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DNA REPAIR '99
Transcription-Coupled Repair of DNA Damage: Unanticipated Players, Unexpected Complexities

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It has been well established that certain types of DNA damage—for example, UV-induced pyrimidine dimers—block the progression of RNA polymerase. Evidence suggesting a relationship between DNA repair and transcription was presented by Mayne and Lehmann (1982), who observed that the recovery of RNA synthesis was more rapid than the overall time course of DNA repair in UV-irradiated human cells. In addition, it was found that, whereas Cockayne syndrome (CS) cells were able to perform normal levels of repair synthesis, they were unable to recover their RNA synthesis after UV irradiation. Thus, it was suggested that the defect in CS cells resides in the repair of damage in transcribed genes. There is now a large body of evidence showing that damage produced by UV and certain chemical carcinogens is repaired more rapidly in transcriptionally active DNA than in the genome as a whole. This rapid repair has been shown to be due to a faster repair of damage in the transcribed strand than in the nontranscribed strand, in both hamster and human genes (Mellon et al. 1987; Leadon and Lawrence 1991). Although the original demonstration of such strand-specific repair of UV damage was made for mammalian cells, it has now also been demonstrated in *Escherichia coli* (Mellon and Hanawalt 1989) and *Saccharomyces cerevisiae* (Smerdon et al. 1990; Leadon and Lawrence 1992; Sweder and Hanawalt 1992) and hence appears to be a highly conserved pathway for excision repair.

The Signal

It has been proposed that the presence of an RNA polymerase stalled at a lesion on the transcribed strand serves as a signal that directs repair to that strand (Mellon et al. 1987). Evidence for just such a mechanism has been found in *E. coli,* in which strand-selective repair is known to depend on the Mfd protein, which appears to displace stalled RNA polymerase from a DNA lesion, bind the UvrA subunit of the excision nuclease, and stimulate the repair of the transcribed strand (Selby and Sancar 1993). Whether the coupling of transcription and repair occurs by a similar mechanism in eukaryotic cells is not yet known. However, strand selectivity of repair in both human and yeast cells has been shown to depend on active transcription by RNA polymerase II. The faster rate of repair of the transcribed strand of a gene correlates with the level of transcription of that gene, and this can be abolished by treatment with α-amanitin, an inhibitor of RNA polymerase II, under conditions that do not effect overall levels of DNA repair (Leadon and Lawrence 1991). In addition, studies with *S. cerevisiae* strains carrying a temperature-sensitive mutation in one of the subunits of RNA polymerase II have directly demonstrated the dependence of strand-specific repair on transcription by RNA polymerase (Leadon and Lawrence 1992; Sweder and Hanawalt 1992).

The generality of transcription-coupled repair (TCR) for damage other than that induced by UV has only recently been established. It has been demonstrated for bulky adducts produced by certain chemical carcinogens (Leadon and Lawrence 1991), suggesting that nucleotide-excision repair (NER) of bulky lesions in general may be targeted preferentially to the transcribed strand. However, methylated purines formed by treatment of cells with dimethyl sulfate are removed equally rapidly from both strands of the dihydrofolate reductase gene and from a transcriptionally silent downstream sequence (Scicchitano and Hanawalt 1989). Since such damage is primarily removed by specific N-glycosylases, this result was interpreted as suggesting that repair initiated by means other than nucleotide excision is not subject to targeting to transcribed strands. In contrast, TCR of thymine glycols formed in yeast by treatment with hydrogen peroxide has been demonstrated (Leadon and Lawrence 1992). However, since this damaged base can be recognized in vitro not only by a specific N-glycosylase but also by the *E. coli* UvrABC complex (Lin and

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Sancar 1989), it was unclear whether its preferential repair in yeast is performed by the same NER complex as that involved in UV-induced pyrimidine dimers. Subsequently, my colleagues and I have demonstrated that human and yeast cells defective in the NER pathway still repair oxidative DNA damage preferentially in active genes (Leadon and Cooper 1993; Cooper et al. 1997; Leadon et al. 1995). These results show that TCR can occur in the absence of NER and that repair of oxidative DNA damage initiated by an N-glycosylase can be coupled to transcription.

CS

CS is a rare sun-sensitivity disorder with a recessive inheritance pattern. It is characterized by severe growth defects, with cachexia, neuronal demyelination, mental retardation, microcephaly, skeletal and retinal abnormalities, and dental caries but no cancer predisposition. More than 140 cases of CS have been reported, and cells from affected individuals define five complementation groups. Most patients exhibit only CS symptoms and belong to groups CS-A and CS-B. The *CSA* gene codes for a protein belonging to the WD-repeat family (Henning et al. 1995), whose members regulate diverse cellular functions, including cell division, signal transduction, mRNA modification, and transcription. The product of the *CSB* gene (Troelstra et al. 1992) contains a region of multiple ATPase/putative helicase motifs characteristic of the expanding and diverse SNF2 protein family. Members of this family can have roles in chromatin remodeling or maintenance, activation or repression of transcription, and DNA recombination or repair.

The gene products defective in CS are required for the TCR of both UV-induced and ionizing radiation–induced DNA (Leadon and Cooper 1993; Venema et al. 1990). Since *CSB* encodes a putative helicase (Troelstra et al. 1992), its product may unwind DNA and, thus, displace a stalled RNA polymerase complex from the DNA, allowing repair proteins access to the lesion. It is also possible that the *CSA* gene product acts as a general mediator that recruits repair proteins to the damaged site. Since the sole representatives of CS groups A and B mutants studied so far are equally devoid of the ability to target repair of UV damage to active genes (Leadon and Cooper 1993; Venema et al. 1990), the requirement for both gene products in this process appears to be absolute in mammalian cells. However, the finding that the *CSA* mutant cell line is only partially defective in preferential repair of ionizing-radiation damage provides the first evidence of separable roles for the two gene products (Leadon and Cooper 1993).

In very rare cases, complementation analyses have assigned some CS patients to XP group B, D, or G; some of these XP/CS patients also present an XP phenotype. The *XPB* (Weeda et al. 1990) and *XPD* (Flejter et al. 1992) genes code for DNA helicases with DNA-dependent ATPase activity that are components of the transcription-factor complex TFIIH. The TFIIH complex corrects the repair defects in *XPB* and *XPD* cell extracts (van Vuuren et al. 1994). TFIIH appears to play a critical role in promoter clearance, a broadly defined event that results in the transition of a transcription-initiation complex to an elongation complex. Association of TFIIH with the transcription complex allows for the phosphorylation of the carboxy-terminal domain of RNA polymerase II and, possibly, for local unwinding of the DNA, using the helicase activity of XPB (Goodrich and Tjian 1994). When promoter clearance occurs, the transcription-initiation factors, including TFIIH, are released, triggering transcriptional elongation by RNA polymerase II. Thus, it is possible that an RNA polymerase II stalled at a DNA lesion may recruit the reassembly of additional factors—for example, TFIIH—that facilitate repair of the DNA lesion and allow resumption of transcription after the repair of the lesion. This may occur through the formation of a quaternary complex containing RNA polymerase II/CSB/DNA/RNA (Tantin 1998).

Xeroderma Pigmentosum Group G

The xeroderma pigmentosum group G (*XPG*) gene (Scherly et al. 1993) encodes a large protein with an endonuclease activity that is required for making the 3′ incision in NER. XPG and *Schizosaccharomyces pombe* Rad2 define two related families of nucleases (Macinnes et al. 1993; Scherly et al. 1993). Rad2 is closely related to human DNaseIV and to *S. cerevisiae* RAD27. These ~43-kD enzymes resemble the 5′ nuclease domains of bacterial DNA polymerases and are able to cleave DNA flap structures to remove unpaired 5′ regions. The second group comprises much larger proteins, of >120 kD, and includes human XPG and its yeast homologues, the *S. cerevisiae* RAD2 and *S. pombe* rad13 proteins. Both XPG and RAD2 are structure-specific endonucleases that nick damaged DNA 3′ to the lesion, in an early step of NER (O'Donovan et al. 1994). Unlike XPB and XPD, the product of the *XPG* gene (Macinnes et al. 1993; Scherly et al. 1993) has no documented role in transcription.

My colleagues and I have found that XP-G patients who exhibit a mild XP phenotype and no other clinical symptoms display normal levels of TCR of oxidative DNA damage (Cooper et al. 1997). The causative mutations in these patients have been identified in both *XPG* alleles, with the maternal allele resulting in a full-length protein with a missense mutation in the presumed active site of the endonuclease (Nouspikel and Clarkson 1994; Nouspikel et al. 1997). Normal levels of TCR

were present in these mutant cells, even though the catalytic activity of the XPG protein was absent. By contrast, we found that patients with severe infantile CS (Vermeulen et al. 1993) show a complete loss of strand-selective repair of oxidative DNA damage (Cooper et al. 1997). These patients have mutations that would lead to severely truncated XPG proteins (Nouspikel et al. 1997). Therefore, TCR of oxidative damage requires a function of the XPG protein that is distinct from its endonuclease activity that is generally associated with NER (O'Donovan et al. 1994). The defect in TCR correlates with truncations of the XPG protein that also lead to the clinical presentation of severe CS. The XPG homologue in yeast, RAD2, also participates in TCR of oxidative DNA damage; however, there is not an absolute requirement for RAD2 in TCR, whereas there is for XPG in human cells (Leadon et al. 1995). Thus, one interpretation of these results is that inefficient repair of endogenous oxidative base damage in critical active genes results in the developmental defects associated with CS.

DNA Mismatch Repair

In both prokaryotes and eukaryotes, DNA mismatch repair plays a prominent role in the correction of errors made during DNA replication and genetic recombination. In *E. coli,* the methyl-directed mismatch repair involves the products of the mutator genes *mutS, mutL, mutH,* and *uvrD*. In vitro, MutS is a DNA mismatch–binding protein, UvrD is DNA helicase II, and MutH is an endonuclease that incises at the transiently unmethylated DNA strand (Modrich and Lahue 1996). No biochemical activity for MutL has been identified. Mutations in MutS and MutL—but not MutH—result in a loss of strand-selective repair of UV damage, implicating a role for these proteins in TCR (Mellon and Champe 1996). However, the addition of either MutS or MutL to an in vitro NER assay does not affect the efficiency of lesion removal (Selby and Sancar 1995).

In eukaryotes, the mismatch-repair system is more complex. Genetic studies have demonstrated that the major DNA mismatch–repair pathway in *S. cerevisiae* requires three bacterial MutS homologues—MSH2, MSH3, and MSH6—and two bacterial MutL homologues—MLH1 and PMS1. Human homologues of the yeast mismatch-repair genes *hMSH2, hMLH1,* and *hPMS2* have been identified and have been shown to be mutated in patients and their kindreds with hereditary nonpolyposis colon cancer (HNPCC). Tumors from patients with HNPCC have high mutation rates in microsatellite sequences, a hallmark of cells with defective mismatch repair.

Human tumor cells defective in either *hMSH2, hMLH1,* or *hPMS2* have been reported to show loss of TCR of UV damage, further strengthening the link between TCR and mismatch repair (Leadon and Avrutskaya 1997; Mellon and Champe 1996). Similarly, human cells defective in the *hMSH2* gene have been reported to be deficient in the removal of oxidative DNA damage, including thymine glycols, from the transcribed strand of an active gene (Leadon and Avrutskaya 1997). However, an *hMLH1* mutant showed normal levels of TCR of oxidative DNA damage. These results provide the first evidence for a protein, hMLH1, that is absolutely required for the removal of UV-induced DNA damage—but not for the removal of oxidative DNA damage—from the transcribed strand of an active human gene. No defects in TCR of UV damage are found in yeast mutants for the *MSH2, MLH1, PMS1,* and *MSH3* mismatch-repair genes (Leadon and Avrutskaya 1998; Sweder et al. 1996), suggesting some functional differences between the yeast and human mismatch-repair proteins. By comparison, the yeast MSH2, MLH1, and PMS1 gene products participate in the TCR of thymine glycols (Leadon and Avrutskaya 1998). However, in contrast to the roles of these gene products in DNA mismatch repair, only double mutants in the MLH1 and PMS1 genes are deficient in TCR of thymine glycols. Cells with mutations in either MLH1 or PMS1 show near-normal levels of TCR of oxidative DNA damage. Surprisingly, although it appears that, in vitro, there is no functional overlap between the human mismatch-repair system and NER, with respect to either damage recognition or removal (Mu et al. 1997), physical interactions between yeast MSH2 and components of NER have recently been demonstrated (Bertrand et al. 1998).

DNA mismatch repair could play at least two roles in TCR. First, mismatch-repair proteins might ensure the fidelity of repair of damage in an active gene by removing errors introduced during DNA repair synthesis. Factors involved in either transcription or repair could serve as strand-discrimination signals for mismatch repair. However, this model would not account for a reduction in lesion removal in mismatch-repair mutants. An alternative, although not mutually exclusive, role for mismatch repair as a general sensor for DNA damage is supported by the finding that TCR is reduced in DNA mismatch–repair mutants. The human hMSH2 protein appears to be a crucial component for the sensing of DNA damage by the mismatch-repair system, since TCR of both UV and oxidative DNA damage in *hMSH2* mutants is slower or absent on the transcribed strand of an active gene. Thus, hMSH2 could bind to the DNA in the vicinity of the stalled transcriptional complex, in a manner similar to the way in which it recognizes and corrects base-base mispairs and small nucleotide insertion/deletion mispairs. It could then recruit other repair proteins, including hMSH6, hMLH1, and hPMS2.

BRCA1

Germ-line mutations in the *BRCA1* gene are associated with predisposition to breast and ovarian cancer and account for approximately half of the inherited cases of these diseases. The loss of the wild-type *BRCA1* allele during neoplastic transformation in these patients indicates that BRCA1 functions as a tumor suppressor. On the basis of its association with Rad51, it has been suggested that BRCA1 acts in concert with DNA repair enzymes to maintain the integrity of the genome during periods of rapid growth (Scully et al. 1997b). BRCA1 also binds to RNA polymerase II and several transcription factors, including TFIIF, TFIIE, and TFIIH (Scully et al. 1997a). This association could reflect BRCA1's proposed function as a transcriptional regulatory protein. However, this finding also suggests an involvement of BRCA1 in TCR.

My colleagues and I have recently shown that mouse embryonic stem cells deficient in BRCA1 are defective in the ability to perform TCR of oxidative DNA damage—but not in the ability to perform TCR of UV-induced damage (Gowen et al. 1998). However, we cannot distinguish between a direct role for BRCA1 in TCR and a role as a transcription factor essential for the expression of genes whose products are required for TCR. If BRCA1 serves as a transcription factor to facilitate TCR, then it would have to modulate a very rapid transcriptional activation of the required genes, since differences in the rates of repair between the transcribed and nontranscribed strands are found ⩽15–30 min after treatment. In addition, the genes activated by BRCA1 would need to be specific for the repair of oxidative DNA damage, since BRCA1 is not required for TCR of UV-induced damage. Therefore, it seems more likely that BRCA1 has a direct role in TCR, possibly in recruiting specific repair proteins. Both the early embryonic death of *Brca1*$^{-/-}$ embryos and the importance of this gene in tumorigenesis are consistent with a role for BRCA1 and TCR in the growth and development of normal cells (Gowen et al. 1996). Deficits in TCR of endogenous oxidative damage could lead to inefficient transcription and the accumulation of mutations in critical genes and, ultimately, to inadequate growth during early development. In adult tissue, an inability to target repair of oxidative DNA damage to active genes could lead to uncontrolled growth during tumorigenesis.

Future Directions

The study of TCR is in an exciting phase. Many of the genes identified as being required for TCR are associated with specific human diseases and clinical phenotypes; for example, defects in *CSA* and *CSB,* as well as certain mutations in *XPG,* all share the hallmark of developmental defects. By comparison, both defects in DNA mismatch–repair proteins and BRCA1 lead to increases in tumors in specific tissues. Therefore, an important area of future investigation will be to determine how these proteins interact with each other. In addition, since some of the proteins involved in TCR perform multiple functions in the cell, it will be important to begin to map which regions of the proteins are required for TCR and which are required for other cellular processes. These types of studies should begin to provide not only valuable insights into the relationship between TCR and specific human diseases but also new targets for antitumor agents.

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