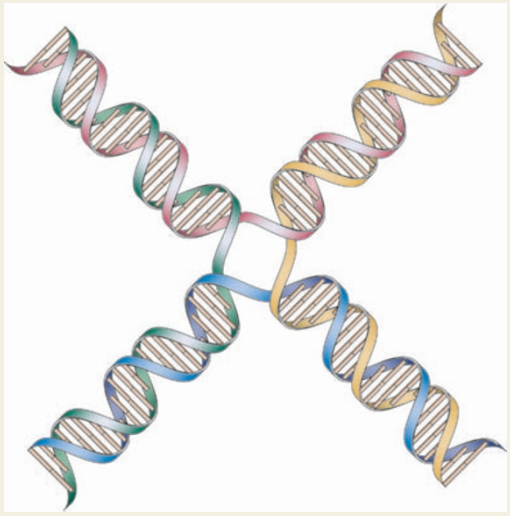
Resolving a Holliday romance

The repair of double-stranded DNA breaks (DSBs) is essential for genomic integrity and cell survival. In addition to a central role in meiosis, homologous recombination is also the main DSB repair pathway in eukaryotic diploid cells. A key step in this process is the formation of a four-way junction intermediate, termed the 'Holliday Junction', which has to be resolved to separate repaired chromosomes. Much of our current understanding has come from studies in bacteria, in which the RuvABC complex mediates resolution of the Holliday Junction. Although human biochemical resolvase activity was discovered in the late 1980's, its exact identity has remained elusive. Now, 40 years after the discovery of Holliday Junctions, work by Stephen West and colleagues (*Science* **303**, 243–246 (2004)) has identified the recombination/repair proteins RAD51C and XRCC3 as components of the human resolvasome.

During homologous recombination, two nicked strands of DNA undergo strand invasion to produce the Holliday Junction (see Figure). The complementary strand is then used as a template for the repair of the damaged one and, once the gaps have been filled, the Holliday Junction is resolved to produce two daughter strands. In an attempt to clarify which factors comprise the human resolvasome, West and colleagues turned to biochemistry: they fractionated chromatin-bound proteins from HeLa cells and enriched for Holliday Junction branch migration and resolution activities *in vitro*. After six rounds of purification, a fraction with resolvase activity was found to be devoid of many proteins known to be required at the early stages of repair, including RAD51, BRCA1 and BRCA2. However, the RAD51 paralogue RAD51C was present in this fraction and was required for resolvase activity. The DNA repair activity of RAD51C is ATP-dependent; consequently, an ATP-binding-deficient mutant of RAD51C exhibited a loss of resolvase activity.

To determine whether other RAD51 paralogues could contribute to resolvasome activity, the authors examined cell lines mutant for *XRCC2*, *XRCC3* and *RAD51C*. They showed that the RAD51C and XRCC3 paralogues are involved in Holliday Junction resolution, whereas other RAD51 paralogues may be involved in branch migration processes.



A ribbon diagram of the four-fold unstacked Holliday Junction.

Mus81 has previously been proposed to be part of the human resolvasome, although several lines of evidence now exist to suggest that this may not be the case. The identification of a human protein with high resolvasome activity represents a significant advance in our understanding of DNA repair mechanisms. However, several questions remain; for example, how is the resolvasome localized after DNA damage, and is this the only resolvasome activity? Undoubtedly, many more proteins must be identified before the resolvasome enigma will be fully resolved.

JON REYNOLDS

Translating prions at the synapse

Jonathan M. Levenson and J. David Sweatt

New studies indicate that an *Aplysia californica* variant of the translational regulator CPEB exhibits prion-like properties, enabling the protein to establish a stable, self-perpetuating and synapse-specific enhancement of neurotransmission. These studies suggest that a radically new kind of signalling — an autocatalytic change in protein conformation — is involved in maintaining long-term memories.

Much progress has been made in the last two decades in understanding the molecular and biophysical basis for long-term memory formation. However, one prominent question still remains: how do long-term memories remain stable in the face of a constant turnover of proteins required to maintain them? This is not a trivial problem — neuronal proteins typically have half-lives of a few hours, whereas long-term memories last months or years. The general solution to the problem of molecular turnover lies in a class of 'mnemogenic' chemical reactions, from the Greek for 'memory forming'[1]. A mnemogenic reaction is one that is stable and self-sustaining, a general theory of which has been discussed previously[1].

Two recent articles by Kausic Si, Eric Kandel and colleagues have identified a novel candidate mnemogenic reaction in the context of long-term facilitation of the sensorimotor synapse in *Aplysia* — cytoplasmic polyadenylation element binding protein (CPEB)-based self-perpetuating activation[2,3]. The authors

Jonathan M. Levenson and J. David Sweatt are in the Division of Neuroscience, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030-3498, USA.
e-mail: jsweatt@bcm.tmc.edu