COMMENTARY

DNA repair fine structure and its relations to genomic instability

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It is timely to review aspects of DNA repair as there have recently been major advances in this field. These insights have provided information regarding new linkages between DNA repair defects and cancer. Several human repair genes have been identified and cloned, and a direct molecular connection has been established between DNA repair and transcription.

The main focus of this review is to examine some new molecular relationships that have emerged pursuant to recent advances in the understanding of the fine structure of DNA repair processes. In particular, relations to genomic instability will be emphasized. Genomic instability is an important hallmark of both cancer and the ageing process, and is a broad term that includes a number of more or less specific changes in DNA. They can be point mutations, deletions, hypermutability, hypermethylation (epimutations), chromosomal rearrangements and/or abnormalities, or degradation of DNA. One form of genomic instability, the dysregulation of the cell cycle progression, affects mutational rates.

Forms of DNA damage

The classic DNA-damaging agent of interest has been UV light which introduces two major photolesions in DNA: the cyclobutane dimer and the 6–4 photoproduct. These lesions are directly linked to skin cancer, because patients with deficiencies in the repair of photolesions develop carcinoma in skin exposed to UV (1). Other bulky lesions in DNA that have been widely studied include those made by carcinogens such as 4-nitroquinoline-N-oxide (4NQO*), N-acetoxyacetylaminofluorene (NAAF), and alkylating agents such as nitrogen mustards (HN2). Several chemotherapeutic agents used to treat tumors directly damage the DNA. Such agents include alkylating agents and cisplatin. These compounds form intrastrand adducts (IA) in DNA and less frequently, interstrand alkylating agents and cisplatin. These compounds form intrastrand adducts (IA) in DNA and less frequently, interstrand alkylating agents and cisplatin. These compounds form intrastrand adducts (IA) in DNA and less frequently, interstrand alkylating agents and cisplatin. These compounds form intrastrand adducts (IA) in DNA and less frequently, interstrand alkylating agents and cisplatin.

The relative biological importance of these lesions is not clear, but it is generally recognized that 8-hydroxydeoxyguanosine (8-OH-dG) is highly relevant, and this has been the most extensively studied adduct among oxidative DNA damages.

DNA repair mechanisms

There are several different repair pathways in mammalian cells, and the prevalent ones are shown in Figure 1. These are (i) one-step reactions, a direct reversal by a single enzyme like photolyase and O\(^6\)-methyl-DNA-alkyltransferase; (ii) single- and multi-step base excision mechanisms (i.e. glycosylases); and (iii) multi-step reactions with pleiotropic specificities from multiple protein components. An example of the single-step reaction is the direct reversal that can be accomplished by the bacterial photolyase enzyme: a cyclobutane pyrimidine dimer is converted into two adjacent pyrimidines, and thereby the lesion is repaired. Another process is the one seen after mismatch formation, often a consequence of a replicative error. In Escherichia coli, these mismatch bases are repaired by a set of enzymes, the MutS, MutL, and MutH proteins. The MutS protein recognizes the lesion and initiates the assembly of a repair complex containing all three proteins. The MutH protein incises at a GATC sequence in the unmethylated strand. Next, MutS, MutL and MutU dependent excision step removes a section of DNA containing the GATC site and the mismatch. The resulting single-stranded gap is filled in by DNA polymerase III (3,4). There is currently a great deal of interest in what the homologous pathway is in mammalian cells, and whether there is interaction between it and nucleotide excision (4,5). Simple base modifications such as monofunctional alkylations can be removed by the base excision repair system, whereas more complex, bulky lesions are dealt with by the nucleotide excision repair pathway. Recombinational repair has been well characterized in bacteria, but these processes are poorly defined in mammalian cells. When there is no available intact template for the DNA polymerase to copy, a recombination must take place. An example of this type of repair is the process involved in the removal of chemotherapeutically introduced DNA ICL which are typically

Fig. 1. Different pathways for repair in mammalian cells.

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introduced after treatment with nitrogen mustards or cisplatin.

The most important DNA repair pathway is nucleotide excision repair (NER), which corrects the majority of bulky lesions in DNA. These lesions include UV-induced photoproducts, and bulky adducts such as those derived from cisplatin and 4NQO. Earlier work to elucidate the enzymology comes from *E. coli*, but now the molecular events are being characterized in human cells. NER involves recognition, incision, degradation, polymerization and finally ligation. The recognition steps involve the ERCC1, XPA and XPF gene products followed by the interaction with the TFIH transcription factor. This factor contains the repair genes XPC and XPD and thus represents a direct molecular link between DNA repair and transcription. A dual incision event is accomplished by the ERCC1 and XPG gene products, and this is followed by exonuclease activity, polymerization and ligation. There are a number of recent reviews that discuss this pathway in detail (6–12) and compare the pathways in bacteria and mammalian cells (13). What will be dealt with more extensively here is that the NER pathways differ in different parts of the mammalian genome: separate pathways operate for the repair of active or essential genomic regions versus regions that are non-coding. The in vitro cell-free extract assays, which have been used with considerable success to determine aspects of the DNA repair enzymology, are all limited to studying inactive DNA. As yet there is no assay for in vitro repair of active genes in mammalian cells. Several laboratories are working on this problem, and that approach is necessary for optimal biochemical analysis of the biochemistry of gene-specific DNA repair. There are distinct DNA repair pathways for active genes and for inactive genomic regions, which include a strand bias of the repair process, and these need to be understood. Further, there can be substantial differences in repair rates between various genes, and there can be variations within genes as well: certain codons are repaired better than others.

### Gene-specific DNA repair

About a decade ago, a general method was developed to measure DNA damage and its repair in individual gene fragments (14). This approach involves the generation of a strand break at the site of a lesion, followed by the resolution of single-stranded DNA by electrophoresis and quantitative Southern analysis. Such experiments have been widely used and are now adapted to the study of several DNA lesions, some of which are listed in Figure 2. A number of different approaches were used to generate strand breaks at the sites of lesions. The method permits reprobing for different genes and different strands of a gene using the same biological sample of DNA (15). The limitations of this technique have been that fairly high doses of DNA damage are necessary, and that the experiments are complicated and time consuming. However, experiments using this technique have yielded much new insight into the fine structure of DNA repair (10,16) and have demonstrated the strand bias of repair (17). This discovery was instrumental in establishing the molecular link between the repair mechanisms and the transcription process.

Early work on gene-specific repair showed that essential or active genes were preferentially repaired when compared to inactive genomic regions or to the bulk of the genome. The bulk of the genome is ~99% non-coding. When DNA repair experiments are done using the general bulk or total DNA of a cell, it essentially provides a measurement of the events in the inactive DNA. In such experiments it is thus not possible to discern whether there is any preferential repair in active parts of the genome. Several results from the work on gene-specific repair have suggested that repair in the essential or active genes reflects the cell’s ability to survive DNA damage. It is therefore possible that gene-specific DNA repair is a better measure of the biological importance of repair than is general, overall genome DNA repair.

In the last few years techniques have been developed to measure DNA repair in genes at low doses of cellular damage (18), and to measure the repair at the nucleotide level (19).

### A cellular hierarchy of the gene-specific repair

There are major differences in the repair efficiency among different genomic regions in mammalian cells. The repair efficiency can change with the transcriptional activity as originally observed in the hamster (20) and human (21) metallothionein genes after modulation of the transcriptional activity. However, repair efficiency can also be independent of the level of expression. A DNA repair hierarchy within the cell spans not only genes but also inactive regions. Some examples are differences in repair among different genes: the *p53* tumor suppressor gene (22), and another DNA damage inducible gene, *gadd153*, are repaired faster than the housekeeping dihydrofolate reductase (*DHFR*) gene (M.K.Evans, unpublished data). Another example is the more efficient repair in the inactive δ-globin gene than in an inactive locus 754 on the X-chromosome, region 754 (23). While transcriptional rates can be important, the repair differences may relate to aspects of chromatin structure or accessibility, to the level of CpG methylation (24) or possibly to whether these regions are associated with the nuclear matrix (25). This repair heterogeneity extends to changes in DNA repair efficiency within a gene. In the hamster *DHFR* gene there is more efficient repair of the 5’ end of the gene than in its 3’ end (26). In a study on repair at the nucleotide level in the tumor suppressor gene *p53*, there were considerable differences in the repair of different codons (19).

### Strand bias of repair and the connection to transcription

Further study of gene-specific DNA repair led to the observation that the repair process was biased towards the transcribed DNA strand (17). The strand bias appears to be due to a direct molecular link between DNA repair and transcription. This connection was first demonstrated in *E.coli*, and the molecular link was identified as the transcription-repair coupling factor, the *mfd* gene product (27). In mammalian cells this link may
be the ERCC6/CSB gene which is mutated in Cockayne’s syndrome. This syndrome is characterized by defective repair of actively transcribed sequences (28). Another demonstration of the repair/transcription link has been the previously mentioned finding that the mammalian basic transcription factor TFIIH contains at least two repair gene products (XPB and XPD). Interestingly, there appears to be no function for the repair genes other than their involvement in transcription (29) and thereby in repair. There have been several reviews of these findings recently (8,13), and the reader is referred to those for further pursuit.

Xeroderma pigmentosum, repair genes and repair phenotypes

Xeroderma pigmentosum (XP) is a rare disorder in which the patients are deficient in NER. It is a defect at the incision step of the process, and the total genomic repair of bulky lesions is absent or low. This repair defect was discovered 27 years ago by Cleaver (30), and the finding led to intensive investigation of the mechanism involved using cells from these patients. This has been very successful, and we are now close to having a complete understanding of the steps involved in the incision part of the excision repair process. There are seven complementation groups (genetically different classifications of XP), and via the use of hamster mutants that resemble XP cells, it has been possible to clone most of these human repair genes (8). The genes were previously called ERCC, but are now named the XP complementation group with that specific gene mutation. An exception is ERCCI, the first cloned gene, that has not yet been identified with any phenotype or disease. Using in vitro repair assays in which purified components are added to cell extracts, it has been possible to reconstitute almost the entire incision process (31,32). Recent work in the field implicates at least 17 proteins in the process of damage excision (33). The XPA protein is involved in the initial damage recognition step and binds to the lesion. It then forms a protein complex with the heterodimer, XPF–ERCC1 and replication protein A (RPA). The basal transcription factor TFIIH is then recruited to the lesion site in association with the XPC protein and the XPG protein. The XPG protein incises 3’ of the lesion and the XPF protein incises 5’ of the lesion. The resulting single-stranded gap is filled in by DNA polymerase δ or ε and sealed by DNA ligase. There appears to be a recruitment for proliferating cell nuclear antigen (PCNA) in NER, possibly in stimulating polymerase activity or increasing the catalytic turnover of the enzymes involved in excision.

The different XP complementation groups display different patterns of residual DNA repair. Until recently our knowledge of the repair phenotype in these cells was based on overall genome repair measurements, but now we also have information about the gene-specific repair patterns. Some of these are shown in Figure 3, where NER patterns in the general genome and in an active gene is displayed. In normal human cells, there is faster repair in the active gene than in the bulk of the genome. This illustrates the preferential repair of active genes in normal human cells. In XP cells there is no repair either in the bulk or in an active gene. XPC represents an interesting repair phenotype that resembles the repair pattern in rodent cells: active genomic regions are repaired, but there is very little repair in the bulk of the genome (34,35). Figure 3 also shows the repair phenotype in cells from a patient with the premature ageing condition, Cockayne’s syndrome. Here, the general genome repair is normal, but these individuals lack the ability to preferentially repair active genes.

DNA repair in genomic instability

Several connections between deficient DNA repair and genomic instability have appeared, and some of these examples will be considered in the following. This connection can be more or less direct.

Mismatch repair deficiencies

As mentioned, mutations in the bacterial genes MutH, MutL, MutS or MutU lead to replication and recombination errors that then lead to base pairing or coding abnormalities (4) in the bacteria. Micro-satellite instabilities (nucleotide repeats, replication errors) that resemble these errors have been observed in a number of human cancers at varying frequencies. It occurs in a common type of malignancy, hereditary non-polyposis colorectal cancer (HNPPC). These patients have mutations in the human homolog to the bacterial Mut genes, and they are deficient in mismatch repair (36,37). The hMLH1, hPMS1 and hPMS2 proteins are homologs of the bacterial MutL protein, and the hMSH2 protein is a homolog of the bacterial MutS protein (38–40). This connection establishes a direct link between DNA repair deficiency and cancer and adds another example (in addition to XP), demonstrating the direct role of DNA repair in the prevention of mutations which can lead to cancer. For further reading on mismatch repair, see (4,41).

Local repair deficiency and chromosomal rearrangements

DNA repair was studied in regions that are hot spots for chromosomal rearrangements in normal B-cells from different
DNA lesions or incomplete repair may be a cause of genomic instability

Fig. 4. DNA lesions or persisting DNA strand breaks may lead to genomic instability.

inbred mice strains. BALB/c mice are very sensitive to plasmacytoma formation. Upon various stimuli they readily develop plasmacytomomas. These tumors are generally associated with chromosomal rearrangements in the 5' c-myc region and in the pvt locus. Another mouse strain, DBA, is very resistant to plasmacytoma formation, and there is virtually no tumor formation after stimulation. Several DNA repair measurements were done in these two mouse strains to look for differences that could explain the predisposition to cancer development and to chromosomal rearrangements. Fresh, stimulated B-cells from normal mice without tumors were exposed to UV light to generate the DNA damage. Strain-specific repair differences were observed in several genomic regions. However, there were no differences in the overall genome repair. There were no strain-specific differences in the repair of structural genes such as DHFR and c-abl, but there were distinct strain-specific differences in the regions that were hot spots for rearrangements (42): in the 5' c-myc and pvt gene regions there was proficient repair in the B-cells from DBA mice, but no repair in the cells from BALB/c mice (43). No strain-specific differences were seen in the run-on transcription rates suggesting that there was no transcription-repair coupling in those regions (E.J.Beecham et al., submitted).

The concept that local DNA repair deficiency can lead to local genomic instability is supported by another study in mammalian cells (44). Here, recombinational events were reduced by the preferential repair of highly transcribed strands of DNA, and it was inferred from the study that deficiency in local repair leads to the persistence of highly recombinogenic DNA damage. In the study by Beecham et al. (43), the remaining UV damage was not particularly recombinogenic, but strand breaks formed at the sites of unrepaired damage could lead to recombination steps such as strand displacement and strand exchanges. This concept is illustrated in Figure 4 which represents a simplified model for the processes leading to those events.

Strand bias of mutation

An increased rate of mutation represents another form of genomic instability. Figure 5 illustrates in very general terms how mutations arise. DNA damage, generated by exogenous or endogenous sources can be subject to a repair process before the DNA undergoes replication. The replication fixes the mutation by insertion of an incorrect DNA base. Consequently, details of both the replication and repair processes play a role in the mutational footprint. Classically, replication has been considered to be the most important process in this regard, but it is now evident that repair is critical as well. In studies on selected systems such as the tumor suppressor gene, p53, a bias towards increased mutation in the non-transcribed DNA template has been reported (45). A mutational strand bias could be the result of a strand bias of repair or a bias of replication during the fixation of the mutations. The replication bias could be a result of differences in the fidelity of the DNA polymerases which replicate the leading and lagging DNA strands. Differences in replication fidelity have been shown in prokaryotic and in some mammalian DNA polymerases in vitro, but it is not known whether there are fidelity differences in mammalian replication in vivo. In a study on mutations in the HPRT gene in human repair-deficient cells, XPA, there were increased mutations in the transcribed strand (46). That bias would have to be explained as a bias in replication. But other results suggest that the fine structure of DNA repair is the critical element.

The strand bias of repair and the strand bias of mutation have been directly compared in experiments in mammalian cells using UV irradiation or carcinogens to damage the DNA. Cells were treated with a bulky DNA-damaging agent, and then allowed time to repair. The gene-specific and strand-specific repair were examined in parallel with DNA sequencing to determine the type and position of the mutations introduced. Such studies have shown a good correlation between repair occurring exclusively in the transcribed DNA strand and mutations introduced in the non-transcribed strand (47,48). It is important to note that immediately after DNA damage with carcinogen, the frequency of lesions was similar in the two DNA strands, suggesting that the strand bias observed was due to differences in the repair.

Another example of the correlations between strand bias of mutation and strand bias of repair comes from studies on p53. This tumor suppressor gene is the most mutated gene in human cancer, and one might suspect that the gene itself was repaired with very low efficiency. That appears not to be the case. In fact, repair of p53 in human cells is very efficient. In cells from a patient with XPC, a group that develop high incidences of skin cancers, the p53 gene was repaired very efficiently and with a very distinct strand bias: repair occurred only in the transcribed strand, and there was no repair in the non-transcribed strand (22). In studies of p53 mutations in skin from patients with this disorder, all mutations were found in the non-transcribed strand (49). This is another example of the tight correlation between DNA repair and mutation, and it highlights the importance of DNA repair in the generation of the mutational footprint.

In a recent study using the ligation mediated (LM) polymerase chain reaction technique to measure DNA repair at the nucleotide level, repair rates within the tumor suppressor gene
p53 were compared to information about hot-spots for DNA damage and for mutation (19). The results showed a good correlation between local deficiency of DNA repair and hot-spots for mutation. Hot-spots for mutation correlated better with sites of inefficient repair than they did with sites of adduct formation. This again establishes the connection between deficient DNA repair and mutational hot-spots, and it also suggests that DNA repair efficiency and mutational footprints may be more important information in relation to risk assessment than knowledge about the initial DNA adduct formed.

Interaction with checkpoint regulators
There is mounting evidence that DNA repair enzymes interact directly with components in the p53 pathway. Transcription of the tumor suppressor gene p53 is known to be induced by DNA damage (50) and p53 then binds to p21 (sdh-l, whf1, cip-1), gadd45, mdm2 and other genes in the pathways leading to cell cycle arrest or to apoptosis. Recently, experiments suggested that there is a direct role of gadd45 in the repair process (51), but this has not been reproduced. There are also some suggestions that p53 itself might directly affect the repair process. An important observation was that p53 binds to the repair genes XPB and XPD, and to the repair gene-containing basic transcription factor TFIIH (52). In addition, cells from patients with Li–Fraumeni syndrome have decreased gene-specific DNA repair capacity (52). In this syndrome, the inherited germline mutations in p53 result in increased susceptibility to cancers such as breast cancer. The level of p53 is markedly reduced in these cells (53,54). It is thus possible that p53 has two functions in relation to DNA repair; one is the checkpoint activity where the cell cycle progression is delayed to allow time for DNA repair before progression through S phase, and another is a direct interaction with TFIIH or other components of the DNA repair machinery. It is widely thought that cells from patients with ataxia telangiectasia (AT) are deficient in the p53 response (55), and that may indicate that they also have some form of a repair defect. However, no repair defect has yet been shown in AT. These cells are known to be defective in their replicative response to DNA damage. There are also preliminary indications that the p21 gene, downstream from p53, might play a role in DNA repair. It has been shown to be involved in replication and it appears to be a cdc-kinase inhibitor. Experiments in this and other laboratories using in vitro assays for DNA repair suggest a role for p21.

Mitochondrial DNA repair
These extrachromosomal organelles harbor up to 10% of the total cellular DNA. There are ~1000 copies of mitochondrial (mt) DNA per cell, each copy with a length of ~15 kb. Mitochondria are sites of oxidative phosphorylation, and thus generate and accumulate oxy-radicals and reactive oxygen species. The exposure of mtDNA to oxidative stress is thought to be a component of the development of malignancy and of the progression of the ageing process. Mitochondrial mutations and deletions occur with a high frequency in many disorders and increase markedly with ageing (56,57). Whereas it is well established that there is recombination and DNA repair in mtDNA in yeast, it has been generally thought that DNA repair was absent or deficient in mtDNA in mammalian cells. In 1974 it was reported that mammalian mtDNA lacked the ability to repair UV-induced pyrimidine dimers (58). This led to the general conclusion that there was no repair in mtDNA, but it is now evident that other lesions are repaired in mammalian mtDNA. A number of repair enzymes have been detected in mammalian mitochondria. They are not encoded in mtDNA but are transported through the membrane. These include uracil DNA glycosylase (59), AP endonuclease (60) and the mtDNA polymerase γ which may be involved in DNA repair. A method for detecting gene-specific DNA damage and repair (14) has been used to measure DNA repair activity in the mt genome in mammalian cells and a variety of mtDNA repair activities have been observed in hamster and human cells (61–66). It has been confirmed that mitochondria cannot repair pyrimidine dimers. However, the mitochondria are very efficient at removing 8-OH-dG (67,68) and they can repair 4NQO adducts and 7-methylguanine adducts formed by mono-functional alkylating agents (65,66). These observations suggest that mitochondria can perform NER in addition to base excision. Moreover, hamster mitochondria can repair cisplatinum-introduced ICLs, suggesting recombinational repair, but they cannot repair cisplatinum-induced IA, a finding consistent with the inability to repair pyrimidine dimers (63). The observation that the mitochondria can repair cisplatinum ICLs raises the question of whether mammalian mtDNA has the capacity for recombinational events. Studies on hybrid cell lines (69,70) or in human populations (71,72) have so far not detected evidence of homologous recombination, but the removal of ICLs from DNA must involve a recombinational step.

Telomeric DNA repair
Telomeres represent unusual and interesting structures for the study of DNA damage and repair because of their unique sequence which consists of tandem hexanucleotide (TTAGGG) repeats (73), their exposed location at the ends of chromosomes, and their association with unique binding proteins (74), as well as with the nuclear matrix (75). Furthermore, they allow for DNA repair studies in a system where there is no steady-state transcription (to date, there is no evidence of transcription in telomeres), and where replication can be modulated (76). Telomeres play a critical role in the maintenance of genomic stability (76,77). Telomeric length has been termed the best biomarker of ageing because in many studies in different biological systems it appears that there is a progressive shortening of these structures with age (78,79). This progressive shortening correlates with a progressive increase in genomic instability.

A method was recently established to measure telomere repair (80). UV was used as the damaging agent, but this technique has general applicability for other bulky lesions. It appeared that there was a higher repair efficiency in the telomeres than in inactive, X-linked genomic regions, although there was less repair in the telomeres than in the active DHFR gene. In this study it was found that telomeric length declined in ageing cells, but so did telomeric DNA repair. It has previously been proposed that the progressive telomeric shortening with age is due to the ‘end replication problem’, but to some extent it could be due to lack of complete replication as a result of the accumulation of DNA damage.

Drug resistance
There has been much interest in whether increased cellular resistance to drugs was associated with an increase in DNA repair. Recent work has supported this notion. The connection is less than convincing for multidrug resistance, but there are

DNA repair fine structure and its relations to genomic instability
Genomic instability is a hallmark feature of cancer and ageing. Several studies that show an increase in DNA repair in cisplatin-resistant cells or tissues. Cisplatin is the preferred drug of treatment for several types of cancer, and it is particularly widely used in the treatment of ovarian and testicular cancers. Many of these patients develop drug resistance, and it is thus of major interest to investigate how this resistance can be overcome. Previous studies had shown that some cisplatin-resistant cells have increased overall genome repair of cisplatin-induced lesions (81), but recent results suggest that the increased repair is at the level of the gene, i.e. enhanced genespecific DNA repair (82,83). A study was done to characterize the repair in cisplatin-resistant cells, comparing gene and overall genome DNA repair of both major cisplatin lesions, IAs and ICLs. Cisplatin-resistant cells had increased repair efficiency compared to the parental cell line, and the increase was most specific for the repair of ICLs at the level of the gene (82). This suggests that DNA repair processes may contribute to the resistant phenotype and illustrates the importance of measuring repair at the gene level and further characterizing the fine structure aspects of DNA repair in many contexts.

The ageing process

Another example of increased genomic instability is that seen in association with the ageing process. Figure 6 illustrates the general concept that DNA metabolism, genomic instability, ageing and cancer all are interactive. The increased genomic instability is manifest in several ways and is associated with the accumulation of DNA damage in the general genome and especially in mtDNA. There has been much speculation that this may be a result of a gradual decrease in DNA repair capacity with increased age. Only recently have the methods used to assess DNA repair been refined enough to begin to detect such a relationship. Using a host cell reactivation assay and measuring DNA repair in lymphocytes in a human population, Wei et al. (84) were able to detect an age-associated decline of ~0.6% per year between ages 31 and 60 years. Other recent studies suggest the possibility that there is a genespecific rather than general genome repair decline with age (85). This notion is supported by the recent observation that telomeric DNA repair can decline with age (80).

Perspectives

DNA repair is a much more integral part of the DNA metabolism than previously recognized. The linkage to transcription and the connection between mismatch repair and colon cancer are just the beginnings of insight into new roles of DNA repair. Some examples of the role of DNA repair in maintaining genomic stability have been discussed in this review, and there are many more. To study the molecular interactions involved in gene-specific repair, we need cell-free, in vitro systems where transcription coupled repair can be measured. Such systems have been available for some time for studies on DNA repair in inactive DNA, but it has not yet been possible to extend this approach to active DNA.

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