During mitosis, transcription is silenced and most transcription factors are displaced from their recognition sequences. By in vivo footprinting analysis, we have confirmed and extended previous studies showing loss of transcription factors from an RNA polymerase II promoter (c-FOS) and, for the first time, an RNA polymerase III promoter (U6) in HeLa cells. Because little was known about nucleosomal organization in mitotic chromosomes, we performed footprinting analysis for nucleosomes on these promoters in interphase and mitotic cells. During interphase, each of the promoters had a positioned nucleosome in the region intervening between proximal promoter elements and distal enhancer elements, but the strong nucleosome positioning disappeared during mitosis. Thus, the nucleosomal organization that appears to facilitate transcription in interphase cells may be lost in mitotic cells, and nucleosome positioning during mitosis does not seem to be a major component of the epigenetic mechanisms to mark genes for rapid reactivation after this phase.

On condensed chromosomes of higher eukaryotic cells during mitosis, transcription by all three nuclear RNA polymerases is silenced (1). Most transcription factors are displaced from their recognition sequences in promoter regions during mitosis (2, 3) although the proteins are still present in the cells, and many of them retain normal DNA binding activities in extracts from mitotic cells. Upon exit from mitosis, previously active genes resume transcription, whereas previously inactive genes remain silent. This “cell memory” suggests that some kind of epigenetic information in chromatin survives mitosis and guides correct reestablishment of transcription complexes in previously active promoters (2, 4). To better understand the structure and roles of mitotic chromatin, we have performed high resolution in vivo footprinting analysis of the promoter regions of the human c-FOS and U6 small nuclear RNA genes during mitosis, especially focusing on nucleosomal organization. We chose these genes because each of them has a nucleosome strongly positioned in the middle of the promoter region (5–7) between proximal promoter elements and distal enhancer elements (Fig. 1), at least during interphase, which seemed to simplify our analysis of mitotic nucleosomal organization. Such nucleosomes have been observed in several genes of higher eukaryotes (8, 9), and it has been suggested that the positioning of these nucleosomes potentiates transcription by locating the cis-acting elements in the adjacent linker regions, where the access of transcription factors to DNA is not prevented and by which the intervening DNA sequences around the histone cores to bring into juxtaposition the widely separated elements and the factors bound to them. In this study, we found that the complex nucleoprotein structures of the c-FOS and U6 promoters were dissociated during mitosis; not only were the transcription factors displaced, but the nucleosome positioning disappeared.

MATERIALS AND METHODS

Cell Culture—The HeLa S3 cell line was provided by the Health Science Research Resources Bank (Osaka, Japan). The cells were grown in Eagle’s minimum essential medium supplemented with 10% fetal bovine serum. Asynchronously growing cells were harvested by trypsinization. We collected mitotic cells by shaking them off the surfaces of the flasks after treatment with 50 ng/ml nocodazole for 16 h (3, 10). For preparation of cells released from mitotic arrest, the mitotic cells collected as described above were allowed to proceed through the cell cycle and to adhere to the surfaces in nocodazole-free medium for 5 h and then were harvested by trypsinization. The mitotic indexes of these cell preparations were determined by microscopy after hypotonic treatment, fixation, and Giemsa staining.

Treatment with Dimethyl Sulfate—DNA extracted from untreated cells (0.3 μg/ml) was treated in vitro with 0.05% dimethyl sulfate (DMS) at 20 °C for 5 min as described previously (11). The cells in suspension were treated with 0.2% DMS in ice-cold phosphate-buffered saline (PBS) for 4 min, collected by centrifugation at 2000 × g for 5 min at 4 °C, washed three times with ice-cold PBS, resuspended in ice-cold Tris-buffered saline (TBS; 25 mM Tris (pH 8.0), 137 mM NaCl, and 2.7 mM KCl), and lysed by addition of an equal volume of 10 mM Tris (pH 8.0), 20 mM EDTA, 1% SDS, and 0.6–1.0 mg/ml protease K. DNA extraction (12) and piperidine cleavage (11) were carried out as described previously.

Irradiation with UV Light—In vitro treatment of DNA with UV light was performed by exposure of 100-μl ice-cold droplets containing 0.1 μg/μl DNA, 10 mM Tris (pH 8.0), and 1 mM EDTA to 1500 J/m² short wavelength UV light from germicidal lamps. The dose rate of UV light was 23–25 J/m²/s. The cells suspended in ice-cold PBS in plastic dishes were irradiated with 1500 J/m² UV light, recovered by centrifugation, resuspended in TBS, and lysed.

Treatment with 4,5; 8-Trimethylpsoralen—Treatment with psoralen plus long wavelength UV light was done essentially as described previously (13). DNA (0.1 μg/μl) was treated in vitro with 2.5 μM psoralen and 20 kJ/m² UV light. The dose rate of UV light was 43–46 J/m²/s. The cells suspended in ice-cold PBS containing 2.5 μM psoralen in plastic dishes were irradiated with 40 kJ/m² UV light, washed twice with PBS, resuspended in TBS, and lysed.

Treatment with DNase I—DNA (0.1 μg/μl) was digested in vitro with 0.1 unit/ml DNase I (Roche Diagnostics, Mannheim, Germany) at 23 °C for 5 min as described previously (7). Treatment of cells with DNase I was performed essentially as described (11). The cells were suspended in ice-cold solution I containing lysolecithin (0.0025% for mitotic cells

1 The abbreviations used are: DMS, dimethyl sulfate; PBS, phosphate-buffered saline; TBS, Tris-buffered saline; LM-PCR, ligation-mediated PCR; TD-PCR, terminal transferase-dependent PCR; pol, RNA polymerase; TBP, TATA-binding protein; CRE, cAMP response element; DR, direct repeat; SRE, serum response element; SRF, serum response factor.

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and 0.01% for asynchronous and released cells), immediately collected by centrifugation at 200 × g for 5 min at 4 °C, and resuspended in solution II containing 3 units/ml DNase I. After incubation at 23 °C for 3 min, they were lysed by the addition of 4 volumes of 10 mM Tris (pH 8.0), 12.5 mM EDTA, 150 mM NaCl, 0.625% SDS, and 0.375 mg/ml proteinase K.

Analysis by Ligation-mediated PCR (LM-PCR) and Terminal Transferase-dependent PCR (TTD-PCR) — LM-PCR and TTD-PCR were carried out by use of the Expand Long Template PCR System (Roche) in the PCR step as described previously (13). DMS-treated DNA (1 μg/sample) and UV light-irradiated DNA (2 μg/sample) were subjected to LM-PCR after piperidine cleavage, whereas DNase I-digested DNA (1 μg/sample) was directly subjected to LM-PCR. Psoralen-treated DNA (2 μg/sample) was subjected to TTD-PCR following restriction digestion (PvuII for c-FOS analysis, SacI for U6 analysis, and PstI for c-MYC analysis) and alkaline reversal. Two sets of primers specific for the promoters (PvuII for c-FOS analysis, SacI for U6 analysis, and PstI for c-MYC analysis) and denoted by a question mark. DNA-protein interactions and protein-protein interactions (34, 35) are illustrated in a very simplified manner. Proteins are represented by gray ovals, circles, and rounded rectangles, whose shape and size are arbitrary. CBP, CRE-binding protein-binding protein. The proteins bound to the DR and to the uncharacterized site have not been identified. Thin arrows indicate the primers used for LM-PCR and TTD-PCR. Because of the space limitation, upstream primers are drawn on the other side of the DNA.

RESULTS AND DISCUSSION

Displacement of Transcription Factors from Recognition Sequences during Mitosis—Using four footprinting agents, DMS, UV light, 4,5’-8-trimethylpsoralen, and DNase I, we analyzed the local chromatin structure of the c-FOS and U6 promoters in three populations of HeLa cells: “asynchronous cells” (mainly interphase, mitotic index = 4%), “mitotic cells” (incubated with nocodazole and collected by shake-off, mitotic index = 98%), and “released cells” (incubated for 5 h after the release from mitotic arrest, mitotic index = 3%). The cells were treated with one of the footprinting agents, and then the genomic DNA was extracted and subjected to LM-PCR or TTD-PCR. As a control, naked DNA was treated in vitro with the agent. We discerned footprints by comparing the resultant pattern of in vitro formation of DNA damage along a specific sequence with the pattern of in vivo formation. The results of the analysis of the proximal and distal regions of the c-FOS promoter are shown in Figs. 2 and 3, respectively. Those of the U6 promoter are shown in Figs. 4 and 5.

DMS is the most commonly used agent for the detection of the sequence-specific binding of transcription factors (11), although it is insensitive to histone-DNA interactions. Treatment of asynchronous cells with this agent produced footprints (usually the sites of G residues protected from alkylolation but sometimes the sites of hyper-reactive G residues) at or near various cis-acting elements in these promoters (Figs. 2–5, the upper parts of lanes 3 and 4). For example, clear protection was found at the cAMP response element (CRE) and at the direct repeat (DR) in the promoter of the c-FOS gene (Fig. 2), which is transcribed by RNA polymerase II (pol II), and at the proximal sequence element in the promoter of the U6 gene (Fig. 4), which is transcribed by pol III. We observed that in contrast to asynchronous cells, mitotic cells had no DMS footprints in these promoters (Figs. 2–5, lanes 5 and 6). The displacement of transcription factors from their recognition sequences during mitosis had been reported previously for three human pol II promoters (2, 3, 14). We confirmed this phenomenon in another pol II promoter and, for the first time, in a pol III promoter. In the cells released from mitotic arrest, the footprints reappeared (lanes 7 and 8).

Transcription factors can modulate the induction of (6-4) photoproducts as well as cyclobutane dimers by UV light at the sites of dipyrimidines (15). Piperidine cleavage of UV light-irradiated DNA enables the detection of (6-4) photoproducts by LM-PCR. In most parts of the c-FOS and U6 promoters in UV light-irradiated asynchronous cells, the modulation of (6-4) photoproduct induction was rather weak (Figs. 2–5, lanes 11 and 12). The strongest enhancement was seen at the 5’-TTTT sequence at position −25 to −28 on the lower strand of the c-FOS promoter (Fig. 2). These nucleotides are in the TATA box (5’-TATAAAAG on the upper strand). The unusual formation of (6-4) photoproducts at the 5’-TT dinucleotides in vivo should be due to the severe bending of DNA caused by the interaction of TATA-binding protein (TBP) with the TATA box (12, 15, 16). Previous cytochemical and immunological studies have revealed that during mitosis at least a fraction of TBP remains associated with condensed chromosomes, especially with previously active genes on them, in contrast to most of the other sequence-specific transcription factors (10, 17, 18). Based on these observations, it has been proposed that TBP (or TFIIID) marks the genes that should be reactivated after mitosis. Therefore, we expected the persistence of the UV light footprint
at the TATA box during mitosis. Contrary to our expectation, mitotic cells failed to show the footprint at the TATA box of the c-FOS promoter (Fig. 2, lanes 13 and 14), suggesting the loss of the DNA bending and hence the loss of the direct binding of TBP to the TATA box. In addition to the c-FOS promoter, another pol II promoter exhibited the disappearance of the UV light footprint at the TATA box during mitosis; as shown in Fig. 6, enhancement of (6-4) photoproduct induction at the 5'-TTTTT sequence at position -23 to -26 on the lower strand of the P2 promoter of the c-MYC gene was observed in asynchronous cells but not in mitotic cells. These results do not support the idea that the direct binding of TBP to the TATA boxes is maintained during mitosis. We speculate that the association of TBP with DNA in mitotic chromatin may be indirect; TBP should be in a large complex, and some members of the complex may remain associated with DNA or structural proteins of chromosomes even during mitosis. For example, some of TBP-associated factors (TAF) can form a histone octamer-like structure that interacts with DNA, and TAFII250 has bromodomains that may recognize acetylated histone (19). The situation may be similar to that of TATA-less promoters. In fact, it has been reported that TBP remains associated with a TATA-less gene (ets-2) as well as genes with TATA boxes during mitosis (10). As to the U6 promoter, we could not analyze the occupancy of its TATA box by using the UV light footprinting assay (Fig. 4, lanes 9–16), because this TATA box (5'-TATATAT at position -29 to -23) did not contain dipyrimidines, the targets of UV light. Thus, the protein binding status of the TATA box of this pol III-transcribed gene is formally unknown, although DNase I footprinting (Fig. 4, lanes 25–32) revealed that a large footprint (at nucleotides -71 to -20) over the proximal sequence element and the TATA box disappeared during mitosis, implying the dissociation of a large protein complex from this region.

We presume that the association of some other sequence-specific transcription factors with DNA in mitotic chromatin may also be indirect. Immunocytochemical studies, which have limited resolution, have revealed a few exceptional transcription factors that remain associated with chromosomes during

![Figure 2. In vivo footprinting analysis of the lower strand of the proximal region of the c-FOS promoter.](image)

![Figure 3. In vivo footprinting analysis of the upper strand of the distal region of the c-FOS promoter.](image)
mitosis (3, 20). For example, serum response factor (SRF) has been found to be retained on mitotic chromosomes, but our analysis of the c-FOS promoter showed that the DMS footprint at the serum response element (SRE), which is recognized by SRF, did not persist during mitosis (indicated by the asterisk in Fig. 3). This might be due to the interactions of SRF with other DNA-binding proteins such as high mobility group proteins (21, 22). The transcription factors that remain associated with chromatin during mitosis, such as TBP and SRF, are potential candidates for epigenetic marks of gene activity (4, 10, 18), but our results mentioned above suggest that even these proteins may lose direct contact with their target DNA sequences.

Disappearance of Nucleosome Positioning during Mitosis—

4,5'-Trimethylpsoralen is an agent suitable for mapping translational positions of nucleosomes (23), because formation of DNA interstrand cross-links by this agent is inhibited by histone octamers as well as transcription factors. Our high resolution method for detecting psoralen cross-links (7, 13) clearly showed large areas of protection from cross-linking, which corresponded to the positioned nucleosomes in the c-FOS and U6 promoters in asynchronous cells (Figs. 2–5, the lower parts of lanes 19 and 20). We should point out the difficulty in determining nucleosome boundaries with single-nucleotide resolution caused by the strong sequence specificity of psoralen and the possibility that the nucleosome may have a set of overlapping positions rather than a single fixed position in each promoter (24). Nevertheless, psoralen footprinting revealed that the nucleosome positioning in these promoters was quite strong. For example, the reduction of the signal at the 5'-TA sequence at nucleotides −177 and −178 in the c-FOS promoter (indicated by the asterisk in Fig. 2) in asynchronous cells was more than 10-fold as compared with naked DNA, and the probability that this sequence was in the linker region appeared very low in this cell population. In contrast to asynchronous cells, mitotic cells did not have the large footprints; the distribution patterns of psoralen cross-links in mitotic cells (Figs. 2–5, lanes 21 and 22) were similar to those of naked DNA (lanes 17 and 18). Because it has been demonstrated that core histones remain associated with mitotic chromosomes (3, 18), we suppose that our result indicates the disappearance of nucleosome positioning, i.e. the random or near random distribution of nucleosomes in these promoters during mitosis, although the possibility of the detachment or modification of the positioned nucleosomes is not formally excluded. In the case of the U6 promoter, we noticed a slight difference between the pattern of cross-linking in mitotic cells and that of naked DNA (Fig. 4); the region around the transcription start site was somewhat more reactive in mitotic cells than in naked DNA, suggesting that there might remain some kind of irregularity during mitosis.

DNase I treatment of asynchronous cells produced a cleavage pattern with a periodicity of −10 nucleotides in the region of the positioned nucleosome in the c-FOS promoter (Figs. 2 and 3, lanes 27 and 28). Because DNase I attacks nucleosomal DNA preferentially at the sites furthest from the surface of the histone octamer, the periodicity suggests that the DNA helix of ...
this region assumed highly preferred rotational orientation on the histone surface within the population of cells (25, 26). Mitotic cells did not show clear periodicity (lanes 29 and 30), and the cleavage patterns were similar to those of naked DNA (lanes 25 and 26). Thus, not only the translational positioning but the rotational phasing of the nucleosome in the c-FOS promoter seemed to disappear during mitosis. We also noticed similar periodicity in the U6 promoter of asynchronous cells (Figs. 4 and 5), but the cleavage patterns were somewhat irregular, and in addition, resembled those of naked DNA, making the interpretation of rotational orientation in this promoter ambiguous.

The footprinting data described above can be summarized as in Fig. 7. Most aspects of the nucleoprotein complexes in the c-FOS and U6 promoters were lost during mitosis; all of the sequence-specific binding of transcription factors that was detectable in interphase cells was not found in mitotic cells. The nucleosome positioning that appeared to facilitate the communication between proximal promoter elements and distal enhancer elements through looping out of the intervening DNA in interphase cells was not observed during mitosis. The association of the unique organization with mitotic chromatin, where transcription is repressed, argues that the disappearance of nucleosome positioning, as well as the displacement of transcription factors, may be among the various mechanisms contributory to the repression (1), at least of these genes.

We presume that the disappearance of nucleosome positioning and the displacement of transcription factors may also contribute to the formation of highly condensed mitotic chromosomes of higher eukaryotes. A possibility has been pointed out that uniformity of internucleosomal distances, which is brought about by adjustment or sliding of nucleosomes, may improve the folding of chromatin into higher order structures (27). The absence of large transcription complexes might also improve the regular stacking of nucleosomes in higher order structures. Because positioned nucleosomes are observed usually in the vicinity of regulatory sequences, it will be important to determine whether the disappearance of nucleosome positioning during mitosis is unique to the c-FOS and U6 genes or occurs in many genes. As far as we are aware, nucleosome positioning in mitotic cells has not been analyzed except for our study, but low resolution DNase I analysis of a few genes during mitosis has been performed: in the human heat shock protein 70 gene, DNase I-hypersensitive sites appear to be retained on mitotic chromosomes, leading to a speculation that the chromatin organization of the promoter is maintained during mitosis (3). In the chicken glyceraldehyde-3-phosphate dehydrogenase gene, however, the locations of some of the hypersensitive sites seem to differ between interphase and mitotic chromatin (28). Our results do not appear to be consistent with the preservation of the local chromatin organization during mitosis. These discrepancies remain to be resolved.

The concurrence of the disappearance of nucleosome positioning and the displacement of transcription factors suggests a possibility of a causal relationship between the two phenomena. Assuming that there are similar levels of DNA-histone interactions during interphase and during mitosis, our results seem to imply that the transcription factors bound to the cis-acting elements can function very effectively as boundaries restricting the location of nucleosomes, supporting the notion that in vivo nucleosome positions are determined predominantly by transcription factors (25, 26, 29). However, we feel that this assumption may require validation, because it has been reported that the human SNF/SWI complexes are inactivated, degraded, or excluded from chromatin during mitosis (30, 31). In this case, the loss of the chromatin remodeling activity probably leads to the loss of the ability to activate target genes by modifying the local nucleosomal organization. It will be interesting to see whether other chromatin remodeling complexes are active in mitotic chromatin and increase the

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**FIG. 6. In vivo UV light footprinting analysis of the lower strand of the TATA box of the c-MYC P2 promoter.** The sequence of this TATA box is 5'-TATAAAAG (from -29 to -22, on the upper strand). The positions of the 5'-TT dinucleotides on the lower strand of the TATA box are indicated on the right of the autoradiogram. Other denotations are similar to those in Fig. 2.

**FIG. 7. Schematic summary of the changes in the chromatin structure of the c-FOS and U6 promoters during mitosis inferred from in vivo footprinting data.** In this illustration, only the c-FOS promoter is drawn, but both promoters show similar changes. During mitosis all transcription factors appear to be displaced from their recognition sequences, although some of them might retain indirect association with chromatin, as suggested by previous cytochemical and immunological studies. Strong nucleosome positioning is observed in interphase cells but not in mitotic cells.
mobility of nucleosomes and the fluidity of chromatin when
chromatin is being remodeled into condensed chromosomes.

Cells should inherit their characteristic patterns of gene
expression and silencing through successive cycles of cell divi-
sion. In mitotic cells, we observed the loss of all of the detect-
able sequence-specific binding of transcription factors in the
c-FOS and U6 promoters, confirming previous reports on the
phosphoglycerate kinase 1, heat shock protein 70, and U2
genes (2, 3, 14). The dissociation of transcription complexes
during mitosis and their reassembly after this phase in previ-
ously active genes suggest that the reassembly is directed by
the information that somehow survives mitosis. Various mech-
isms of the transfer of epigenetic information through
nucleosomes does not seem to be a major component of the
at least in the c-FOS and U6 promoters, the physical location of
from the recognition sequences of transcription factors. Thus,
we observed the loss of nucleosome positioning during mitosis,
not been detected yet, especially the indirect binding. However,
does not exclude the possibility of the protein binding that has
factors from mitotic chromosomes in this and previous studies
mitosis (4, 10). The absence of the footprints of transcription
complexes and the reassembly of the transcription complex after
during mitosis (4, 10). The absence of the footprints of transcription
facilitate the reoccupancy of the sites by the transcription fac-
tors and the reassembly of the transcription complex after
mitosis (4, 10). The absence of the footprints of transcription factors in mitotic chromosomes in this and previous studies
does not exclude the possibility of the protein binding that has
not been detected yet, especially the indirect binding. However,
we observed the loss of nucleosome positioning during mitosis,
and this is not consistent with the exclusion of nucleosomes from
the recognition sequences of transcription factors. Thus, at least in the c-FOS and U6 promoters, the physical location of
nucleosomes does not seem to be a major component of the
mechanisms of the transfer of epigenetic information through
mitosis.

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