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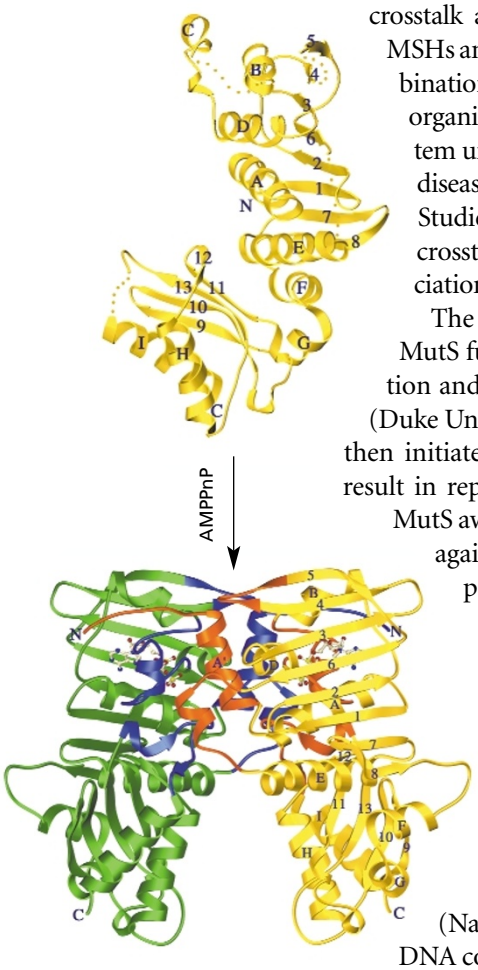
# Repair affairs

DNA damage repair has a storied past in bacteria and yeast. The characterization of bacterial factors—such as the MutL and MutS complexes, thought to mediate crosstalk and bind mismatches, respectively—and of a myriad of yeast RADs, MSHs and MLHs, which perform a variety of activities in DNA repair and recombination, has led to the understanding of processes fundamental to virtually all organisms. More recently, findings that defects in the DNA damage repair system underlie the mutator phenotype and cancer susceptibility, as well as other diseases with a wide array of phenotypes, have spurred even greater interest. Studies of DNA damage repair have now achieved critical mass, stimulating crosstalk between multiple disciplines—as was evident at the American Association for Cancer Research's recent conference on DNA Repair Defects*.




Wei Yang

Binding of ATP induces MutL transformation from monomer to dimer and results in the formation of an ordered secondary structure.

The biggest controversy in the field concerns a seminal issue: how does MutS function? The MutS complex binds to mismatches, but its precise function and dependence on ATP are unclear. In a keynote address, Paul Modrich (Duke University) detailed his views: the MutS complex binds to heteroduplexes, then initiates downstream events—possibly including signal transduction—that result in repair of the mismatch and ATP-hydrolysis-dependent translocation of MutS away from the site. The complex then dissociates from DNA, until it once again binds a mismatch. This 'translocation' model contrasts with one proposed by Richard Fishel (Thomas Jefferson University), the 'sliding clamp', in which a mismatch provokes ADP exchange with ATP within the MutS complex. The binding of ATP changes the conformation of MutS from a 'pac-man' to a 'doughnut'; MutS then translocates in an ATP-hydrolysis-independent fashion and transduces a signal to the repair machinery—or to the apoptosis machinery (in multicellular organisms) in the event of severe damage. The complex can remain attached to the DNA and serve as a 'sensor', or it can be recycled by ATP hydrolysis and concomitant release of the clamp.

An alternative view of MutS function was put forth by Wei Yang (National Institutes of Health), whose crystal structure of a bacterial MutS-DNA complex suggests that neither model is quite the best fit. These data indicate that the translocation model is based on tetramerization of MutS, a state of MutS rarely detected under physiological conditions and one with no known functional relevance. At first glance, the 'sliding clamp' fits better: the MutS complex clearly recognizes distorted DNA, the strength of its binding correlates directly with the level of distortion, and various arrangements of sub-domains (which Yang calls

"Rube Goldbergian") can accommodate many DNA conformations. But agreement with the 'sliding clamp' is also not complete: the 'ring' that binds DNA appears to be an induced fit; that is, it is formed only when bound to a mismatch, and is unlikely to retain the 'ring' when the complex translocates. The tight association between the protein and mismatched DNA also argues against the possibility of sliding. Still, one feature of both models—signal transduction to the repair apparatus and beyond—seems valid, as indicated by Jean Y.J. Wang (University of California, San Diego). Wang has found evidence that MSH2 and MLH1 are involved in activation of the ATM kinase—an effector of c-Abl- and p73-mediated apoptosis—and MSH2 and MLH1 may even physically interact with ATM.

Speaking of ATM, in a second keynote address, Yosef Shiloh (Tel Aviv University) gave an account of this molecule's growing prominence. First identified as the product of the gene mutated in ataxia telangiectasia (AT), it is now thought that ATM is involved in the regulation of such cellular notables as p53, MDM2, BRCA1 and NBS1. But the ATM account was only one of many to show how much progress has been made in revealing how repair proteins, and those downstream, underlie a diverse set of diseases. Mark Kaplan and John Petrini (University of Wisconsin) pointed out that similar yet clinically distinct diseases, such as AT, AT-like (caused by mutations in *MRE11*) and Nijmegen breakage syndrome (caused by mutations in *NBS1*) result from disruption of interacting proteins that function in double-strand break repair but also participate in diverse aspects of cellular metabolism. Another example is that of a set of genetically heterogenous syndromes caused by defects in nucleotide excision repair—xeroderma pigmentosum (XP), Cockayne syndrome and trichothiodystrophy—characterized by ultraviolet sensitivity and premature ageing. Some of these phenotypes are due to mutations that destabilize the transcription complex TFIIH, and Jan Hoeijmakers (Erasmus University) predicts that 'exhaustion' of TFIIH may be the cause, a possibility that he is testing in mouse models.

The involvement of DNA damage repair defects in cancer was also an important theme. The mutator phenotype—caused by mutations of genes involved in mismatch repair, which lead to microsatellite instability (MSI) and predispose to tumours—is being dissected by a combination of approaches. Following the initial observations in tumours, mouse models have been instrumental in discerning the molecular basis of MSI. Raju Kucherlapati (Albert Einstein College of Medicine) discussed how targeted mutations in *Mlh1* and *Msh2*, which are heterodimeric partners, cause MSI—a point underscored by Tom Kunkel (National Institute of Environmental Health and Safety), who estimated that mutations in these two genes are responsible for approximately 40% of MSI tumours. But mutant alleles of *Msh3* and *Msh6*, the protein products of which interact with Mlh1 and Msh2, can also predispose to tumours (albeit less frequently)—but not MSI. The roles of these proteins are also being examined in yeast, as explained by Eric Alani (Cornell University); these data suggest that variable interactions between the factors contribute to different aspects of double-strand break repair. But as Kunkel pointed out, the human homologues of some of these genes do not fully complement the yeast mutant phenotypes, suggesting possible divergence in function. Kunkel also raised several caveats: a weakness of population studies of mutations in repair genes is that age- and race-matched controls have not been used, and aberrant expression may lead to the titration of heteromeric partners, which may in turn cause mutant phenotypes.

DNA damage repair has come a long way from basic research days. Evaluating data from a wide variety of fields offered a rare opportunity to recombine ideas, and the hybrid vigour fuelled by this cross-pollination—between fields as diverse as yeast genetics and structural biology—is a testament to the increasing relevance of DNA damage repair to many of the most important basic and clinical research fields in genetics.

**DNA Repair Defects; an AACR Special Conference in Cancer Research; January 14–18, 2000; San Diego, California, USA. Organizer: Richard Kolodner (University of California, San Diego, and the Ludwig Institute of Cancer Research).*