Fanconi anemia (FA) is an autosomal recessive disorder characterized by diverse developmental abnormalities, progressive bone marrow failure, and a markedly increased incidence of malignancy. FA cells are hypersensitive to DNA cross-linking agents, suggesting a general defect in the repair of DNA cross-links. Some forms of hexavalent chromium [Cr(VI)] are implicated as respiratory carcinogens and induce several types of DNA lesions, including ternary DNA–Cr–DNA interstrand cross-links (Cr–DCC). We hypothesized that human FA complementation group A (FA-A) cells would be hypersensitive to Cr(VI) and Cr(VI)-induced apoptosis. Using phosphatidylserine translocation and caspase-3 activation, human FA-A fibroblasts were found to be markedly hypersensitive to chromium-induced apoptosis compared with CRL-1634 cells, which are normal human foreskin fibroblasts (CRL). The clonogenicity of FA-A cells was also significantly decreased compared with CRL cells after Cr(VI) treatment. There was no significant difference in either Cr(VI) uptake or Cr–DNA adduct formation between FA-A and CRL cells. These results show that FA-A cells are hypersensitive to Cr(VI) and Cr-induced apoptosis and that this hypersensitivity is not due to increased Cr(VI) uptake or increased Cr–DNA adduct formation. The results also suggest that Cr–DCC may be proapoptotic lesions. These results are the first to show that FA cells are hypersensitive to chromium-induced apoptosis in vitro.

Materials and Methods

Cell Culture

CRL cells (American Type Culture Collection CRL-1634 cells) are normal human foreskin fibroblasts isolated from a newborn black male. FA-A cells (Coriell Cell Repositories GM01309) are FA-A human fibroblasts isolated from a black male 12 years of age. Both CRL and FA-A cells were maintained in minimal essential medium Eagle–Earle media ( Gibco, Grand Island, NY, USA) supplemented with 20% fetal bovine serum (Hyclone Laboratories, Inc., Logan, UT, USA), 2x essential and nonessential amino acids, vitamins, and 2 mM L-glutamine.

Received 11 February 2002; accepted 20 May 2002.
Chromium Preparation
Sodium chromate (Na$_2$CrO$_4$× 4H$_2$O) (J.T. Baker Chemical Co., Phillipsburg, NJ, USA) was dissolved in double-distilled water and sterilized through a 0.2-µm filter before use.

Phosphatidylserine Translocation
The phosphatidylserine (PS) translocation assay was used to investigate the sensitivity of FA-A and CRL cells to Cr-induced apoptosis. This assay measures PS translocation from the inner (cytoplasmic) leaflet of the plasma membrane to the outer (extracellular) leaflet in the early stages of apoptosis. Annexin V protein has a strong, specific affinity for PS (36), and PS on the outer leaflet is available for binding labeled Annexin V. Positive cells exhibit green fluorescence around the plasma membrane. CRL and FA-A cells were seeded at $10^5$ cells/60-mm dish and incubated for 24 hr prior to Cr(VI) exposure. Cells were treated with a final concentration of 0, 1, 3, 6, or 7 µM Cr(VI) for 24 hr in complete media. After 24 hr, the cells were rinsed twice with 1X phosphate-buffered saline (PBS) and incubated for an additional 24 hr in fresh media before analysis. Cells were gently harvested by trypsinization, combined with nonadherent cells from the culture medium, and centrifuged at 600g for 5 min. Cell pellets were washed once in 1X PBS and resuspended in 100 µL binding buffer [10 mM HEPES (pH 7.4), 150 mM NaCl, 5 mM KCl, 1 mM MgCl$_2$, 1.8 mM CaCl$_2$, containing 2 µL Annexin(V)-FLUOS (Roche, Indianapolis, IN, USA)]. Samples were incubated in the dark at room temperature for 15 min. Thirty microliters of each sample was loaded on a microscope slide and the percentage of Annexin(V)-stained cells was determined by counting five fields that contained at least 30 cells each on an Olympus AX70 microscope (Olympus, Lake Success, NY, USA) with a fluorescent filter set suitable for FLUOS analysis (excitation at 460–490 nm and emission at 515 nm).

Caspase-3 Activity
Caspase-3 is derived from the proenzyme CPP32 at the onset of apoptosis and plays a pivotal role in programmed cell death (37–40). Caspase-3 exhibits the highest similarity to C. elegans cell death gene of the ICE (interleukin-1β-converting enzyme) proteases (41). Therefore, caspase-3 is an excellent biochemical indicator of apoptosis. The caspase-3 fluorescent assay detects a shift in fluorescence emission of 7-amino-4-trifluoromethyl coumarin (AFC). AFC is conjugated to a specific tetrapeptide sequence that normally emits blue fluorescence. After the substrate is cleaved by caspase-3, the liberated AFC emits a yellow-green fluorescence at 505 nm. Nearly confluent 150-cm$^2$ flasks were passaged at a 1:3 ratio and incubated for 24 hr prior to Cr(VI) exposure. CRL and FA-A cells were treated with a final concentration of 0, 1, 3, 6, or 7 µM Cr(VI) for 24 hr in complete media. After 24 hr the cells were rinsed twice with 1X PBS, the media was replaced, and the cells were incubated for an additional 24 hr before analysis. Cells were harvested by cell scraping and combined with nonadherent cells from the culture medium. Caspase-3 activity was determined using the FluorAce Apopain Assay Kit (Bio-Rad, Hercules, CA, USA) according to manufacturer’s protocol. Cells were centrifuged at 600×g for 5 min. Cell pellets were rinsed once in 1X PBS and resuspended in 100 µL ice-cold apopain lysis buffer [10 mM HEPES, pH 7.4, 2 mM EDTA, 0.1% 3-(T-cholamidopropyl)dimethylammonio]-1-propanesulfonic acid (CHAPS), 5 mM dithiothreitol (DTT), 1 mM phenylmethyl-sulfonyl fluoride (PMSF), supplemented with protease inhibitors (10 µg/mL pepstatin A, 10 µg/mL aprotinin, 20 µg/mL leupeptin) (Sigma, St. Louis, MO, USA)]. Cell suspensions were vortexed gently, then frozen/thawed 4 times by transferring from an isopropanol-dry ice bath to a 37°C water bath. Cell suspensions were then centrifuged at 12,000×g for 30 min at 4°C to pellet cell debris. Protein concentrations of the resulting supernatants were determined with the DC Protein Assay II (Bio-Rad). Samples containing an equal amount of protein were diluted to 1 mL and transferred to wells of a Costar 48-well plate (Corning, Corning, NY, USA). Ten microliters of apopain substrate (Ac–DEVD–AFC) (Bio-Rad kit) and 40-µL 25× reaction buffer (Bio-Rad kit) were added to each sample and control. Caspase-3 enzymatically cleaves the AFC from the peptide and releases free AFC, which then produces a blue-green fluorescence. The samples were gently mixed, and the fluorescence was determined using a Cytofluor 4000 fluorescence multwell plate reader (PE Biosystems, Foster City, CA, USA) (excitation at 320–400 nm and emission at 505–555 nm). Fluorescence readings were obtained at t = 0, t = 30, t = 60, t = 90, and t = 120 min after addition of substrate. The amount of AFC released from the substrate was determined by linear regression of an AFC standard curve (per manufacturer’s instructions) at the time point at which the apopain positive control showed the greatest increase. Caspase-3 activity was determined and expressed as the ΔAFC/min.

Clonogenicity
CRL and FA-A cells were seeded at $10^5$ cells/100-mm dish and incubated for 24 hr prior to Cr(VI) exposure. Cells were treated with a final concentration of 0, 0.01, 0.1, 0.5, 1, 2, or 3 µM Cr(VI) for 24 hr in complete media. Cells were washed twice with 1X PBS, collected by trypsinization, counted, and resuspended at 2,000 cells/100-mm dish in triplicate. The plates were incubated for 7–8 days and then rinsed with 1X PBS and incubated with crystal violet stain (80% methanol, 2% formaldehyde, and 2.5 g/L crystal violet) for 15 min at room temperature. The plates were thoroughly rinsed with distilled water and allowed to dry. Colonies were counted and the means ± SE of triplicate cultures were used to determine clonogenic survival as a percentage of control cultures.

Chromium Uptake
CRL and FA-A cells were seeded at $3 \times 10^5$ cells/100-mm dish and incubated for 24 hr prior to Cr(VI) exposure. Three extra dishes of each cell type were seeded for determining final cell number. Cr(VI) was prepared as above and spiked with Na$_2$CrO$_4$ (ICN, Irvine, CA). CRL and FA-A cells were treated with a final concentration of 0, 3, or 7 µM Cr(VI) for 3 hr at 37°C. Following Cr(VI) treatment, cells were harvested by trypsinization and centrifuged at 300×g for 5 min at 4°C. Cell pellets were washed twice in 1X PBS and lysed in 500 µL lysis buffer (10 mM Tris-Cl, 0.5% sodium dodecyl sulfate [SDS], 0.5% Triton X-100). One hundred microliters of each sample was combined with Ecolite scintillation cocktail (ICN, Irvine, CA, USA). Disintegrations per minute (DPM) were determined on a Beckman LS3801 scintillation counter (Beckman Instruments, Fullerton, CA, USA). Final cell number was determined in replicate dishes on a Coulter cell counter (Coulter, Louton, UK). Data were normalized to cell number.

Chromium–DNA Adducts
Cr(VI) was prepared as above and spiked with Na$_2$CrO$_4$ (ICN). CRL and FA-A cells were treated with 0, 3, or 7 µM Cr(VI) for 2 hr at 37°C. Following Cr(VI) treatment, cells were harvested by trypsinization and centrifuged at 300×g for 5 min at 4°C. Cell pellets were washed twice in 1X PBS and lysed in 500 µL lysis buffer (10 mM Tris-Cl, 0.5% SDS, 0.5% Triton X-100) containing 20 mg/mL proteinase K overnight in a 55°C water bath. Samples were then incubated with 10 mg/mL RNase for 4 hr in a 37°C water bath. DNA was extracted from the cell lysates, using phenol-chloroform extraction and ethanol precipitation. The DNA was then quantified by its spectrophotometric absorbance at 260 nm. DNA-bound $^{51}$Cr was quantified by scintillation counting of an aliquot of each sample in EcoLite scintillation cocktail (ICN). DPM were then used to calculate Cr–DNA adducts per 10,000 DNA base pairs.

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**Results**

Cr(VI) caused a dose-dependent increase in the number of Annexin V–positive FA-A cells (Figure 1). The percent apoptosis in the CRL cells, as determined by PS translocation, was 12.1 and 16.4% after treatment with 6 and 7 µM Cr(VI), respectively, for 24 hr followed by a 24-hr recovery period. This is similar to results shown in a previous report using human lung fibroblasts (42). In comparison, the percentage of apoptotic FA-A cells was significantly more than that of CRL cells at 43.9 and 52.4% at 6 and 7 µM doses, respectively.

To confirm the hypersensitivity of FA-A cells to Cr(VI)-induced apoptosis using a biochemical assay, we measured caspase-3 activity of extracts from Cr(VI)-treated CRL and FA-A cells. Cr(VI) caused a dose-dependent increase in caspase-3 activation in the FA-A cells (Figure 2). The FA-A cells again showed significantly more apoptosis than the CRL cells at 6 and 7 µM Cr(VI). The caspase-3 activity/µg protein in the CRL cells was 0.06 and 0.22 units after treatment with 6 or 7 µM Cr(VI), respectively, for 24 hr, followed by a 24-hr recovery period. In comparison, caspase-3 activity/µg protein in the FA-A cells was 0.75 and 1.59 units at 6 and 7 µM doses, respectively (12- to 14-fold increase).

Clonogenicity is an indicator of long-term cell survival and replicative potential after exposure to a toxic agent. Cr(VI) caused a dose-dependent decrease in clonogenic survival in both the CRL and the FA-A cells (Figure 3). The FA-A cells showed significantly less clonogenic survival after 1, 2, and 3 µM Cr(VI) treatment compared with CRL cells. The percent clonogenic survival for 1, 2, and 3 µM Cr(VI) was 28.7, 5.4, and 0.2% for the FA-A cells compared with 89.6, 18.6, and 4.4% for the CRL cells, respectively.

We performed Cr(VI) uptake analysis to determine if the differences in apoptosis and clonogenicity could be explained by differential Cr(VI) uptake. There was a dose-dependent increase in Cr(VI) uptake from 0 through 7 µM Cr(VI) (Figure 4). However, there was no significant difference in Cr(VI) uptake between CRL and FA-A cells at any of the concentrations tested. Three and 7 mm Cr(VI) resulted in approximately $8.5 \times 10^{-4}$ and $1.4 \times 10^{-3}$ mmol Cr per cell, respectively.

We also measured total Cr–DNA binding in both the CRL and FA-A cells to determine if the differences in apoptosis and clonogenicity could be explained by differences in Cr–DNA adduct formation. Although Cr(VI) caused a dose-dependent increase in Cr–DNA adduct formation in both CRL and FA-A cells (Figure 5), there were no significant differences in Cr–DNA adduct formation between CRL and FA-A cells at either the 3 or 7 µM dose. There was a slight but not statistically significant trend toward a higher adduct level in the CRL cells than in the FA-A cells. Three micromolar Cr(VI) resulted in approximately 0.02–0.03 Cr–DNA adducts per 10,000 base pairs. Seven micromolar Cr(VI) resulted in approximately 0.04–0.08 Cr–DNA adducts per 10,000 base pairs. Previous studies using a 10-fold higher concentration (75 µM) Cr(VI) resulted in approximately 2 Cr–DNA adducts/10,000 base pairs (27).

**Discussion**

The carcinogenic and transformagenic effects of Cr(VI) have been associated with...
the cytotoxicity of certain Cr(VI)-containing compounds at the site of administration in vivo (1) and in cell culture systems (12,29). In human occupational settings, exposure to levels of particulate Cr(VI) compounds usually associated with lung cancers also effect high levels of cell death, which manifest as nasal perforations and respiratory tract ulcerations (1). Several investigations have established the induction of apoptosis by Cr(VI) in treated normal human fibroblasts (29,42,43); thus, understanding the mechanisms of Cr-induced toxicity and cell death may help elucidate mechanisms of carcinogenicity.

The intracellular reduction of Cr(VI) generates several DNA-reactive species that can lead to myriad genetic lesions. Although a wealth of information exists concerning the genotoxicity of Cr(VI), the specific types of DNA damage that may be responsible for the toxic effects of Cr(VI) have not yet been determined. At least one type of genetic lesion formed as a result of Cr(VI) reduction (Cr–DDC) results in guanine-specific arrest of DNA replication (26,27). Although Cr–DDC may represent lethal lesions formed by Cr(VI), information is lacking on the effects of Cr(VI) on DNA cross-link repair-deficient cells. The focus of this investigation was to examine the cellular effects of FA-A cells on FA-A cells, which are specifically deficient in the repair of DNA interstrand cross-links (35).

The ultimate fate of a cell exposed to a genotoxin such as Cr(VI) is heavily dependent upon the severity of the initial insult. At low concentrations, cells exposed to Cr(VI) primarily undergo growth arrest, presumably to allow time for repair. As the concentration of Cr(VI) is increased, the predominante cell fate becomes terminal growth arrest followed by apoptosis (29). The data from the present study are consistent with this model. The clonogenicity assay measures the long-term survival of a population after Cr(VI) exposure and accounts for both growth arrest and apoptosis. We have recently shown that DPC are not genotoxic. In Biological Effects of Heavy Metals, Vol 2 (Foulkes EC, ed). Boca Raton, FL: CRC Press, 1990;19–75.

## References and Notes

1. IARC. Chromium, nickel and welding. IARC Monogr Eval Carcinog Risk Hum 48:1–648 (1990).
2. Plunkett ER. Handbook of Industrial Toxicology. New York:Chemical Publications, 1929.
3. Amur MD, Doull J, Klassen CD. Cassaret et Doull’s Toxicology, 4th ed. New York:Maxwell-MacMillan-Pergamon, 1991.
4. Ishikawa Y, Nakagawa K, Satoh Y, Kitagawa T, Sugano H, Hirano T, Tsuchiya E. Hot spots of chromium accumulation at bifurcations of chromate workers’ branches. Cancer Res 54:2342–2346 (1994).
5. Burke T, Fagliano J, Goldoff M, Hazen RE, Iglewicz R, McKeel T. Chromite ore processing residue in Hudson County, New Jersey. Environ Health Perspect 92:131–137 (1991).
6. Freeman NCS, Stern AH, Lioy PJ. Exposure to chromium dust from homes in a chromium surveillance project. Arch Environ Health 50:213–228 (1995).
7. Wise JP, Stearns D, Wetterhahn K, Patierno SR. Cell-mediated dissolution of carcinogenic lead chromate particles: role of individual dissolution products in clastogenesis. Carcinogenesis 15:2249–2254 (1994).
8. Leonard A. Mechanisms in metal genotoxicity: significance of in vitro approaches. Mutat Res 198:321–326 (1988).
9. Cohen M, Latta D, Doogan T, Costa M. Mechanisms of metal carcinogenesis: the reactions of metals with nucleic acids. In: Biological Effects of Heavy Metals, Vol 2 (Foulkes EC, ed). Boca Raton, FL: CRC Press, 1990;19–75.
10. De Flora S, Bagnasco M, Serra D, Zanacchi P. Genotoxicity of chromium compounds. Mutat Res 238:99–172 (1990).
11. Standeven A, Wetterhahn KE. Is there a role for oxygen species in the mechanism of chromium (VI) carcinogenesis? Chem Res Toxicol 4:461–625 (1991).
12. Paterno SR, Barth D, Lendolph JR. Transformation of Cr(VI)/1/2 mouse embryo cells to focus formation and anchorage independence by insoluble lead chromate but not soluble calcium chromate: relationship to mutagenesis and internalization of lead chromate particles. Cancer Res 48:5280–5288 (1988).
13. Montalini A, Zentilin L, Pagliuca S, Levis AG. Solubilization by nitrilotriacetic acid (NTA) of genetically active Cr(VI) and Pb(II) from insoluble metal compounds. J Toxicol Environ Health 21:387–394 (1987).
14. Wise JP, Drenstein J-M, Patierno SR. Inhibition of chromosomal clastogenesis by ascorbate: relationship to particle dissolution and uptake. Carcinogenesis 14:429–434 (1993).

15. Wise JP, Leonard JC, Patierno SR. Clastogenicity of lead chromate particles in hamster and human cells. Mutat Res 276:99–79 (1992).

16. Standeven AM, Wetterhahn KE. Chromium (VI) toxicity: uptake, reduction, and DNA damage. J Am Cell Toxicol 8:1275–1283 (1999).

17. Miller CA III, Cohen MD, Costa M. Complexing of actin and other nuclear proteins to DNA by cis-diaminedichloroplatinum (II) and chromium compounds. Carcinogenesis 12:289–276 (1991).

18. Miller CA III, Costa M. Characterization of DNA-protein complexes induced in intact cells by the carcinogenic chromate. Mol Carcinog 1:125–133 (1988).

19. Cupo DY, Wetterhahn KE. Repair of chromate-induced DNA damage in chick embryo hepatocytes. Carcinogenesis 5:1705–1708 (1984).

20. Fornace AJ Jr, Seres DS, Lechner JF, Harris CC. DNA-protein cross-linking by chromium salts. Chem Biol Interact 36:345–354 (1981).

21. Sugiyama M, Tsuzuki K, Ogura R. Effect of ascobic acid on DNA damage, cytotoxicity, glutathione reductase and formation of paramagnetic chromium in Chinese hamster V-79 cells treated with sodium chromate. J Biol Chem 266:3383–3383 (1991).

22. Sugiyama M, Patierno SR, Cantoni O, Costa M. Characterization of DNA lesions induced by Cr(VI) in synchronous and asynchronous cultured mammalian cells. Mol Pharmacol 29:606–613 (1986).

23. Sugiyama M, Wang X-W, Costa M. Comparison of DNA lesions and cytotoxicity induced by calcium chromate in human, mouse and hamster cell lines. Cancer Res 46:4547–4551 (1986).

24. Xu J, Bubley GJ, Dietrick B, Blankenship LJ, Patierno SR. Chromium (VI) treatment of normal human lung cells results in guanine-specific DNA polymerase arrest, DNA-DNA crosslinks and S-phase blockade of cell cycle. Carcinogenesis 17:1511–1517 (1996).

25. Singh J, Bridgewater LC, Patierno SR. Differential sensitivity of chromium-mediated DNA interstrand crosslinks and DNA-protein crosslinks to disruption by alkali and EDTA. Toxicol Sci 45:72–76 (1998).

26. Bridgewater LC, Manning FC, Patierno SR. Base-specific arrest of in vitro DNA replication by carcinogenic chromium: relationship to DNA interstrand crosslinking. Carcinogenesis 15:2421–2427 (1994).

27. Bridgewater LC, Manning FC, Woo ES, Patierno SR. DNA polymerase arrest by adducted trivalent chromium. Mol Carcinog 9:122–133 (1994).

28. Evan G, Littlewood TA. A matter of life and cell death. Science 291:1317–1322 (1999).

29. Pritchard DE, Ceryk S, Ha L, Fornsaglio JL, Hartman SK, O’Brien TJ, Patierno SR. Mechanism of apoptosis and determination of cellular fate in chromium(VI)-exposed populations of telomerase-immortalized human fibroblasts. Cell Growth Differ 12:487–496 (2001).

30. Sasaki MA, Tomonura A. A high susceptibility of Fanconi anemia to chromosome breakage by DNA cross-linking agents. Cancer Res 33:1829–1838 (1973).

31. Strathdee CA, Buchwald M. Molecular and cellular biology of Fanconi anemia. Am J Pediatr Hematol Oncol 14:177–185 (1992).

32. Auerbach AD, Fanconi anemia diagnosis and the diospyrosbute (DEB) test. Exp Hematol 21:731–733 (1993).

33. D’Andrea AD, Grompe M. Molecular biology of Fanconi anemia: implications for diagnosis and therapy. Blood 90:1275–1278 (1997).

34. Buchwald M, Moutzacchi E. Is Fanconi anemia caused by a defect in the processing of DNA damage? Mutat Res 408:75–90 (1998).

35. Zhen W, Evans MK, Haggerty CM, Börh VA. Deficient gene specific repair of cisplatin-induced lesions in Xeroderma pigmentosum and Fanconi’s anemia cell lines. Carcinogenesis 14:919–924 (1993).

36. Martin SJ, Reutelingsperger CP, McGahan AJ, Rader JA, van Schie RC, LaFace DM, Green DR. Early redistribution of plasma membrane phosphatidylserine is a general feature of apoptosis regardless of the initiation stimulus: inhibition by overexpression of Bcl-2 and Abl. J Exp Med 182:1545–1550 (1995).

37. Goldberg YP, Nicholson DW, Rasper DM, Kalchman MA, Kide H, Rahman RA, Bomm M, Kazemi-Esfarjani P, Thomsen NA, Vaillancourt JP, et al. Cleavage of huntington by apopain, a proapoptotic cysteine protease, is modulated by the polyglutamine tract. Nat Genet 12:442–449 (1996).

38. O’Brien TJ, Xu J, Patierno SR. Effects of glutathione on chromium-induced DNA crosslinking and DNA polymerase arrest. Mol Cell Biochem 221:173–182 (2001).

39. Rotonda J, Nicholson DW, Fazl XM, Gallant M, Galcaro Y, Labelle M, Peterson EP, Raper DM, Ruel R, Vaillancourt JP, et al. The three-dimensional structure of apopain/CPP32, a key mediator of apoptosis. Nat Struct Biol 3:619–625 (1996).

40. Xue J, Manning FCR, Patierno SR. Preferential formation and repair of chromium-induced DNA adducts and DNA-protein crosslinks in nuclear matrix. Carcinogenesis 15:1443–1450 (1994).

41. Zhitkovich A, Voitkun V, Costa M. Glutathione and free amino acids form stable complexes with DNA following exposure of intact mammalian cells to chromium(VI). Carcinogenesis 16:907–913 (1995).

42. Voitkun V, Zhitkovich A, Costa M. Cr(III)-mediated crosslinks of glutathione or amino acids to the DNA phosphate backbone are mutagenic in human cells. Nucleic Acids Res 26:2024–2030 (1998).

43. Manning FCR, Xu J, Patierno SR. Transcriptional inhibition by carzinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

44. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

45. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

46. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

47. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

48. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

49. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

50. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).

51. Xu J, Manning FCR, Patierno SR. Transcriptional inhibition by carcinogenic chromate: relationship to DNA damage. Mol Carcinog 6:270–279 (1992).