DNA repair by photolyase (photoreactivation) and nucleotide excision repair (NER) are the major pathways to remove UV-induced cyclobutane-pyrimidine dimers (CPDs). The nucleolus is a nuclear subcompartment containing the ribosomal RNA genes (rDNA) of which a fraction is transcribed by RNA polymerase I (RNAP-I), and the rest is silenced. Here yeast was used to investigate how photoreactivation and NER contribute to repair of active and inactive rDNA. Cells were irradiated with UV light and exposed to different repair conditions. Nuclei were isolated, and the active genes were separated from the inactive genes by restriction endonuclease digestion. CPDs were measured in total rDNA, in both fractions, and in the GAL10 gene. Repair in rDNA was as efficient as in GAL10 indicating that both pathways have unrestricted access to the nucleolus. Photoreactivation was much faster than NER and therefore was the predominant repair pathway. Active genes were faster repaired by photolyase than were silenced genes providing evidence for an open chromatin structure during repair. The transcribed strands of active genes, but not of inactive genes, were slightly faster repaired by NER providing evidence for transcription-coupled repair by RNAP-I. There was no pronounced inhibition of photoreactivation by RNAP-I in the transcribed strand, which is in contrast to genes transcribed by RNAP-II and RNAP-II and suggests different stabilities of RNAP-I and RNAP-II stalled at CPDs.

Repair of DNA lesions is essential to prevent mutations, cell death, or cancer (1). Since packaging of eukaryotic DNA in nucleosomes and higher order chromatin structures restricts DNA accessibility, all DNA-dependent processes including repair and transcription are mutually affected by structural and dynamic properties of chromatin (2–4). Here we investigated how two different repair mechanisms, photoreactivation and nucleotide excision repair (NER), find access to ribosomal DNA and repair UV lesions in the nucleolus of yeast cells.

NER and photoreactivation are the major pathways to remove UV-induced DNA lesions, cis-syn cyclobutane-pyrimidine dimers (CPDs), and pyrimidine-pyrimidone (6-4) photoproducts (6-4PPs) (5). Photoreactivation is a direct repair mechanism where a damage-specific enzyme (photolyase) reverts CPDs in a light-dependent reaction. Photolyases are found in many prokaryotes and eukaryotes, including yeast (5–8). Photoreactivation in yeast cells is modulated by chromatin structure and transcription (2). Photolyase is fast in nucleosome-free regions and slow in nucleosomes and therefore is an ideal molecular tool to investigate DNA accessibility in chromatin of living cells (9–11). There is preferential repair of the nontranscribed strands in genes transcribed by RNAP-II and RNAP-III, whereas photoreactivation of the transcribed strands is partially inhibited by RNAP-II and RNAP-III blocked at CPDs (9, 12, 13).

In contrast to photolyase, NER is a multistep mechanism that removes a large range of DNA lesions including CPDs and 6-4PPs (5). NER is divided in two subpathways, global genome repair and transcription-coupled repair (1, 14–16). Global genome repair refers to repair in nontranscribed parts of the genome and is modulated by nucleosomes (17, 18) and other protein/DNA interactions (11, 12, 19, 20). Transcription-coupled repair refers to preferential repair of the transcribed strand, an observation that was originally made in mammalian and hamster cells (21) and later in many more organisms including yeast (22, 23). RNAP-II stalled at a DNA lesion may serve as a damage recognition enzyme and promote NER (1, 16). Transcription-coupled repair was found in genes transcribed by RNAP-II, while genes transcribed by RNAP-III lack transcription-coupled repair in mammalian cells (24) and show a slight inhibition of NER on the transcribed strand in yeast (12).

The nucleolus is a subcompartment of the nucleus specialized in biosynthesis of ribosomes, a dense, protein crowded factory of transcription, RNA-processing and ribosome assembly (25). It harbors the clusters of rRNA genes (rDNA) coding for the large ribosomal RNA transcripts. rDNA is transcribed by RNAP-I, but only a fraction of the genes is active. Active genes are free of nucleosomes, while silenced genes maintain nucleosomes (26–28). Repair of UV lesions in ribosomal genes is still not clear. Removal of CPDs by NER was absent in rodent cells and inefficient in human cells (29–31). 6-4PPs, however, were efficiently repaired (32). NER of mammalian rDNA showed no strand bias and appears therefore not to be coupled to RNAP-I transcription (29, 30). Repair of rDNA in yeast Saccharomyces cerevisiae is different. First, CPDs are efficiently removed by NER. Second, experiments with mutants that compromise global genome repair revealed preferential repair of the transcribed strand and suggested that TC NER may exist in rDNA transcribed by RNAP-I (33). Since that study analyzed the total rDNA population and did not discriminate between actively transcribed and silenced genes, it re-
In contrast to NER, photoreactivation or the combination of photoreactivation and NER were never investigated in the nucleus.

Here we have investigated repair of UV lesions by both pathways in total rDNA as well as in the separated active and inactive rDNA genes. We found that photoreactivation is the predominant pathway for CPD repair in all situations. Moreover, we noticed that preferential repair of the transcribed strand by NER is restricted to the active rDNA genes thus supporting transcription-coupled repair. In addition, we observed structural changes in chromatin following damage induction and repair, but the active genes remained in a relatively open conformation.

Materials and Methods

Yeast Strains—S. cerevisiae W303.1a (Mata, ade2-1, ural3-1, his3-11,15, trpl-1, leu2-3,112, can1-100) was kindly provided by Dr. R. Sternfels. AMY3 (Mata, ade2-1, ural3-1, his3-11,15, trpl-1, leu2-3,112, can1-100 rad1::URA3) was generated by deletion of part of the RAD1 gene in W303.1a using construct pR1.6 (kindly provided by Dr. L. Prakash). AMY3 exhibits a strong UV sensitivity typical for rad1 strains.

UV Irradiation and Repair—UV irradiation and repair of DNA was done as described previously (34). Yeast cultures were grown at 30°C in YPD (1% Bacto yeast extract, 1% Bacto peptone, 2% dextrose) (35) to a density of about 0.5 x 10⁷ cells/ml. Cells were harvested and resuspended in 50 mM MOPS, 150 mM potassium acetate, 2 mM MgCl₂, 0.5 mM spermidine, 0.15 mM spermine, all adjusted to pH 7.2. The suspension was vortexed with 2 ml of glass beads (diameter, 0.5 mm; acid washed and equilibrated in NIB) until about 90% of the cells were broken (checked under light microscope for loss of contrast of broken cells). The cell suspension was resuspended in 400 µl of restriction buffer (33 mM Tris acetate, 10 mM magnesium (Cl₃), 0.2 mM EDTA, pH 7.5, 0.114% acetic acid, 1 mM EDTA for 20 h at 64 V. The psoralen cross-links were reversed by irradiation with 254 nm light (about 30 J/m⁻² s) for 12 min, and the DNA was depurinated in 0.25 N HCl for 12 min, blotted to Zeta GT nylon membranes, and hybridized with radioactively labeled strand-specific DNA probes that abut the restriction site (34).

Radioactive Probes—DNA fragments for generation of radioactive probes were generated by whole cell PCR. The oligonucleotides used for the 387-bp rDNA probe contained 5'-AGTTCCCTACTAATGACAAGG-3’ (top strand) and 5'-AGTTCCCTCCTAAATGCAAAGT-3’ (bottom strand). The oligonucleotides used for the 225-bp GAL10 probe contained 5'-CCGCCAGTACATGCTGATAGATAATGTA-3’ (top strand) and 5'-CCGCCAGTACATGCTGATAGATAATGA-3’ (bottom strand). Strand-specific probes were generated by primer extension with one oligonucleotide for each strand using Qiagen T3 polymerase. Probes for both strands were generated by random priming using the oligo-labeling kit (Amersham Biosciences).

Results

We used the yeast strains AMY3 (rad1Δ) with an inactivated NER to analyze photoreactivation and W303.1a for analysis of NER and NER with photoreactivation. Cells were grown in YPD, irradiated with 150 J/m² in minimal medium containing glucose, and exposed to photoreactivating light for up to 2 h in minimal medium supplemented with the appropriate amino acids. For NER, the cultures were incubated in the dark. Since photoreactivation is a very fast process, photoreactivation and NER were done at 24–26°C and not at 30°C. To investigate repair of the total rDNA cluster, DNA was isolated and cut with NheI, which generates a 4.4-kb fragment of the transcribed region and a 4.7-kb fragment containing the 5'-end of the rRNA gene and the spacer (Fig. 1A). To detect the CPDs, the DNA was cut with T4 endonuclease V at CPDs, fractionated by alkaline agarose gel electrophoresis, blotted to a nylon membrane, and hybridized to strand-specific probes abutting from the NheI site (black bar, Fig. 1A). This indirect end-labeling technique allows the mapping of CPDs along the DNA sequence and the measurement of the fraction of undamaged restriction fragments (9, 17, 22, 34).

A plot of data is shown for AMY3 (rad1Δ) and W303.1a (RAD1) (Fig. 1, B and C). Nonirradiated DNA (−UV) and DNA not treated with T4 endonuclease V (−T4) show the intact restriction fragment (4.4 kb, top band). Treatment of damaged DNA with T4 endonuclease V generated a smear with some bands, which represent the distribution of pyrimidine clusters (+UV, +T4). The CPD patterns are different in the nontranscribed strand and the transcribed strand demonstrating strand specificity of the assay. The top band (4.4 kb) represents the fraction of undamaged DNA. The initial damage was on average 0.17 ± 0.03 CPDs/kb in the nontranscribed strand and 0.2 ± 0.04 CPDs/kb in the transcribed strand probably reflect-
Photoreactivation Is the Predominant Pathway to Remove CPDs from the Nucleolus—Repair of CPDs is visualized by a time-dependent decrease of the CPD bands and an increase of the intact 4.4-kb restriction fragment (Fig. 1A). The removal of CPDs was homogenous. There are no sites that were resistant to repair. DNA repair of the whole 4.4-kb fragment was quantified, and the average of three independent experiments is displayed in Fig. 1D. AMY3 (rad1Δ) revealed very efficient repair by photolyase on both strands. About 50% of the lesions were removed by exposing cells to photoreactivating light for 15 min, and more than 80% of the lesions were removed after 2 h. No repair was observed when cells were kept in the dark demonstrating that the NER pathway was inactivated. Repair in the NER-proficient strain W303.1a showed slow removal of CPDs by NER when cells were incubated in the dark. A substantial fraction of lesions (about 60%) remaining unrepaired after 2 h. Please note that NER was slow since the experiments were done at low temperature (24–26°C). In contrast, exposure of those cells to photoreactivating light showed that the combination of NER and photoreactivation very rapidly removed CPDs. 50% of the lesions were repaired in less than 15 min. This experiment demonstrates that both pathways repair CPDs in the nucleolus, but photoreactivation is the predominant pathway under the light conditions applied in those experiments.

A Strand Bias of NER Indicates Transcription-coupled Repair in rDNA—It was previously reported that the transcribed strand of total rDNA was slightly faster repaired than the nontranscribed strand suggesting transcription-coupled NER (33). Consistent with that report, we observed preferential repair of the transcribed strand by NER as well (Fig. 1D). The difference between the two strands is small compared with the strand bias observed in genes transcribed by RNAP-II (13). This might reflect either a small number of active genes in the rDNA population, or transcription-coupled repair might be less pronounced compared with RNAP-II-transcribed genes. To address this topic, we investigated repair in active and inactive fractions separately.

Isolation of DNA from Active and Inactive rDNA—Psoralen cross-linking and nuclease digestion studies have established that actively transcribed rDNA is devoid of nucleosomes, while inactive genes are packaged in nucleosomes (27, 28, 37). It was further shown that restriction enzymes such as NheI efficiently cut in active rRNA genes of yeast but not in the inactive nucleosomal genes (36). We used this approach to purify DNA fragments of active genes for repair analysis. Yeast cells were UV-irradiated and incubated for repair as described above. Nuclei were isolated and digested with NheI, which liberates a 4.4-kb fragment of active rDNA (Fig. 2A). The DNA originating from inactive genes, NheI-digested nuclei was purified and fractionated in neutral agarose gels, and the rDNA fragments were identified after blotting using an rDNA probe, which hybridized to the 4.4-kb NheI fragment (Fig. 2B). The DNA originating from inactive genes, which was resistant to NheI digestion, showed up as long DNA fragments (>9.1 kb, inactive fraction of rDNA). The 9.1-kb fragment was a partial digest of two adjacent active genes and was not further used for repair analysis. The fraction of active genes that was released by NheI is represented by the 4.4-kb band.
Altered Chromatin Accessibility Induced by UV Irradiation and Repair—If UV lesions block transcription elongation of RNAP-I, one might expect that inactivation could lead to a reformation of nucleosomes in rDNA and make it less accessible to restriction enzymes. We therefore measured the fraction of 4.4-kb fragments released by NheI during the repair experiments. In unirradiated cells, this fraction was about 20% of total rDNA (Fig. 2C, −UV). After UV irradiation, the fraction decreased indicating that UV-irradiated chromatin became less accessible to the restriction endonuclease (0 min repair). The decrease was only about 25%, although ~75% of the genes received at least one transcription-blocking CPD in the transcribed strand. Thus, damage induction in transcribed genes altered the structure of some genes but was not sufficient to generate a chromatin structure that was as resistant to nuclease digestion as inactive nucleosomal rDNA. Hence, a large fraction of the active genes remained in a partially open chromatin conformation.

In W303.1a, which is proficient in NER and photoreactivation, the fraction of released genes increased with increasing repair times in the presence and absence of photoreactivating light (Fig. 2C). However, in the NER-deficient AMY3 cells no increase of the released fraction was observed during exposure to photoreactivating light. The effects were small, but they were observed in all three independent experiments. Thus, the increased release in W303.1a cells suggests that some rRNA genes may open chromatin either as a consequence of repair within the gene or as a consequence of repair in other genes (see “Discussion”). Since yeast photolyase in contrast to NER does not repair 6-4Ps, the increased accessibility to NheI might depend on removal of that photoproduct.

NheI Digestion of Nuclei Releases Only Open and Active rDNA—Active genes with an open chromatin structure bind more psoralen than nucleosomal inactive genes leading to different gel retardation of the cross-linked active DNA (slow migration, s-band) and inactive DNA (fast migration, f-band) during repair. This is observed for NER and NER with photoreactivation (Fig. 3). Lanes 2 in Fig. 3 show DNA fragments that were cross-linked after NheI digestion of nuclei. Only the s-band is visible at 4.4 kb demonstrating that only DNA of active genes was released by NheI digestion. The released active rDNA represents about 65% of total active rDNA. Since ~25% of active rDNA is found in the partial digests (9.1 kb), we estimate that the inactive rDNA (>9.1 kb) contains less than 10% of the active genes. Lanes 5, 7, and 9 show the total fraction of active (s) and inactive ('f') rDNA after damage formation and repair. Active rDNA remains a minor fraction throughout the experiment. Lanes 4, 6, and 8 show the products of NheI-digested nuclei. No f-bands are detected demonstrating that only active and no inactive rDNA was released by NheI digestion.

We also noticed some subtle differences in psoralen cross-linking that might suggest that chromatin structure changes after damage induction and during repair (Fig. 3). First, while DNA released by NheI from nonirradiated cells showed a heavily cross-linked band typical for active genes (lanes 2), the DNA released from irradiated and repaired cells revealed a broader band reflecting a more heterogeneous population of cross-linked material (lanes 4). This indicates that a fraction of the genes is less accessible to psoralen and might have been partially refolded in nucleosomes. However, it is important to realize that UV irradiation did not result in a complete refolding of nucleosomes on transcribed genes. Thus, the released genes remained in a relatively open conformation. Second, psoralen cross-linking at different repair times indicates that the slow band characteristic for active genes is regenerated to some extent during repair. This is observed for NER and NER with photoreactivation (Fig. 3B, lanes 6 and 8) and for photoreactivation alone (Fig. 3A, lane 6) but not in the absence of repair (Fig. 3A, lane 8). Thus, the psoralen cross-linking data suggest...
that structural transitions occur in chromatin as a consequence of UV irradiation and repair. The structural basis and the mechanism of those transitions will be investigated in more detailed experiments.

Photoreactivation Is the Predominant Pathway of CPD Repair in the Active and Inactive Genes—For analysis of DNA damage and repair, the 4.4-kb NheI fragment of the active rDNA and the longer fragments of the inactive rDNA (>9.1 kb) were purified from preparative gels, and the CPDs were analyzed as described in Fig. 1. Active, active rDNA; Inactive, inactive rDNA; TS, transcribed strand; NTS, nontranscribed strand; PR, photoreactivation; +T4 and −T4, DNA treated with T4 endonuclease V or mock-treated, respectively.

A Strand Bias in Repair of Active Genes Is Consistent with Transcription-coupled NER and an Inhibition of Photolyase by RNAP-I—NER shows preferential repair of the transcribed strand in the active fraction. No strand bias was observed in the inactive fraction (Fig. 6, B and D). This is an indication that RNAP-I promotes repair of CPDs by NER in the transcribed strand, a phenomenon called transcription-coupled repair. On the other hand, photoreactivation is slightly slower in the transcribed strand, and again this strand bias was not measured in the inactive fractions (Fig. 6, A and C). Therefore, RNAP-I blocked at CPDs might inhibit CPD repair by photolyase as it was observed in genes transcribed by RNAP-II and RNAP-III (12, 13). The strand bias of photoreactivation and NER in rDNA was small, but it was reproducibly observed in all three independent experiments. The error bars (Fig. 6) obtained by averaging the individual data points of all independent experiments overlap since the absolute repair values were slightly different in the different UV experiments, but the relative values (e.g. nontranscribed strand versus transcribed strand) were not changed. Summarizing the results of fractionated rDNA (Figs. 4, 5, and 6) and total rDNA (Fig. 1), we conclude that there is a contribution of transcription-coupled repair and an inhibition of photolyase by RNAP-I to DNA repair of rDNA.

Unrestricted Access of Repair Enzymes to the Nucleolus—Having observed efficient repair in the nucleolus, we investigated how nucleolar repair compares with repair of a genomic locus outside of the nucleolus. Fig. 7 shows a comparison of photoreactivation (AMY3) and NER (W303.1) between the rDNA and the GAL10 gene. The GAL10 gene was chosen since it is repressed and folded in nucleosomes when cells are grown in glucose (38). Repair of GAL10 was analyzed by indirect end labeling as described previously (not shown) (13). The data reveal that photoreactivation of rDNA is slightly faster than photoreactivation of GAL10, and there is no dramatic difference in NER. Thus, the yeast nucleolus does not play an inhibitory role with respect to the accessibility of repair proteins.

**DISCUSSION**

Yeast *S. cerevisiae* has two mechanisms to repair UV-induced DNA lesions, photoreactivation and NER (8). Photoreactivation was shown to be more efficient than NER and appeared to be the predominant pathway for CPD repair, while NER is required to remove non-CPD lesions (2, 9, 12, 13). Here we show that photoreactivation is also the predominant pathway for CPD repair in the nucleolus in the active and silenced rRNA genes. The predominance of photoreactivation depends on the light conditions, which probably are saturating in our experiments. At dim light conditions, however, NER might become the predominant pathway.

In yeast, the nucleolus is a morphologically distinct compartment that covers about a third of the nucleus, contains fibrillar centers, a dense fibrillar component, and granular components similar to that of higher eukaryotes, and appears morphologically more compact than the rest of the nucleus (25, 39). We have shown that NER repairs rDNA as efficiently as the inactive GAL10 gene, which is located on chromosome II outside of the nucleolus, and photoreactivation is even faster (Fig. 7). Thus, despite the compartmentalization, the components of both pathways find unrestricted access to nucleolar chromatin. It is interesting to note that CPDs are inefficiently removed by NER in human and hamster cells, but strand breaks in human cells and 6-4PPs, intrastrand adducts, and interstrand cross-links in rodent cells are more efficiently repaired (29, 30, 32, 40–42). Thus, DNA repair in nucleoli appears not to be directly related to nucleolar compartmentalization but rather to the specific properties of damage recognition and processing by the different repair pathways.
Repair is intimately linked to chromatin structure and transcription. Nucleosomes restrict the accessibility of DNA and inhibit NER and photoreactivation, while transcription opens up chromatin, disrupts nucleosomes, and makes DNA more accessible (2, 43). It is therefore conceivable that DNA lesions that block RNA polymerases and thereby inactivate transcription might cause alterations in chromatin structure and consequently inhibit DNA repair. Alternatively, the DNA repair process itself might be coupled to chromatin remodeling activities that alter chromatin as a consequence of repair (2, 4, 44). Thus, it is important to know how ribosomal genes are organized, how transcription affects the chromatin structure, and what consequences DNA lesions might have on the structural organization.

Active rRNA genes are depleted of nucleosomes, while inactive genes are folded in nucleosomes (27, 28, 36). Photolyase is an enzyme that strongly discriminates between nucleosomes and nucleosome-free DNA both in vitro and in yeast and therefore can be used as a tool to test whether DNA is folded in nucleosomes in vivo (9). Here we found that the inactive rDNA was repaired by photolyase as fast as the GAL10 gene, which is packaged in nucleosomes when cells were grown in glucose (38). Thus the photoreactivation data are consistent with a nucleosomal conformation of inactive rRNA genes. Moreover, photoreactivation of the nontranscribed strand of the active rDNA was much faster than nucleosomal DNA (68% CPDs removed in 15 min compared with 45 and 50% in the inactive rDNA and GAL10, respectively). This is direct evidence obtained in live cells that rDNA of inactive genes is in a less accessible, nucleosomal conformation, while the active rRNA genes are in a more accessible, more open, and presumably non-nucleosomal conformation. In addition, the same photoreactivation data demonstrate that the NheI-released rDNA fragments maintained an open state after damage induction and during the time course of repair.

Cells can modulate the proportion of active and inactive rRNA gene copies in response to variations in environmental conditions (27, 45) implying that damage induction somewhere in the genome or in the rDNA could affect rRNA synthesis by varying the number of active gene copies. Psoralen cross-linking in mouse cells showed that the fraction of open (active) rDNA remained constant during repair, and there was no indication for chromatin rearrangements following UV damage formation (30). This is consistent with our observation that photolyase repairs active genes faster than inactive genes (see above). On the other hand, we made two observations that indicate that UV damage formation caused subtle alterations in chromatin accessibility. UV irradiation resulted in a reduction of NheI-released chromatin fragments, and psoralen cross-linking revealed a broad band in the released fraction consistent with a heterogeneous chromatin population. Thus, a fraction of the active rDNA was remodeled and suffered a structural change toward a more compact structure, which affected NheI and psoralen accessibility. However, UV irradia-
RNAP-I and RNAP-II are firmly blocked at CPDs on the tran-
ter removal of the damage (49, 51). The human transcription
complex, shortens the transcript, and allows re-elongation af-

ference. Here we find that photolyase in vivo is only slightly inhibited in the
transcribed strand of active rRNA genes, which is in contrast to the
strong inhibition observed in the GAL10 and URA3 genes transcribed by RNAP-II (9, 13). Apparently photolyase has almost normal access to CPDs in transcribed strands of active rDNA. Different transcription rates are unlikely to explain that
result since both the GAL10 and rDNA genes are heavily transcribed (38, 52). Therefore, the photoreactivation data imply
differential stability of RNAP-I and -II blocked at CPDs. The short persistence of RNAP-I at a lesion might reduce the
recruitment of repair factors and provide an explanation for the
weak strand bias of NER in active RNAP-I genes.

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Repair in Ribosomal Genes
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