The Viral Protein Apoptin Induces Apoptosis in UV-C-irradiated Cells from Individuals with Various Hereditary Cancer-prone Syndromes

Ying-Hui Zhang, Peter J. Abrahams, Alex J. van der Eb, and Mathieu H. M. Noteborn

ABSTRACT

Apoptin, a protein derived from chicken anemia virus, has previously been shown to induce apoptosis in a p53-independent and Bel-2-stimulated manner in transformed and tumorigenic human cells but not in normal diploid human cells, suggesting that it is a potential agent for tumor therapy. Here we report that Apoptin can induce apoptosis in UV-C-irradiated diploid skin fibroblasts from individuals with various hereditary cancer-prone syndromes that are characterized by a germ-line mutation in a tumor suppressor gene. The same effect is found when these cells are irradiated with X-rays. In contrast, diploid skin fibroblasts from healthy donors or from individuals with DNA repair disorders are not responsive to Apoptin-induced apoptosis upon UV-C or X-ray irradiation. After transfection of untreated cells, Apoptin is found predominantly in the cytoplasm, whereas in UV-C-exposed Apoptin-responsive cancer-prone cells, it migrates to the nucleus, where it causes rapid apoptosis. Apoptin remains localized in the cytoplasm after UV-C treatment of diploid cells from healthy individuals. The induction of apoptosis by Apoptin in cancer-prone cells with a germ-line mutation in a tumor suppressor gene is UV dose-dependent and transient, just like many other UV-induced processes. These results suggest that Apoptin may be used as a diagnostic tool for detection of individuals with an increased risk for hereditary cancer and premalignant lesions.

INTRODUCTION

Many viruses have evolved genes encoding proteins that efficiently prevent the infected cells from entering apoptosis (1–3). On the other hand, a growing number of viruses actively induce apoptosis (2–4). We have reported that chicken anemia virus can induce apoptosis in infected hemopoietic cells of its natural host through the action of the viral protein VP3 (now named Apoptin; Ref. 5). Apoptin is a small protein of 121 amino acids that contains stretches rich in proline and basic amino acids and signals for nuclear localization and nuclear export but otherwise shows no sequence similarity to any known viral or cellular polypeptide (5–8).

The induction of apoptosis by Apoptin is independent of p53 and is stimulated rather than inhibited by overexpression of the antiapoptotic gene Bcl-2; it is not inhibited by a number of caspase inhibitors (9–11). The protein has the unique property of inducing apoptosis specifically in tumor cells and transformed cells, but not in normal diploid human cells (12). In addition, we recently observed that when normal diploid human cells are transfected with the Apoptin gene together with the transforming early region of SV40, the cells rapidly enter apoptosis (13). This shows that even brief expression of a transforming gene is sufficient to render normal cells susceptible to the apoptosis-inducing activity of Apoptin.

The latter results prompted us to examine whether exposure to other carcinogenic agents, such as UV or ionizing radiation, would also influence the response to apoptosis by Apoptin. The exposure of cells to DNA-damaging agents, such as radiation, results in transient activation of a whole array of responses, such as activation of signal transduction pathways, induction of expression of a variety of genes, stabilization of p53, inhibition of DNA replication and cell cycle arrest (14–17), and also a number of poorly defined phenomena that resemble SOS responses in bacteria, such as ER\(^{3}\) (3, 10) and enhanced mutagenesis (18). Although a single treatment with radiation clearly will not cause normal human diploid cells to become oncogenically transformed, the radiation does elicit the above-mentioned transient responses. Diploid human cells all respond in a basically similar way to radiation treatment, but certain diploid cells are known to react abnormally (18, 19). This is particularly clear in diploid fibroblasts from individuals who carry a germ-line mutation in a tumor suppressor gene and thus show a genetic predisposition to certain types of cancer. Such fibroblasts exhibit an unusually high ER response (ER\(^{super+}\)) but otherwise behave normally. This property has been found in cells from a variety of cancer-prone syndromes, such as LFS, DNS, and Lynch type-2 syndrome (19, 20), indicating that the loss of one allele of a tumor suppressor gene is sufficient to cause an unusually high ER response. On the other hand, normal or very low ER levels have been found in cells from patients with the cancer-prone DNA repair disorder XP and the non-cancer-prone DNA repair disorder TTD (19).

In the present study, we have examined the effect of UV-C or X-irradiation on the induction of apoptosis by Apoptin in both normal diploid human cells and cells from three different hereditary cancer-prone syndromes that carry germ-line mutations in tumor suppressor genes, as well as in cells from cancer-prone or non-cancer-prone DNA repair disorders. Fibroblasts from the cancer-prone syndromes carrying a germ-line mutation in a tumor suppressor gene reacted strongly and rapidly entered Apoptin-induced apoptosis both after UV-C irradiation and after treatment with X-rays. In contrast, radiation treatment did not render cells from healthy donors or from XP and TTD patients susceptible to Apoptin.

MATERIALS AND METHODS

Cell Strains. Diploid skin fibroblasts VH10 and VH25 were derived from healthy individuals (20). Cell strain 2675T, derived from a LFS patient, is characterized by a germ-line mutation in one allele of the p53 gene and an early onset of osteosarcoma (19, 21). A partial pedigree, the pattern of inheritance, and the clinical features of the family of the donor have been described by Srivastava et al (22). Cell strain 2525T, derived from the father of the LFS patient, has two wild-type p53 alleles and has a normal ER level (19, 23), whereas 2675T cells are ER\(^{super+}\) (19). Cell strains F9605 and F8928 (provided by Dr. W. Bergman, Department of Dermatology, Leiden University Medical Center, Leiden, the Netherlands) were derived from two patients with DNS (24–26). The donors of both F9605 and F8928 suffered from melanoma, and both cell lines are ER\(^{super+}\) (20). Cell strains 401 and 502 were established from members of a Lynch type-2 syndrome family with a high incidence of hereditary cancer and premalignant lesions.

The abbreviations used are: ER, enhanced reactivation; LFS, Li-Fraumeni syndrome; DNS, dysplastic nevus syndrome; XP, xeroderma pigmentosum; TTD, trichothiodystrophy; mAb, monoclonal antibody; DAPI, 4',6-diamidino-2-phenylindole; CMV, cytomegalo-virus.

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1 To whom requests for reprints should be addressed, at Leadd BV, P. O. Box 9503, 2300 RA, Leiden, the Netherlands. Phone: 31-71-5278736; Fax: 31-71-5271736; E-mail: noteborn@leadd.nl.
of breast, ovarian, colon, and stomach cancers (19). Subject 401 developed colon and bilateral breast cancer with meningiomas at the age of 46 years. Cell line 502 was derived from her daughter who, at the age of 25 years, is still cancer free. Thus far, no genetic information is available about any member of this family, but it is assumed that the Lynch type-2 syndrome is one of the cancer-prone diseases characterized by a germline mutation in some tumor suppressor genes (23). The ER response of these two cell lines is abnormally high (19). Cell strains XP6CA (complementation group C), XP21RO (complementation group C), and XP3NE (complementation group D) were derived from XP patients. The cells are hypersensitive to UV-C light and are characteristically defective in DNA repair, whereas the patients exhibit a strong predisposition to cancer in sun-exposed areas of the skin (27). Two cell strains, TTD3BR and TTD4BR, were obtained from individuals suffering from another DNA repair syndrome, TTD, in which defects in DNA repair do not give rise to tumor formation (28).

UV-C and X-Ray Irradiation. Before irradiation, the medium was removed and stored. The cultured cells were rinsed twice with PBS and irradiated with UV-C or X-rays. UV-C irradiation was performed with a 30-w low-pressure mercury germicidal lamp (predominantly 254 nm; model TUV; Philips Electronic Instruments Inc.) at a dose rate of 0.5 J/m²/s, which was monitored with an IL 770A germicidal-erythemal radiometer (International Light Inc., Newburyport, MA). The X-ray source was an Andrex 225 SMART apparatus (Andrex St, Copenhagen, Denmark), which was used at 200 kV and 4 mA with a 1-mm Al filter. Dose and dose rate were monitored with a PTW dosimeter. After irradiation, the stored medium was added, and the irradiated cultures were incubated for DNA transfection.

DNA Transfection and Indirect Immunofluorescence. All cells were grown on glass microscope slides to an approximately 40% confluence in 5-cm cultures were incubated for DNA transfection. In addition, UV irradiated with UV-C (10 J/m²) and then transfected with either plasmid pCMV-VP3, encoding Apoptin, or plasmid pCMV-Des, encoding desmin. At various time intervals after transfection, expression of desmin in transfected cells were studied by indirect immunofluorescence as described previously (12). The percentage of Apoptin- or desmin-positive cells was around 1% of the total cells.

RESULTS

Apoptin Induces Apoptosis in UV-C-treated Skin Fibroblasts from Individuals with Hereditary Cancer-prone Syndromes but not in Fibroblasts from Normal Humans. To establish whether UV-C irradiation can trigger Apoptin-induced apoptosis in normal human fibroblasts, cell cultures of VH10, VH25, and 2525T were irradiated with UV-C (10 J/m²) and then transfected with either plasmid pCMV-VP3, encoding Apoptin, or plasmid pCMV-Des, encoding desmin. At various time intervals after transfection, expression of Apoptin in the cells was monitored by indirect immunofluorescence with the use of Apoptin-specific mAbs 85.1 or 111.3, whereas the cells were screened for induction of apoptosis by nuclear DNA staining with DAPI, which was shown to correlate with other apoptotic characteristics such as oligonucleosomal DNA fragmentation (29).

In unirradiated cultures of normal fibroblasts VH10, VH25, and 2525T, 16–20% of Apoptin-expressing cells were irregularly stained with DAPI, indicative of apoptosis (Fig. 1A). This low level of apoptosis is most likely due to the transfection procedure, because cells expressing the negative control protein desmin exhibited the same low percentage of apoptosis (data not shown; Ref. 19). In all of these cells, Apoptin is expressed predominantly in the cytoplasm, as shown for VH25 cells (Fig. 2). After UV-C irradiation, the normal cells VH25, VH10, and 2525T, as expected, remained fully resistant to Apoptin-induced apoptosis. As can be seen in Fig. 3, in the normal cells (e.g., VH25), Apoptin was primarily localized in the cytoplasm after UV-C treatment.

Next we investigated the effect of UV irradiation on Apoptin-induced apoptosis in fibroblasts from the cancer-prone syndromes LFS, DNS, and Lynch type-2 syndrome. Fig. 1A shows that in unirradiated cells, the 15–20% levels of apoptosis were similar to those in normal cells, and Apoptin was localized in the cytoplasm (Fig. 2). After UV-C irradiation, however, the cancer-prone cells 2675T, F9605, F8928, 401, and 502 rapidly underwent Apoptin-induced apoptosis after UV-C irradiation (Fig. 1B). In cancer-prone cells (e.g., 2675T, F9605, and 401), in contrast to healthy cells, Apoptin was concentrated in the nuclei (Fig. 3). In the same cell preparations, only 2–3% of the cells not expressing Apoptin showed apoptotic characteristics (data not shown). Expression of desmin in the same cells irradiated with UV-C caused a background level of 12–20% of apoptosis (Fig. 1C), which ruled out the possibility that apoptosis induction in the cancer-prone cells (Fig. 1B) is due to the effect of UV irradiation and/or the transfection procedure.

UV Dose Response of Apoptin-induced Apoptosis. In addition, we examined whether the unusual effect of UV-C irradiation on these cancer-prone cells could also be caused by a higher UV dose in normal cells. To that end, we determined the UV dose effect on Apoptin-induced apoptosis in the cancer-prone cell lines [2675T (LFS), F9605 (DNS), and 401 (breast/ovarian cancer syndrome)] and in normal VH10 cells. The cells were irradiated with various doses of UV-C (0, 5, 10, 15, 20, or 25 J/m²) and transfected the next day with either plasmid pCMV-VP3 or pCMV-Des. Four days after transfection, the cells were fixed and analyzed for the induction of apoptosis.

As shown in Fig. 4, A–C, at a low dose of 5 J/m², cell strains 2675T, F9605, and 401 displayed hardly more Apoptin-induced apoptosis than the unirradiated cells. However, at doses of ≥10 J/m², almost all of these cells rapidly underwent apoptosis. In contrast, normal VH10 cells did not display UV-dose-dependent Apoptin-induced apoptosis (Fig. 4D), indicating that cancer-prone cells responded differently.
from the normal cells. In the same cell cultures, the expression of desmin as a negative control caused a slight induction of apoptosis, which was probably due to the apoptotic effect of UV-C light at higher doses (Fig. 4, A–D).

**Time Course of Apoptin-induced Apoptosis.** To determine whether the effect of Apoptin in the cancer-prone cells is a transient phenomenon, we investigated the induction of apoptosis by Apoptin in VH10 normal cells and in cancer-prone 2675T, F9605, and 401 cells at various time intervals after UV-C (10 J/m²) irradiation. At each time point (0, 6, 12, and 24 h and 2, 4, and 6 days) after UV-C irradiation, DNA transfection was performed, and cells were fixed and analyzed 4 days later for Apoptin-induced apoptosis.

As can be seen in Fig. 5, cell strains 2675T, F9605, and 401 underwent Apoptin-induced apoptosis when transfected immediately after UV-C irradiation. Transfection of these cells within the first 24 h after UV-C exposure resulted in apoptosis percentages of 91–96% measured 4 days after transfection with the Apoptin gene. Transfection at later time points, however, led to a gradual decrease of Apoptin-induced apoptosis in all three cancer-prone cell lines. Six days after UV-C exposure, apoptosis induction reached the same level as that in normal VH10 cells (Fig. 5).

These results indicate that the susceptibility to Apoptin in UV-C-irradiated cancer-prone cells is a transient phenomenon that is maximally expressed within 1 day after UV treatment.

**X-ray Treatment of Cells from Hereditary Cancer-prone Patients also Results in Apoptin-induced Apoptosis.** In addition, we have also examined the effect of X-ray treatment on apoptosis induction by Apoptin in human diploid cells. Before transfection, part of the cell cultures was treated with X-rays (dose, 5 Gy). Diploid fibroblasts derived from healthy individuals (VH10) or from persons with a hereditary cancer-prone syndrome (LF2675 and 401) were transfected with a plasmid encoding Apoptin. As a negative control, the cells were transfected with a plasmid encoding the protein desmin.

Table 1 shows that all analyzed nonirradiated cells (VH10, LF2675, and 401) did not show Apoptin-induced apoptosis. In combination with X-ray treatment, however, the cell lines derived from the cancer-prone individuals underwent apoptosis, whereas those derived from healthy persons did not. Five days after transfection, the majority of the X-ray-treated Apoptin-positive cancer-prone cells had become apoptotic. As a control, the cells treated with X-rays and expressing the nonapoptotic protein desmin did not become apoptotic.

UV-C-exposed Cells from Individuals with DNA Repair Disorders Are Not Susceptible to Induction of Apoptosis by Apoptin. To investigate whether fibroblasts from individuals with the cancer-prone DNA repair disorder XP become responsive to Apoptin after exposure to UV-C, three cell strains, XP6CA, XP21RO, and XP3NE (complementation groups C, C, and D, respectively), were studied. One day before transfection, the cells were irradiated with a low dose of 1.0 J/m², because they are very sensitive to UV-C irradiation (19).

The results showed that Apoptin-expressing cells did not exhibit higher levels of apoptosis at 4 days after transfection than cells expressing desmin (data not shown). To rule out the possibility that the UV dose of 1 J/m² was too low, we also irradiated the cells with UV doses varying between 0.5 and 6 J/m². Fig. 6 shows that the levels

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**Fig. 2.** Localization of Apoptin in nonirradiated human VH25, 2675T, F9605, and 401 fibroblasts. Cells were transfected with pCMV-VP3, and indirect immunofluorescence was carried out 4 days after transfection. Left panels, localization of Apoptin, which was detected with mAb 85.1. Right panels, DNA staining with DAPI (original magnification, ×1250).

**Fig. 3.** Induction of apoptosis by Apoptin in UV-C-irradiated human VH25, 2675T, F9605, and 401 fibroblasts. One day after UV-C (10 J/m²) administration, irradiated cells were transfected with pCMV-VP3 and analyzed with indirect immunofluorescence at 4 days after transfection. Left panels, localization of Apoptin. Right panels, DNA staining with DAPI (original magnification, ×1250).
of apoptosis induction at each UV dose were similar in Apoptin- and desmin-transfected cells. The cell strain XP3NE is particularly sensitive in these assays, presumably due to its high UV susceptibility. In addition, DAPI staining of the UV-treated cells shows that they already exhibit apoptosis without expressing Apoptin (Fig. 7). In contrast to cancer-prone cells carrying a germ-line mutation in a tumor suppressor gene, in XP cells, Apoptin is situated in the cytoplasm when the cell starts to undergo apoptosis. These results indicate that UV treatment itself induces apoptosis in XP cells, but not Apoptin.

In addition to XP cells, we have also investigated the effect of UV-C irradiation on Apoptin-induced apoptosis in cells from individuals suffering from the non-cancer-prone DNA repair disorder TTD. Two TTD cell lines, TTD3BR and TTD4BR, were treated with UV-C (8 J/m²) and transfected 1 day later with a plasmid encoding either Apoptin or desmin. No significant Apoptin-induced apoptosis was observed in the TTD cells, even after UV-C treatment. Expression of desmin in UV-C-irradiated TTD3BR and TTD4BR cells also did not result in apoptosis (data not shown).

**DISCUSSION**

In the present study, we show that UV-C irradiation of normal diploid fibroblasts does not sensitize them to the apoptosis-inducing activity of Apoptin; however, irradiation of fibroblasts of a certain category of cancer-prone individuals renders the cells susceptible to Apoptin.

We were prompted to test the effect of UV irradiation in cells from cancer-prone syndromes by the observation that diploid human fibroblasts are normally resistant to the apoptosis-inducing activity of Apoptin but become susceptible when they are transfected with the transforming large T gene of SV40 (13). This indicated that stable transformation is not required for triggering Apoptin sensitivity, but that the immediate effects of SV40 T antigen expression are sufficient to sensitize the cells to Apoptin. The question then arose as to whether exposure to a carcinogenic agent would have an effect similar to the expression of a transforming viral gene. Although it was clear that a single exposure to a mutagenic/carcinogenic agent, such as UV light, will probably not transform even a single fibroblast in an irradiated culture, it nevertheless seemed to be of interest to examine the effect of UV irradiation on the cellular response to Apoptin. UV light activates a large number of (mostly transient) cellular responses, collectively called stress responses. It was conceivable that these responses also would affect the interaction with Apoptin. Our present results with the diploid fibroblasts from normal individuals clearly show that this is not the case. Surprisingly, however, diploid fibroblasts from the five cancer-prone individuals tested became fully responsive to Apoptin after UV irradiation but are nonresponsive without UV treatment. The cancer susceptibility of the individuals from whom the cells were derived is caused by germ-line mutations in tumor suppressor genes: (a) one mutated allele of the p53 gene and one wild-type allele (2675T cells from a LFS patient); (b) two mutant alleles of p16INK4a (F9605 and F8928 cells from DNS/multiple melanoma patients); and (c) an unknown gene defect in the 401 and 502 cells from members of a family with Lynch type-2 syndrome. Although it is not yet known which gene is mutated or deleted in cells from the latter syndrome, it is likely that a tumor suppressor gene is involved.

The UV-induced sensitivity to Apoptin correlates with a strongly enhanced induction by UV of the ER response (ERsupert +; Refs. 19 and 20). We have previously shown that high ER responses are also found in UV-irradiated fibroblasts from a variety of other cancer-prone syndromes, but not in fibroblasts from normal donors. Our observa-
tions with the fibroblast strains from the three cancer-prone syndromes predict that fibroblasts from other cancer-prone syndromes that show high ER will also become susceptible to Apoptin after UV irradiation. If this turns out to be the case, UV-induced sensitization to Apoptin could possibly be used as an easy diagnostic marker to identify individuals with an increased cancer risk due to a germ-line mutation of a tumor suppressor gene.

The intriguing question of why cells that have lost one or both alleles become sensitive to Apoptin after UV irradiation remains. Previous work has shown that UV exposure of cells from cancer-prone individuals causes normal induction of all stress responses studied except ER, which is induced much more strongly than in normal cells. We now show that these cells exhibit a second abnormal response, the sensitization by UV light and X-rays to the apoptosis-inducing activity of Apoptin. Both the high ER response and the susceptibility to Apoptin are transient, reaching a maximum value 1 day after UV treatment, and disappear again after 4–6 days. Sensitization to Apoptin is accompanied, as usual, by the translocation of the protein from the cytoplasm to the nucleus. This indicates that this category of diploid cells can undergo a transient tumor cell-specific alteration with respect to intracellular Apoptin localization that is not found in normal diploid cells (12).

UV-induced sensitization to Apoptin is not found in diploid fibroblasts from XP patients. XP patients are strongly predisposed to skin cancer, but the tumors appear only in areas of the skin that are exposed to sunlight (UV light). Hence, tumor formation is thought to be caused by a high incidence of UV-induced mutations (30). Indeed, the Apoptin protein does not translocate from the cytoplasm to the nucleus in XP cells, even at 4 days after UV treatment, when the level of apoptosis induction in fibroblasts with a mutation in tumor suppressor genes approaches 100%. Apparently, the tumor proneness in the two categories of syndromes (germ-line mutation of one or both alleles of a tumor suppressor gene versus homozygous mutation of both alleles of a DNA repair gene) has different origins. The mechanism responsible for the abnormal UV-induced response to Apoptin in fibroblasts from cancer-prone syndromes is unknown. A possible explanation could be that the products of (certain) tumor suppressor genes play a role in negative regulation of some but not all radiation-induced stress responses. Reduced levels of a tumor suppressor gene product could then result in an increased stress response. This might be an explanation for the high ER levels observed. However, the relationship between the levels of tumor suppressor proteins and the radiation-induced response to Apoptin appears to be different. Diploid cells from normal individuals do not exhibit the UV-induced response to Apoptin at all, even at doses of 25 J/m², although they do show an ER response. Diploid cells from cancer-prone individuals also fail to respond to UV in doses of up to 5 J/m², but they become fully sensitized to Apoptin at doses of 10 J/m² or more. Thus, induction of the latter phenotype requires a certain radiation threshold for the effect to become apparent and is completely absent in normal fibroblasts. Hardly any induction of ER is observed in normal cells at 5 J/m², which also indicates a certain threshold for induction of the ER response. The present findings show that fibroblasts from cancer-prone syndromes with mutations in tumor suppressor genes exhibit at least two abnormal radiation-induced responses, higher ER and sensitization to Apoptin. Whether these responses or as yet undiscovered, abnormal responses play a role in the cancer predisposition associated with these genetic syndromes is unclear.

We have previously reported that normal cells are resistant to the cell-killing effect of Apoptin and that in such cells, the protein is...
localized mainly in the cytoplasm. In contrast, tumor cells are susceptible to Apoptin and show nuclear localization of the protein. Hence, the critical event in the UV-induced sensitization of the cancer-prone cells to Apoptin may be the translocation of the protein from the cytoplasm to the nucleus. Apparently, there are two conditions in normal diploid cells that can lead to Apoptin translocation and apoptosis induction: (a) expression of a viral transforming gene (SV40 large T); and (b) mutation of at least one allele of a tumor suppressor gene combined with radiation treatment. At present, it is not clear whether molecular events are responsible for the translocation of the Apoptin protein.

Because sensitivity to Apoptin is a trait characteristic of tumor cells, it is tempting to speculate that (some of) the abnormal responses contribute to cancer proneness and hence that cancer predisposition is not caused only by the high probability that the remaining wild-type allele of a tumor suppressor gene becomes inactivated. Factors other than the loss of an allele of a tumor suppressor gene may play a role in cancer susceptibility, as was recently suggested by an observation by Venkatachalam et al. (31). These authors showed that a considerable fraction of the spontaneous tumors arising in heterozygous p53 knockout mice have retained the wild-type p53 allele in a functional state. Hence, the high incidence of cancer in the p53+/− mice cannot be explained exclusively by the high probability of the remaining wild-type allele becoming inactivated. Another indication that stress responses and cancer predisposition are connected was suggested by our previous observation on the occurrence of UV-induced stress responses in cells from XP patients. Whereas the majority of fibroblasts from XP patients show the same level of UV-induced stress responses as normal cells (except that much lower UV doses are used in XP cells than in normal cells), a small fraction of XP cells was found to lack the ER response. Consultation of the case histories of the patients from whom the cells were obtained revealed that they showed the characteristic properties of XP patients, except that they had not developed skin cancer (19, 32), despite the relatively advanced age of some of them. Similar results were obtained with cells from UV-sensitive TTD patients who also fail to develop skin cancer: these cells also turned out to be ER− (33). These data also suggest a correlation between ER and cancer predisposition, i.e., the absence of ER correlates with an apparent cancer resistance.

The results of the present study have revealed not only a novel activity of the Apoptin protein but also an unexpected property of normal fibroblasts from individuals with a high cancer predisposition due to mutation of a tumor suppressor gene. We are presently using the data in attempts to elucidate the molecular basis of Apoptin action and of the radiation-induced changes in the cancer-prone fibroblasts.

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