Participation of Iron and Nitric Oxide in the Mutagenicity of Asbestos in \textit{hgprt}^-, \textit{gpt}^+ Chinese Hamster V79 Cells$^1$

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ABSTRACT

Crocidolite asbestos is known to cause cellular damage, leading to asbestososis, bronchogenic carcinoma, and mesothelioma in humans. The mechanism responsible for the carcinogenicity of asbestos is not known. Iron associated with asbestos is thought to play a role by catalyzing the formation of reactive oxygen species, which may cause DNA damage, leading to mutations and cancer. Here, we examined whether asbestos can induce mutations in Chinese hamster \textit{hgprt}^+ V79 cells or transgenic \textit{hgprt}^-, \textit{gpt}^+ V79 cells (G12). Treatment with 6 \textmu g/cm$^2$ crocidolite for 24 h caused a 2-fold increase in the mutation frequency at the \textit{gpt} locus of G12 cells, but no increase at the \textit{hgprt} locus of V79 cells. The mutation frequency at the \textit{gpt} locus of G12 cells increased with increasing treatment dose of crocidolite. The mutations induced by crocidolite appeared to be due to the generation of reactive oxygen species catalyzed by iron associated with the fibers, because treatment of G12 cells in iron-free medium with fibers from which redox active iron had been removed with desferrioxamine B prevented all of the \textit{gpt} mutations above untreated control levels. In addition, treatment of cells with a soluble form of iron, 1.5 mM ferric ammonium citrate, resulted in an increase in mutation frequency at the \textit{gpt} locus of \textsim 1.5-fold above that of untreated G12 cells with no increase in mutations at the \textit{hgprt} locus of V79 cells with ferric ammonium citrate. We also investigated the effect of nitric oxide on the mutagenicity of crocidolite in G12 cells. When G12 cells were treated with 3 \textmu g/cm$^2$ of crocidolite in the presence of nitric oxide-generating compound, 200 \textmu M diethytriamine/NO, the mutation frequency increased to a level that was more than additive for crocidolite or diethytriamine/NO treatment alone. These results strongly suggest that the presence of iron and nitric oxide may either lead to the generation of another reactive, mutagenic species, such as peroxynitrite, or that nitric oxide inhibits a DNA repair enzyme(s), leading to an increase in mutations.

INTRODUCTION

Asbestos refers to a group of hydrated fibrous silicates. Because of the physical properties of asbestos, \textit{e.g.}, heat resistance, flexibility, and chemical inertness, it has been widely used for industrial purposes. However, exposure to asbestos is known to increase the risk of bronchogenic carcinoma and mesothelioma (1, 2). The mechanism responsible for the toxicity and carcinogenicity of asbestos is not yet known. The carcinogenicity of asbestos fibers is related to their size and durability (reviewed in Refs. 3 and 4). However, it has been shown that asbestos catalyzes many of the same reactions that iron does, such as lipid peroxidation (5), DNA strand breaks (6), and the formation of 8-oxodG$^+$ (7–10). Crocidolite, a form of asbestos containing up to 27% iron by weight, is more carcinogenic in humans than another form of asbestos, chrysotile, which contains 2–3% iron by weight (2). Therefore, it has been proposed that the iron from asbestos catalyzes the formation of reactive oxygen species, such as superoxide radical (O$_2^-$), hydrogen peroxide (H$_2$O$_2$), and hydroxyl radical (HO$^+$), via iron-catalyzed Haber-Weiss reactions (3, 11). By catalyzing the formation of these species, iron may play an important role in the carcinogenicity of asbestos (3, 12).

Crocidolite exposure of human lung epithelial cells, target cells for the development of bronchogenic carcinoma, resulted in production of nitric oxide (NO') via induction of the inducible form of nitric oxide synthase, and formation of 8-oxodG$^+$ (10). An increase in 8-oxodG$^+$ was dependent on the presence of iron associated with asbestos and the production of NO' (10). The formation of 8-oxodG$^+$ can occur as the result of iron-catalyzed HO' attack on DNA or as the result of hydroxylation by the protonated form of peroxynitrite (ONOO$^-$; Ref. 13). Peroxynitrite is formed from the reaction of NO' with O$_2$ (14) and can lead to point mutations in bacteria and in human cells (15). NO' itself can cause DNA strand breaks and DNA damage (16, 17). It also interacts rapidly with oxygen molecules to generate N$_2$O$_5$, which causes deamination of DNA bases leading to mutations (18).

Several types of asbestos have been shown to induce chromosomal aberrations and sister chromatid exchanges in mammalian cells (19, 20). However, studies on the mutagenicity of asbestos at the \textit{hgprt} locus in rodents have been negative (21). Hei \textit{et al.} (22) observed a 50-fold increase in mutations in crocidolite-treated, human-hamster hybrid cells (A$_x$) in which the mutational marker (a$_x$) is in a target chromosome not essential for cell viability (23). These investigators did not observe an increase in mutations at the \textit{hgprt} locus in these same cells after crocidolite treatment. Based on very similar observations in A$_x$ cells treated with ionizing radiation, Hei \textit{et al.} (22) concluded that oxygen radicals were responsible for the observed mutations. The negative results with these two mutagenic agents at the \textit{hgprt} locus are thought to be due to the fact that oxygen radical damage causes multilocus deletions (22, 24, 25). Because the \textit{hgprt} gene is on the X chromosome, multilocus deletions in the region of the \textit{hgprt} gene would be lethal and, therefore, not detectable (24, 25). Recently, another recombinant system has been developed, which successfully detects multilocus deletions arising from oxygen radicals. In the recombinant cells (G12) used for this system, \textit{hgprt} V79 cells were transfected with the smaller \textit{Escherichia coli} xanthine-g$ppt$ gene (24). The recombinant \textit{g$ppt$} gene is a single allele located on an autosomal chromosome, which helps to protect the cells from the lethality of multilocus deletions. The \textit{g$ppt$} locus on the G12 cell line has been shown to have enhanced yield for oxygen radical-induced mutations resulting from X-rays or bleomycin (26). The experiments presented here focused on understanding the chemistry that leads to mutations induced by asbestos. Therefore, we investigated the role of iron and nitric oxide in the mutagenicity of crocidolite in V79 cells and the transgenic G12 cells. Crocidolite treatment of G12 cells resulted in a 2-fold increase in mutation frequency, compared with untreated G12 cells. The increase in mutation frequency was dependent on iron associated with asbestos. In the presence of NO', crocidolite exposure caused a synergistic increase in mutations in the \textit{g$ppt$} locus of G12 cells but not in the \textit{hgprt} locus of V79 cells. These results strongly suggest that the presence of iron and nitric oxide may either lead to the generation of another reactive, mutagenic species, such as peroxynitrite, or that nitric oxide inhibits DNA repair enzyme(s), leading to an increase in mutations.

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3 The abbreviations used are: 8-oxodG, 2'-deoxy-7-hydro-8'-oxoguanosine; \textit{hgprt}, hypoxanthine-guanine phosphoribosyl transferase; \textit{g$ppt$}, guanine phosphoribosyltransferase; DF, desferrioxamine B; DETA, diethytriamine; FAC, ferric ammonium citrate.
MATERIALS AND METHODS

Crocidolite and chrysotile fibers were obtained from Dr. Richard Griesemer, National Institute for Environmental Health Sciences/National Toxicology Program (Research Triangle Park, NC). DF was purchased from Ciba-Geigy Corp. (Summit, NJ). Ferric ammonium citrate, 6-thioguanine, aminopterin, hypoxanthine, and thymidine were purchased from Sigma Chemical Co. (St. Louis, MO). DETA/NO was obtained from Dr. Larry Keefer, NIH (Frederick, MD).

Cell Culture. Chinese hamster hgp t − V79 cells and the transgenic hgprt −, gpt + G12 cells were obtained from Dr. Toby G. Rossman (New York University, New York, NY). The cells were cultured in Ham’s F12 medium (Life Technologies, Inc., Grand Island, NY) with 3 μM FeSO4 (F12 + Fe) or without FeSO4 (F12 − Fe). The F12 + Fe or F12 − Fe medium were supplemented with 5% fetal bovine serum (Summit Biotechnology, Fort Collins, Co.), 50 μg/mL gentamicin (Whittaker, M. A. Bioproducts Inc., Walkersville, MD), and 1.176 g/L NaHCO3.

Preparation of Treatment Solutions. Crocidolite, chrysotile, or FAC was suspended in 1.176 g/L NaHCO3 immediately before treatment and was added into complete culture medium to give the desired dose.

DF-pretreated crocidolite was prepared by incubation of crocidolite in 50 mM NaCl (pH 7.5) with 1 mM DF for 90 days. The NaCl solution with 1 mM DF was periodically changed during this period. The redox active iron was shown to be mobilized from crocidolite over this time period (27). DF-crocidolite was then washed with sterile, distilled water five times. DF-crocidolite was suspended as described for regular crocidolite.

DETA/NO was weighed in an oxygen-free glove box. The DETA/NO solution was freshly prepared with ice-cold 10 mM NaOH and was kept on ice before treatment of cells. Expended DETA/NO was prepared by incubating DETA/NO (10 mM) in H2O for 7 days at room temperature.

Treatment of Cells. When handling V79 or G12 cells, the light inside the hood was turned off to prevent mutations caused by UV light. Cell lines were freshly cultured from frozen stocks every 6 weeks. V79 and G12 cells were cultivated in F12 − Fe medium, because it has been shown previously that asbestos fibers acquired iron from the medium (30), which led to increased DNA damage in A549 cells (10). As a positive control for iron and to eliminate any other possible contributions by the fibers, the G12 or V79 cells were treated with a soluble form of iron, 1.5 mM FAC, for 24 h. The mutation frequency in FAC-treated G12 cells was ~1.5-fold higher than in untreated G12 cells (Table 2), but there was no increase in FAC-treated V79 cells (data not shown). These results show that it is possible to detect the mutagenicity of iron at the gpt locus, but not the hgprt locus, and that the mutagenicity of iron is likely due to reactive oxygen species.

Table 1 Mutagenicity of crocidolite in V79 and G12 cells

<table>
<thead>
<tr>
<th>Samples</th>
<th>% survival</th>
<th>Mutants per 106 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>Crocidolite (6 μg/cm²)</td>
<td>11 ± 3³</td>
<td>61 ± 4⁴</td>
</tr>
<tr>
<td>V79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100</td>
<td>5 ± 1</td>
</tr>
<tr>
<td>Crocidolite (6 μg/cm²)</td>
<td>13 ± 3³</td>
<td>6 ± 2</td>
</tr>
</tbody>
</table>

³V79 and G12 cells were cultured in F12 + Fe medium and treated with 6 μg/cm² crocidolite for 24 h. The mutation frequency was measured as described in "Materials and Methods." The results are expressed as the means of three different experiments ± SD.

⁴Significantly different from the untreated control (Student’s t test, P < 0.01).
oxidation was observed in the native crocidolite-treated cells than in observed previously for oxidation of DNA in A549 cells that more cells treated with crocidolite that had not been preincubated with DF in F12 + Fe medium, the mutation frequency increased —30%. However, when G12 cells were treated with 6 /xg/cm² DF-crocidolite in F12-Fe medium, there was no increase in mutations compared with untreated control (Table 3). The 3 /tg/cm² crocidolite treatment did not induce a significant number of mutations above background. However, exposure of G12 cells to 3 /tg/cm² crocidolite in the presence of 200 µM DETA/NO caused an increase in the mutation frequency ~4-fold higher than that of untreated G12 cells. To determine whether this synergistic effect was due to by-products of DETA/NO breakdown rather than NO, G12 or V79 cells were treated with expanded DETA/NO (200 µM) for 24 h in the presence or absence of crocidolite (3 /tg/cm²) in F12 + Fe medium. The DETA/NO alone remained mutagenic in both G12 and V79 cells, but there was no synergistic effect of the expanded DETA/NO with crocidolite in G12 or V79 cells (data not shown). The results indicate that the by-products were not involved in the synergistic response observed, because no synergistic increase in mutations compared with the untreated control (data not shown). These results suggest that the mutations induced by FAC or chrysotile exposure were due to reactive oxygen species or a species of similar reactivity.

Hardy and Aust (30) observed that DF-crocidolite, preincubated in FeSO₄ solutions or in medium containing FeSO₄ (F12 + Fe), acquired iron from the medium, leading to a significant increase in DNA strand breaks in vitro compared with DF-crocidolite preincubated in solution or medium not containing iron. Chao et al. (10) observed that the amount of DNA oxidation in A549 cells increased in cells treated with DF-crocidolite in F12 + Fe compared with DF-crocidolite in F12-Fe, where there was very little damage and concluded that the iron acquired by these fibers from the medium was biologically active, damaging DNA. Consistent with these observations, when G12 cells were treated with 6 µg/cm² DF-crocidolite in F12-Fe medium, there was no increase in mutations compared with untreated control (Table 2). However, when G12 cells were treated with 6 µg/cm² DF-crocidolite in F12 + Fe medium, the mutation frequency increased ~30%. A 34% increase in mutations over DF-crocidolite was observed in cells treated with crocidolite that had not been preincubated with DF but cultured in F12 + Fe medium. This is consistent with what was observed previously for oxidation of DNA in A549 cells that more oxidation was observed in the native crocidolite-treated cells than in the DF-crocidolite-treated cells, even in F12 + Fe (10). Thus, iron, either associated with the fiber or acquired from the culture medium, appeared to be involved in the mutagenicity of crocidolite.

Synergistic Effect of Nitric Oxide on the Mutagenicity of Crocidolite. Exposure of A549 cells to crocidolite resulted in induction of the inducible form of nitric oxide synthase, an increase in NO' production, and the formation of 8-oxodG (10). The formation of 8-oxodG in crocidolite-treated A549 cells was dependent on both iron associated with crocidolite and NO' and was thought to be due to the formation of a new oxidizing species, ONOO⁻, or inhibition of a DNA repair enzyme(s) by NO'. Therefore, we examined whether the presence of NO' affected the mutation frequency of crocidolite in G12 cells. Because NO' was not being produced in response to crocidolite in G12 cells (data not shown), DETA/NO was used as a nitric oxide donor with a half-life of ~20 h (31, 32). The slow, steady production of NO' from DETA/NO mimicked the production of NO' in crocidolite-treated A549 cells. The G12 cells grown in F12 + Fe medium were treated with 3 µg/cm² crocidolite either in the presence or absence of 200 µM DETA/NO for 24 h. The concentration of extracellular nitrite generated from 200 µM DETA/NO was ~118 µM after the 24-h treatment of G12 cells. DETA/NO itself was mutagenic in G12 cells (Table 3). The 3 µg/cm² crocidolite treatment did not induce a significant number of mutations above background. However, exposure of G12 cells to 3 µg/cm² crocidolite in the presence of 200 µM DETA/NO caused an increase in the mutation frequency ~4-fold higher than that of untreated G12 cells. To determine whether this synergistic effect was due to by-products of DETA/NO breakdown rather than NO, G12 or V79 cells were treated with expanded DETA/NO (200 µM) for 24 h in the presence or absence of crocidolite (3 µg/cm²) in F12 + Fe medium. The DETA/NO alone remained mutagenic in both G12 and V79 cells, but there was no synergistic effect of the expanded DETA/NO with crocidolite in G12 or V79 cells (data not shown). The results indicate that the by-products were not involved in the synergistic response observed, because no synergistic

**Table 2 Role of iron in mutagenicity of crocidolite**

<table>
<thead>
<tr>
<th>Samples</th>
<th>Samples</th>
<th>% survival</th>
<th>Mutants per 10⁶ cells (gpt⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (F12 + Fe)</td>
<td>Control (F12 - Fe)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
<td>28 ± 3</td>
<td></td>
</tr>
<tr>
<td>DF-Croc.⁶ (6 µg/cm²) (F12 + Fe)</td>
<td>DF-Croc.⁶ (6 µg/cm²) (F12 - Fe)</td>
<td>65 ± 8'</td>
<td>67 ± 5'</td>
</tr>
<tr>
<td>40 ± 6'</td>
<td>28 ± 3'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC⁺ (2 mM) (F12 - Fe)</td>
<td>Chrys.⁶ (6 µg/cm²) (F12 - Fe)</td>
<td>103 ± 3</td>
<td>71 ± 8'</td>
</tr>
<tr>
<td>45 ± 5'</td>
<td>27 ± 5'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chrys. (30 µg/cm²) (F12 - Fe)</td>
<td>Chrys. (30 µg/cm²) (F12 + Fe)</td>
<td>18 ± 9'</td>
<td>28 ± 7'</td>
</tr>
<tr>
<td>54 ± 8'</td>
<td>54 ± 8'</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁶ G12 cells grown in either F12 + Fe or F12 - Fe were exposed to various treatments for 24 h. The mutation frequency was measured as described in "Materials and Methods." The results are expressed as the means of three different experiments ± SD.

**Table 3 Role of iron and nitric oxide in mutagenicity of crocidolite**

<table>
<thead>
<tr>
<th>Samples</th>
<th>G12 (gpt⁻)</th>
<th>V79 (hgp⁻)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>24 ± 4 (100)⁶</td>
<td>5 ± 1 (100)</td>
</tr>
<tr>
<td>Crocidolite (3 µg/cm²)</td>
<td>28 ± 3 (32 ± 6')</td>
<td>5 ± 1 (33 ± 5')</td>
</tr>
<tr>
<td>DET-A/NO (200 µM)</td>
<td>49 ± 8' (63 ± 3')</td>
<td>64 ± 11 (52 ± 5')</td>
</tr>
<tr>
<td>Crocidolite (3 µg/cm²)/DETA/NO</td>
<td>90 ± 16' (19 ± 2')</td>
<td>59 ± 18 (18 ± 3')</td>
</tr>
</tbody>
</table>

⁶ G12 cells grown in F12 + Fe were exposed to various treatments for 24 h. The mutation frequency was measured as described in "Materials and Methods." The results are expressed as the means of three different experiments ± SD.

**Figure 1. Cytotoxicity and mutagenicity of crocidolite in G12 cells.** G12 cells were treated with indicated doses of crocidolite for 24 h. The cytotoxicity of crocidolite was determined by the percentage of relative colony-forming ability, as described in "Materials and Methods." The results represent an average of three individual experiments (A); bars, SD. The mutation frequency in crocidolite-treated G12 cells was determined at the gpt locus by selection in thioguanine-containing medium, as described in "Materials and Methods." The results represent an average of three individual experiments (B); bars, SD.
increase was observed when exposed DETA/NO was used with crocidolite. To investigate whether the increased mutations in crocidolite-exposed G12 cells in the presence of DETA/NO was due to hydroxyl radicals or a similarly reactive species, V79 cells were also treated with 3 μg/cm² crocidolite either in the presence or absence of 200 μM DETA/NO. Exposure of V79 cells to 3 μg/cm² crocidolite resulted in no increase in mutations above background. Treatment of V79 cells with 200 μM DETA/NO showed a similar mutation frequency to that of G12 cells treated with DETA/NO. However, the exposure of V79 cells to 3 μg/cm² crocidolite in the presence of DETA/NO did not cause an increase in mutation frequency, compared with V79 cells treated with DETA/NO alone (Table 3). These results are consistent with what was observed in A549 cells (10), that in the presence of iron and NO' a new oxidizing species, \( \text{e.g. ONOO}^- \), was being produced or DNA repair enzymes were being inhibited, resulting in an increase in the formation of 8-oxodG.

**DISCUSSION**

Data presented here showed that crocidolite and chrysotile were mutagenic at the \( gpt \) locus in G12 cells and that the mutations probably resulted from DNA damage caused by the hydroxyl radical or a similarly reactive species. The observation that these two forms of asbestos were mutagenic at the \( gpt \) locus of G12 cells, but not the \( hgprt \) locus of V79 cells, is consistent with results in these cell lines reported for other mutagens, which damaged DNA via reactive oxygen species. This is also consistent with what Hei et al. (22, 33) reported for chrysotile and crocidolite mutagenicity at the \( a_t \) locus in A549 human-hamster hybrid cells but not at the \( hgprt \) locus in the same cells. The difference in the mutation frequencies observed between these two genetic loci is not surprising, because it is well known that the mutation frequency for a given mutagen can vary with the mutational marker being examined.

The induction of mutations in crocidolite-treated G12 cells appeared to be dependent upon iron intrinsic to the fibers and/or acquired from the medium. DF-crocidolite treatment of G12 cells in F12 — Fe medium did not induce any mutations, whereas treatment in F12 + Fe medium produced a statistically significant increase in mutations. Because the toxicity of DF-crocidolite was no different whether the cells were treated in F12 — Fe or F12 + Fe medium, this would suggest that the difference in the mutations observed was not due to changes in the physical properties of the fibers resulting from the chelator treatment. Treatment of G12 cells with native crocidolite in F12 + Fe medium resulted in a 34% increase in mutations relative to DF-crocidolite in F12 + Fe medium. The fact that more chrysotile than crocidolite was required to observe mutations in the G12 cells may be due to the fact that the fibers contain much less iron than crocidolite, 2–3% compared with 27%, respectively. The amount of iron mobilized from chrysotile fibers in vitro was 70% less than from crocidolite. Another factor, which may have contributed to this, is that the surface charge of chrysotile is positive, whereas that of crocidolite is negative (34) and may affect the cellular uptake of the fibers necessary for iron release in the cells. Thus, a higher treatment dose of chrysotile may be needed for mutagenicity to obtain enough iron to produce the DNA damage.

It appeared that NO' treatment enhanced the mutagenicity of crocidolite by causing more oxidative damage to the DNA. DETA/NO treatment caused mutations in both G12 cells and V79 cells but enhanced the mutagenicity of crocidolite only in G12 cells. NO' itself has been shown to cause DNA strand breaks and DNA damage (16, 17). NO' can react rapidly with \( O_2 \) to generate \( N_2O_5 \), which causes deamination of DNA bases leading to mutations (18). This may explain the mutations induced by DETA/NO in both V79 and G12 cells, because the \( gpt \) locus and the \( hgprt \) locus should be similarly sensitive to point mutations and small deletions (26). However, the synergistic enhancement of the DETA/NO mutations with crocidolite cotreatment only in the G12 cells strongly suggests that oxidative damage leading to multilocus deletions has been synergistically increased by this cotreatment. It may be that iron was entirely responsible for the generation of reactive oxygen species, which led to the DNA damage causing the mutations, and that NO' prevented the repair of this damage by inhibiting the necessary repair enzyme(s) (35, 36). A second possibility is that \( O_2 \) produced by reduction of \( O_2 \) by iron, reacted with NO' to produce ONOO', which could oxidize the DNA leading to a synergistic increase in mutations.

In conclusion, asbestos appears to cause DNA damage (10) and mutations in mammalian cells as a result of oxidative damage to the DNA. The presence of iron, intrinsic to the fibers or acquired from the medium, was required for the induction of mutations. However, NO' synergistically enhanced the induction of mutations in the mammalian cells, most likely as a result of enhanced oxidative damage to the DNA. If these same reactions occur in vivo, this may lead to the development of bronchogenic carcinoma in asbestos-exposed lungs. The synergistic interaction observed between iron and NO' suggests two other intriguing possibilities that may relate to the induction of lung tumors. Macrophages in the lung, activated by phagocytosis of asbestos fibers, will produce \( O_2 \) and NO' (38), perhaps potentiating DNA damage in target epithelial cells. In addition, simultaneous exposure to asbestos and cigarette smoke has been shown to synergistically increase the development of bronchogenic carcinoma. Because cigarette smoke contains 300–700 ppm NO' and fatty acids, which can mobilize iron from asbestos (39), it is very possible that the combined presence of cigarette smoke and asbestos would enhance the oxidation of DNA in bronchial epithelial cells, leading to cancer.

**REFERENCES**


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