato, J.-i. & Ikeda, H. *Nature* **388**, 900–903 (1997).
2. Grunstein, M. *Curr. Opin. Cell Biol.* **9**, 383–387 (1997).
3. Hecht, A., Laroche, T., Strahl-Bolsinger, S., Gasser, S. M. & Grunstein, M. *Cell* **80**, 583–592 (1995).
4. Lieber, M. R., Grawunder, U., Wu, X. & Yaneva, M. *Curr. Opin. Genet. Dev.* **7**, 99–104 (1997).
5. Jackson, S. P. & Jeggo, P. A. *Trends Biochem. Sci.* **20**, 412–415 (1995).
6. Moretti, P., Freeman, K., Coodly, L. & Shore, D. *Genes Dev.* **8**, 2257–2269 (1994).
7. Palladino, F. *et al. Cell* **75**, 543–555 (1993).
8. Porter, S. E. *et al. Nucleic Acids Res.* **24**, 582–585 (1996).
9. Boulton, S. J. & Jackson, S. P. *Nucleic Acids Res.* **24**, 4639–4648 (1996).

RNA structure

A molecular contortionist

Jennifer A. Doudna

RNA molecules kink, bend, loop and twist themselves into a wonderful variety of shapes. These took centre stage in June, at the first meeting devoted solely to RNA structure*. Due to the abundance of biologically important RNAs and the development of technical advances to study them, RNA structural biology has now come of age. And it is clear that ribonucleic acids are capable of a level of structural complexity that was once thought to be confined to proteins.

Although RNA lacks the chemical diversity of proteins, the many conformational degrees of freedom of its phosphate backbone, along with the unique hydrogen-bonding and stacking properties of its nucleotide bases, provide ample resources for three-dimensional folding. This has been exploited by evolution — RNA molecules are integral parts of the cellular machinery for protein biosynthesis, RNA processing, chromosome end replication and protein transport (Table 1). RNA molecules are sometimes catalysts (ribozymes), and the functional diversity of this molecular jack-of-all-trades implies structural complexity.

At first glance, the principles of RNA folding seem to be simple and rather dull,

because the four nucleotide building blocks readily form hydrogen-bonded base pairs and a corresponding double helix. But, unlike its DNA sibling, RNA rarely exists as a long, straight duplex. Instead, many RNA molecules fold back on themselves to produce short stretches of base-pairing interspersed with unpaired 'internal loops', bulges and terminal loops. And these loops and bulges are the key to the formation of complex RNA structures.

Internal loops, it turns out, are surprisingly ordered — the loop nucleotides make unconventional, yet specific, interactions.

For example, according to the nuclear magnetic resonance (NMR) and crystal structures of the loop-E region of 5S ribosomal RNA, purine nucleotides within the 'loop' are pinched together in sheared base-pairs, the bases of one strand stacking on bases in the opposite strand (P. Moore and T. Steitz, Yale Univ.). Although the overall structure is helical, the major groove of the loop region is stapled shut by magnesium ions that bridge the phosphate backbones.

It is not known whether this dramatically distorted geometry is recognized by the ligand for the loop-E region, the L25 ribosomal protein. But other RNA internal loops change shape on binding their ligands, for example the Tat and Rev responsive-element RNAs of the human immunodeficiency virus (HIV) and an RNA that binds the small molecule theophylline (A. Pardi, Univ. Colorado). The NMR structure of the unbound tetraloop receptor — an internal loop that binds to GAAA tetraloops and is common in large RNAs — reveals a 'closed' helical conformation, containing cross-strand purine stacking that resembles the loop-E structure (J. Feigon, UCLA). When the tetraloop is docked, however, the receptor helix is opened to allow stacking of the tetraloop bases in the minor groove.

Localized regions of RNA can be dynamic, perhaps providing the basis for movement on a grand scale within large RNAs. Crosslinking of active conformers of the *Tetrahymena* self-splicing intron, for example, reveals that helices within this roughly 400-nucleotide RNA can move by as much as 60 Å (T. Cech, Univ. Colorado). In the wish-bone-shaped hammerhead ribozyme (Fig. 1), movement of the helical arms is probably more limited, but it may be required to position an active-site magnesium ion close to the labile bond at the moment of cleavage (D. Herschlag, Stanford Univ.).

Metal ions are central to RNA structure and catalysis — a point that emerged as a major theme of the meeting. For example, more than 100 magnesium ions are needed for the several hundred nucleotides of ribonuclease P to be folded (C. Fierke, Duke

Table 1 The ABCs of RNA taxonomy

RNA ABCs	Description
cRNA	Ribozymes and autocatalytic molecules
gRNA	Template, or guide sequences, for editing of RNA messages
mRNA	Messenger that carries information from DNA to be translated into protein
rRNA	Essential components of the ribosome, the protein biosynthetic machinery
snRNA	Small nuclear components of the mRNA splicing machinery called the spliceosome
snRNA	Small nucleolar RNAs that specify methylation sites in rRNA, and may have other chaperone-like functions
tRNA	Transfer molecules that carry amino acids
Other examples:	
Telomerase RNA	Chromosome end-replication template
Signal-recognition particle (SRP) RNA	Essential component of SRP, involved in protein transport in cells
Xist RNA	Required for X-chromosome inactivation during development

*RNA Structure, Univ. California, Santa Cruz, 25–29 June 1997.