rylation reaction. Phosphorylation of Asp 351 would require even deeper inclination of the N-domain, which is blocked by the A-domain in the E_2 state. In comparison, the orientation of the A-domain as in the E_1Ca^{2+} state leaves the phosphorylation site accessible to such a close association. It has been proposed that Brownian motion of the N-domain in the E_1 state could bring the N-domain close enough to the P-domain[13]. Additional structures of other intermediates in the catalytic cycle would certainly be very helpful in answering the unresolved issues. With the second structure in the reaction cycle of Ca^{2+}-ATPase, we are beginning to learn the details of its mechanism. For further insights, we eagerly await high-resolution structures of other conformational states.

C. Roy D. Lancaster is in the Department of Molecular Membrane Biology, Max Planck Institute of Biophysics, Heinrich-Hoffmann-Strasse 7, D-60528 Frankfurt am Main, Germany. email: Roy.Lancaster@mpibp-frankfurt.mpg.de URL: http://www.mpibp-frankfurt.mpg.de/lancaster

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Double, double coils or trouble

How do DNA duplexes pair up and stay linked? This togetherness is necessary for proper cell maintenance and division, such as during homologous recombination, but the mechanisms are not well understood. Now, in a recent paper (Hopfner, K.-P. *et al. Nature* **418**, 562–566; 2002), researchers suggest how a set of proteins called the Mre11 complex may crosslink DNA.

Mre11 (a double-strand break repair nuclease) and Rad50 (an ATPase) are the primary components of the Mre11 complex, and both are found in all kingdoms of life. They form a heterotetramer in 2:2 stoichiometry and appear to function together in numerous processes including telomere maintenance, synaptonemal complex formation, meiotic DNA processing, non-homologous DNA end joining, and recombination.

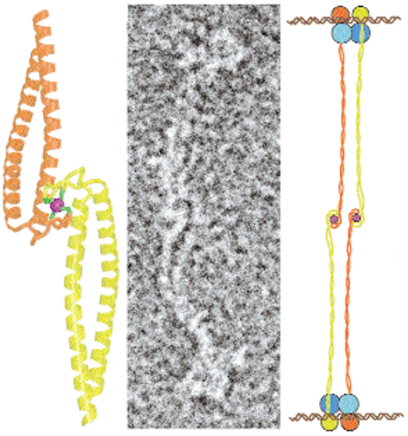
Hopfner *et al.* focus on Rad50, which contains a long coiled coil. Near the middle of this region, there is a CXXC motif thought to be involved in protein–protein interactions. To test this hypothesis, the researchers analyze portions of Rad50 that include this sequence.

In solution, these Rad50 polypeptides readily form dimers — but only in the presence of zinc. An X-ray crystal structure shows that, in the dimer, each monomer (orange or yellow in the left panel) forms an antiparallel coiled coil, with the CXXC motif at the apex.

The structure confirms that the CXXC motif mediates Rad50 homodimerization. Four Cys residues (two from each Rad50 polypeptide) chelate a zinc atom, and this assembly is stabilized by additional interactions. Mutational studies provide *in vivo* evidence for the importance of this zinc-mediated partnership. When the first Cys in the CXXC Rad50 motif is mutated to Gly, deleterious phenotypes are observed even though the mutant protein can still bind to its Mre11 partner.

Doubling up of the Rad50 coiled-coil domains may provide a mechanism for linking DNA duplexes in the flexible fashion needed to carry out the diverse processes mediated by the Mre11 complex. *In vivo*, each coiled-coil domain is connected to the ATPase domain in the same polypeptide. The ATPase domains could bind to Mre11 proteins, which could interact with DNA (as depicted in the right panel). Hopfner *et al.* use electron microscopy to explore this idea further.

They image Mre11 complexes with and without zinc. With the metal, they see many dumbbell-shaped particles that



seem to be hooked together in the middle (center panel). The ends of the dumbbell are interpreted as Rad50 ATPase domains bound to Mre11 nucleases (drawn as blue circles in the right panel) and the center portion is presumed to be pairs of coiled coils hooked *via* zinc in a limber tail-to-tail manner (as illustrated in the right panel). They estimate that the length of the center region of the human Mre11 complex dumbbell is ~1,200 Å, which, nicely, is the predicted distance between sister chromatids *in vivo*.

Tracy Smith