Intracellular reduction of carcinogenic Cr(VI) leads to the extensive formation of Cr(III)-DNA phosphate adducts. Repair mechanisms for chromium and other DNA phosphate-based adducts are currently unknown in human cells. We found that nucleotide excision repair (NER)-proficient human cells rapidly removed chromium-DNA adducts, with an average t_{1/2} of 7.1 h, whereas NER-deficient XP-A, XP-C, and XP-F cells were severely compromised in their ability to repair chromium-DNA lesions. Activation of NER in Cr(VI)-treated human fibroblasts or lung epithelial H460 cells was manifested by XPC-dependent binding of the XPA protein to the nuclear matrix, which was also observed in UV light-treated (but not oxidant-stressed) cells. Intracellular replication of chromium-modified plasmids demonstrated increased mutagenicity of binary Cr(III)-DNA and ternary cysteine-Cr(III)-DNA adducts in cells with inactive NER. NER deficiency created by the loss of XPA in fibroblasts or by knockdown of this protein by stable transfection experiments with protein preparations from human cells have identified six core factors that are required for recognition and excision of bulky DNA modifications: XPA protein, XPC HR23B complex, replication protein A heterotrimer, multisubunit transcription factor II complex, and two structure-specific nucleases, XPG and XPF-ERCC1 (3). NER consists of two subpathways that specialize in the removal of DNA lesions from either the entire genome (global NER) or the transcribed strands (transcription-coupled NER) (2). The difference in these two subpathways lies in the mechanisms of lesion detection. The initial damage recognition in global NER is usually performed by the XPC-HR23B complex (4, 5), which may require additional factors for sensing DNA modifications that cause relatively minor duplex distortions. For example, efficient global repair of cyclobutane pyrimidine dimers (CPDs) and recruitment of XPC are dependent on the presence of the UV-DDB (UV-damaged DNA-binding factor) protein complex (6, 7). In transcription-coupled NER, DNA lesions are detected by stalling of RNA polymerase II, followed by the recruitment of the NER core machinery with the help of three additional proteins, CSA, CSB, and XAB2 (2, 8).

The most common substrates for NER are bulky base lesions causing a major disruption of hydrogen bonding (2). Smaller chemical modifications of DNA bases formed by oxidative damage and alkylating agents are usually repaired by the base excision repair process (2, 9). Although major caretakers of DNA bases are now known, the nature of human repair processes involved in preserving the integrity of the DNA phosphate backbone is not well understood. The DNA phosphate group is a frequent site of adduct formation by chemical carcinogens and chemotherapeutic drugs (10–12). Alkylation of DNA phosphates generates alkylphosphotriesters that, in *Escherichia coli*, are repaired via a non-NER process involving the Ada protein (13). Ada homologs have not been found in human cells (1, 9), raising the question of whether DNA phosphate adducts could be substrates for NER, which has not yet been clearly addressed. Protein extracts from hamster cells have been found to excise only very small amounts of methylnitroester-containing oligonucleotides (14), but this result could have reflected the inefficiency of the *in vitro* NER. However, persistence of DNA alkylphosphotriesters in human fibroblasts was reported to be independent of the NER status (15), although the employed analytical methodology was not very specific.

In this work, we examined the role of cellular NER in the removal of DNA phosphate modifications by determining the intracellular persistence and biological activity of chromium-DNA adducts in human cells with normal and deficient NER. Various Cr(III)-DNA adducts are formed after intracellular uptake and reduction of Cr(VI), which is a recognized human carcinogen causing major environmental concerns and signifi-
cant exposure in several dozens of occupations (16). The main forms of chromium-DNA adducts in mammalian cells are ternary complexes generated by cross-linking of cysteine and histidine to DNA via a phosphate-bound Cr(III) atom (17, 18). All forms of chromium-DNA adducts in mammalian cells are терминальные and propagate for 48 h. Replicated progeny of the plasmids was isolated and electroporated into the E. coli MBL50 strain, and the yield of bacterial transformants and supF mutants was scored on ampicillin- and ampicillin/ara-containing plates, respectively.

Cytotoxicity—For analysis of clonogenic survival, 500–1000 cells were seeded onto 100-mm dishes and treated with Cr(VI) or cisplatin for 3 h or with H2O2 for 1 h, and colonies were counted after 12–16 days. Short-term toxicity was determined by trypan blue staining. A caspase-cleaved poly-(AD-ribose) polymerase fragment was detected by Western blotting using anti-85 kDa poly(ADP-ribose) polymerase antibody (Cell Signaling), and protein extracts were obtained by lysis of cells in buffer containing 50 mM Tris (pH 8.0), 250 mM NaCl, 1% Nonidet P-40, 0.1% SDS, 5 mM EDTA, 2 mM Na3VO4, 10 mM Na2O4, 10 mM NaF, and protease inhibitors. Intact lamin A and cleaved lamin A were detected in whole cell lysates obtained by boiling cells in SDS-PAGE loading buffer.

Knockdown of XPA Expression in H460 Cells—Stable down-regulation of XPA expression in lung epithelial H460 cells was achieved by infection with a pRETRO-XPA retroviral vector encoding a hairpin-forming small interfering RNA (siRNA). This vector was constructed by digestion of pRETRO-SUPER with HindIII and BglII, followed by ligation with a 5′-gatgccccGCTACTGGAAGCCATGCTAtcctaagagaTACA-GCCATGCCTCAGTATccttttggaaa-3′/5′-aggttcctaaanaGCTACTG-GAGGCGATGCCTGAtccttttggaaa-3′ double-stranded oligonucleotide. The nucleotides directed to XPA are indicated in uppercase letters. Viral particles were packaged in 293T cells by cotransfection with plasmids encoding vesicular stomatitis virus G envelope protein and Moloney murine leukemia virus capsid protein and reverse transcriptase. H460 cells were infected twice at 24-h intervals and selected in the presence of 1.5 μg/ml puromycin for 48 h. The efficiency of XPA down-regulation was determined by Western blotting of protein extracts obtained as described for poly-(AD-ribose) polymerase analysis.

RESULTS

Repair of Chromium-DNA Adducts in NER− and NER+ Human Cells—The role of NER in the removal of chromium-DNA adducts was first examined by determining the rate of repair of chromium adducts from chromosomal DNA in NER-competent cells and those deficient in one of the essential NER proteins. Chromium-DNA adducts were formed by treatment of SV40-immortalized human fibroblasts with 5 μM Cr(VI) for 3 h, a dose that did not induce any detectable toxicity or cell cycle changes over a 36-h post-exposure interval as determined by fluorescence-activated cell sorter analysis (G1 phase, 52.4% versus 49.6% for control and chromium-treated XPA− cells, respectively; S phase, 25.6% versus 26.2%; and G2/M phase, 19.8% versus 20.6%). The first DNA samples were collected 3 h after the treatment to ensure that both Cr(VI) metabolism and Cr(III)-DNA adduct were complete. Fig. 1A shows that the loss of chromium-DNA adducts from XPA− cells was much faster relative to XP-A cells and that it followed single-component log-linear kinetics during the first 24 h. At 36 h post-exposure, XP-A cells retained 15.5 times more chromium-DNA adducts than the isogenic XPA+ counterpart. XP-A cells displayed no decrease in the amount of DNA-bound chromium during the first 9 h, whereas XPA− cells lost 70% of the chromium adducts over this time. The initial levels of chromium-DNA adducts in XP-A/AXPA− cells were essentially identical and were similar to those in WT/SV cells expressing the endogenous XPA gene (20, 22, and 20 chromium adducts/104 DNA phosphates, respectively). To further verify the importance of NER in the removal of chromium-DNA damage, we measured the rate of repair of chromium adducts in NER− WT/SV fibroblasts and two NER− cell lines that are deficient in other NER proteins, XPC and XPF (Fig. 1, B and C). XP-C and XP-F fibroblasts also exhibited a very slow removal of chromium-DNA adducts, which was comparable with XP-A cells. The average half-life of chromium-DNA adducts in three SV40-transformed NER− cells was 43.9 h versus 6.7 h in two NER+ cells (6.5-fold difference). NER of chromium-DNA damage did not appear to be affected by SV40 immortalization, as primary IMR90 fibroblasts had a similar rate of repair, with t1/2 = 8.2 h (Fig. 1C). The residual loss of DNA-bound chromium in XP cells was probably caused by slow ligand exchange reactions with intracellular inorganic phosphate (20).
Nuclear Dynamics of the XPA Protein in UV Light- and Cr(VI)-treated Cells—Recent studies using localized UV irradiation of cellular nuclei have found that the XPA protein becomes immobilized at the sites of DNA damage (23, 24). In the absence of DNA damage, the majority of XPA rapidly moves throughout the nucleus, indicating the absence of its association with nuclear structures. Because NER is the only known function of XPA, stable binding of this protein to nuclear DNA could be used as the indicator of DNA lesions processed by NER in vivo. Unlike UV irradiation, DNA damage by chemical agents could not be directed to a particular nuclear location, which requires a different strategy for the detection of immobilized XPA-NER complexes. We reasoned that the presence of immobilized XPA-NER complexes could become evident by washing out nucleoplasmic XPA with detergent extractions. We studied binding of XPA to nuclear structures using a mild low salt fractionation procedure, which preserves nuclear morphology and yields a well developed interior nuclear matrix (25). Potential precipitation and aggregation artifacts were further minimized by performing this procedure in situ. To validate our approach, we first examined the nuclear distribution of the XPA protein in UV light-treated WT/SV cells (Fig. 2A). As expected, UV light-treated (but not control) cells exhibited a strong nuclear association of XPA. Interestingly, even after the complete in situ digestion of chromatin DNA with DNase I (evidenced by the lack of 4′,6-diamidino-2-phenylindole signal), anti-XPA staining remained similar to that in permeabilized nuclei, indicating that the majority of immobilized XPA protein was bound to the nuclear matrix of UV light-damaged cells. Immobilization of XPA protein at the sites of UV light-damaged DNA was previously found to be XPC-dependent (24). Similarly, we found that the stable association of XPA with permeabilized nuclei and the nuclear matrix of UV light-treated cells required the presence of functional XPC protein (Fig. 2B). Thus, these experiments showed that our in situ fractionation procedure was capable of detecting the presence of damaged DNA-bound XPA-NER complexes.

Immunostaining of Cr(VI)-exposed WT/SV fibroblasts also revealed a strong nuclear retention of the XPA protein and its recruitment to the nuclear matrix (Fig. 2A). Control experiments revealed no increase in binding of secondary antibodies to nuclei of Cr(VI)-treated cells (data not shown). Time course studies showed that nuclear binding of the XPA protein was significantly decreased after 18 h and was no longer detectable after 24 h (data not shown), at which point cells removed ~95% of the chromium-DNA adducts (Fig. 1B). Unlike NER-proficient cells, treatment of XP-C fibroblasts with 5 μM Cr(VI) did not cause any increase in XPA binding to the nuclear structures at 3 h post-exposure (Fig. 2B). This result was not caused by the inefficient formation of chromium-DNA damage in XP-C cells, as they and WT/SV fibroblasts had very similar initial levels of chromium-DNA adducts (19 and 20 chromium adducts/10^4 DNA phosphates, respectively). XPA association with nuclei of XP-C cells was also absent at longer post-exposure times and up to five times higher concentrations of Cr(VI) (data...
not shown), indicating an absolute requirement of functional XPC protein for the assembly of XPA-containing NER complexes at chromium-damaged DNA. To test whether oxidative DNA damage can also stimulate tight nuclear binding of XPA, we immunostained WT/SV cells treated with a toxic dose of H2O2 (50 μM, 1% clonogenic survival) (Fig. 2C). There was no detectable increase in stable XPA complexes in these cells, indicating that accumulation of XPA in the nuclear matrix of cells treated with mildly toxic doses of Cr(VI) was not a result of processing of oxidative DNA lesions. Tight nuclear binding of XPA was also absent in cells exposed to lower concentrations of H2O2 (10 and 25 μM) (data not shown).

Replication of Chromium-modified Plasmids in XPA− and XPA+ Cells—The role of NER in repair of individual chromium-DNA adducts was examined by replicating chromium-modified pSP189 plasmids in XPA− and XPA+ fibroblasts. Propagation of Cr(III)-adducted plasmids in XPA− cells produced on average a three times higher number of the supF mutants relative to XPA+ cells (Fig. 3A). XPA deficiency only modestly decreased the yield of replicated progeny of Cr(III)-modified plasmids, indicating that the major genotoxic lesions are probably not substrates for NER. Reaction of Cr(III) with DNA generates monofunctional Cr(III)-DNA adducts, a fraction of which undergo further rearrangements to produce DNA interstrand cross-links (26). DNA cross-links are potent polymerase-blocking lesions (26, 27) and repaired by XPA-independent processes (28, 29). Exposure of mammalian cells to Cr(VI) generates cysteine-Cr(III)-DNA cross-links. Shown are means ± S.D. from four to six independent experiments. Exposing mammalian cells to Cr(VI) generates cysteine-Cr(III)-DNA cross-links. Shown are means ± S.D. from four to six independent experiments.

Effect of NER Status on Toxicity of Cr(VI) in Human Fibroblasts—To examine the biological significance of chromium-DNA adducts and NER in Cr(VI) injury, we studied cytotoxic responses in XPA− and XPA+ fibroblasts (Fig. 4). XPA+ cells showed a much higher short-term toxicity and greatly enhanced apoptotic cleavage of poly(ADP-ribose) polymerase and lamin A, respectively; D and E, clonogenic survival of XPA− and XPA+ fibroblasts treated with Cr(VI) or cisplatin (cisPt), respectively. Shown are means ± S.D. (n = 3–6).

Because the lung is the main target of toxic and carcinogenic effects of Cr(VI), we also examined the role of NER in response to chromium-DNA damage in human lung epithelial H460 cells. As with fibroblasts, exposure of H460 cells to Cr(VI) stimulated tight binding of XPA to the nuclear structures, which persisted after digestion of chromosomal DNA by DNase I (Fig. 5A). The importance of NER and chromium-DNA adducts in cytotoxic responses of these cells was investigated by down-regulating XPA levels through stable expression of targeting siRNA (Fig. 5B). The siRNA-expressing cells showed a 70% decrease in the XPA amount relative to the parental or vector-transfected cells, and this significantly inhibited their ability to repair major Cr(VI)-induced DNA adduct.
NER capacity by increasing the half-life of chromium-DNA adducts by 3.0-fold, from 7.1 to 21.6 h (Fig. 5C). Down-regulation of XPA levels by siRNA did not change the initial levels of chromium-DNA modifications (at 1 μM chromium, 10.7 and 9.4 chromium adducts/10^4 DNA phosphates for XPA knockdown and control cells, respectively; and at 5 μM chromium, 59.9 and 64.9 chromium adducts/10^4 DNA phosphates). The difference in survival between vector- and siRNA-transfected H460 cells was somewhat smaller than that observed between XPA and XPA+/fibroblasts, which could be attributed to the remaining activity of NER in siRNA-expressing H460 cells. Unlike Cr(III)-induced damage, vector- and siRNA-transfected H460 cells exhibited similar clonogenic survival after exposure to H_2O_2 (~0.8 and ~0.82 slopes, respectively). Thus, a protective role of NER against Cr(VI) toxicity is common to cells of different histological origin and reflects the importance of this repair process in the removal of chromium-DNA monoadducts.

**DISCUSSION**

Time course analyses of chromium-DNA adducts in normal and XP fibroblasts from three complementation groups clearly showed that NER status is the main determining factor in the intracellular persistence of these lesions. Increased mutagenicity of two chromium-DNA adducts in NER− cells and a longer half-life of chromium-DNA modifications in lung epithelial H460 cells with down-regulated expression of the XPA protein further confirmed the importance of human NER in the removal of chromium-DNA damage. Human NER was quite efficient in the detection and removal of chromium-DNA adducts, as indicated by a short half-life of these lesions, averaging 7.1 h for four NER− human cell lines. For comparison, (6-4) photoproducts, which are considered to be the best natural NER substrate, have a half-life of ~2 h in mammalian cells (32, 33). CPDs, another major UV light-induced DNA lesion, are removed by NER at a much slower rate, with t_1/2 = 17 h (33). The rate of NER of bulky benz[a]pyrene-7,8-dihydriodiol 9,10-epoxide-DNA adducts was found to be dependent on the amount of the initial damage, with the half-life varying from 4 to ~24 h for a low and high number of adducts, respectively (34). Thus, based on the half-life comparison with other lesions, chromium-DNA adducts appear to be a good substrate for cellular NER. Another measure of susceptibility to repair is the rate of lesion removal per unit of time. Using the reported 50% repair values and the initial amount of damage (34), we calculated that the maximal rate of NER of benz[a]pyrene-7,8-dihydriodiol 9,10-epoxide-DNA adducts was ~500 lesions/min/diploid cell. The same type of calculations showed that (6-4) photoproducts formed at NER-saturating UVC doses (32, 33) were removed at a rate of ~13,000/min/cell. Our data for chromium-DNA adducts yielded remarkably rapid NER rates of 49,000 and 51,000 chromium lesions/min/cell for SV40-immortalized and primary IMR90 fibroblasts, respectively. This high absolute repair rate reflected processing of a very high number of adducts initially formed in the cells (20–25 chromium adducts/10^4 DNA phosphates). The calculated rates of repair are certainly biologically plausible considering that a human cell contains on the order of 10^9 molecules of each core NER factor (35). Our results do not mean that chromium-DNA adducts are recognized and removed by NER more efficiently than (6-4) photoproducts. The most abundant forms of UVC light-induced DNA damage are slowly repaired CPDs (2, 32, 33), which probably sequeser many NER factors and thereby decrease the actual number of repair complexes available for the removal of (6-4) photoproducts.

The NER substrate has been defined as a DNA lesion formed by chemical modification of the DNA structure that causes a significant disruption of base pairing (36, 37). DNA duplex distortion alone is not sufficient to activate the NER process, as DNA mismatches of various sizes are resistant to repair by NER. However, the presence of DNA duplex distortions in the vicinity of a DNA modification is required for NER because non-distorting C-4' deoxyribose substitutions are repaired by human NER only in combination with disrupted base pairing (36). In the case of UV light-induced lesions, there is a very good concordance between the susceptibility to NER and the extent of DNA distortion by the lesion: a slowly repaired CPD induces a minor kink of 9°, whereas rapidly repaired (6-4) photoproducts bend DNA by 44° (38). Consequently, easy repairability of bulky DNA adducts has been commonly attributed to their induction of major distortions in the DNA structure. DNA phosphate adducts do not generate major helix distortions, although the presence of structural changes is clearly detectable. As a consequence of charge neutralization, one phosphate adduct bends DNA by 3.5° (39) and unwinds the duplex by ~2° (40). Clonogenic survival of XP-A fibroblasts containing one unrepairable chromium adduct/500 DNA phosphates was only modestly decreased (Fig. 3, 5 μM chromium dose), providing biological evidence that chromium-phosphate adducts do not induce major structural changes, as they were well tolerated by human cells. Our findings on a rapid repair of chromium-DNA phosphate adducts indicate that the bulkiness by itself could be a very important determinant of a good NER substrate, perhaps because lesion verification is a rate-limiting step in NER and the presence of large chemical modifications is easy to detect. Unlike weakly distorting CPDs, whose removal by NER requires p53-dependent expression of the p48 subunit of the UV-DDB complex (2, 6), NER of chromium-DNA adducts does not appear to be p53-dependent, as SV40-immortalized cells with functionally inactivated p53 and primary IMR90 fibroblasts repaired chromium adducts with essentially identical rates. This result is consistent with the idea that weakly distorting, but bulky modifications can be efficiently detected and processed by the core NER machinery. Cr(III) forms hexacoordinate complexes arranged in an octahedral configu-
Unlike linear alkyl groups, cannot be positioned in either of the DNA grooves. Even on the basis of the molecular weight ($M_r = 207$ for the cysteine-chromium cross-link), chromium-DNA adducts are $\sim 10$ times larger than the corresponding methyl- or ethylphosphotriesters, and this may largely account for the much better reactivity of chromium lesions relative to alkylphosphate adducts (14, 15).

Biochemical fractionation studies of UV light-irradiated cells have previously detected nuclear retention of a portion of total XPA after nuclease digestions (40, 41). This was not interpreted as evidence of nuclear matrix binding because of a different operational designation of this nuclear component, which was defined as nuclear material remaining after nuclease digestion and extraction with 2 M NaCl. The interior nuclear matrix obtained by 2 M NaCl extractions consists of a network of thin core filaments supported by nuclear RNA, whereas the low salt procedure (as employed here) yields a better preserved nuclear morphology and a more developed interior matrix containing thick polymorphic fibers (25). This suggests that XPA complexes participating in global NER are probably bound to the polymorphic fibers of the interior nuclear matrix, whereas components of transcription-coupled repair, such as CSA (42), associate with the RNA-rich core filaments.

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Repair of Chromium-DNA Adducts
Human Nucleotide Excision Repair Efficiently Removes Chromium-DNA Phosphate Adducts and Protects Cells against Chromate Toxicity
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