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Similar Nucleotide Excision Repair Capacity in Melanocytes and Melanoma Cells

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Abstract

Sunlight UV exposure produces DNA photoproducts in skin that are repaired solely by nucleotide excision repair in humans. A significant fraction of melanomas are thought to result from UV-induced DNA damage that escapes repair; however, little evidence is available about the functional capacity of normal human melanocytes, malignant melanoma cells, and metastatic melanoma cells to repair UV-induced photoproducts in DNA. In this study, we measured nucleotide excision repair in both normal melanocytes and a panel of melanoma cell lines. Our results show that in 11 of 12 melanoma cell lines tested, UV photoproduct repair occurred as efficiently as in primary melanocytes. Importantly, repair capacity was not affected by mutation in the N-RAS or B-RAF oncogenes, nor was a difference observed between a highly metastatic melanoma cell line (A375SSM) or its parental line (A375P). Lastly, we found that although p53 status contributed to photoproduct removal efficiency, its role did not seem to be mediated by enhanced expression or activity of DNA binding protein DDB2. We concluded that melanoma cells retain capacity for nucleotide excision repair, the loss of which probably does not commonly contribute to melanoma progression. Cancer Res; 70(12); 4922–30. ©2010 AACR.

Introduction

UV light from the sun causes a variety of lesions in the genome that distort the structure of DNA, resulting in blocks to gene transcription and DNA replication. Epidemiologic evidence strongly indicates that UV-induced DNA damage is a primary cause of skin cancer, including melanoma (1, 2), an aggressive form of skin cancer that arises from specialized pigmented cells called melanocytes. Although comprising only 5% to 10% of human skin, melanocytes synthesize the pigment melanin, which provides skin tone, hair color, and protection from UV radiation. The significant increase in incidence strongly indicates that UV-induced DNA damage is a primary cause of skin cancer, including melanoma (3, 4) therefore merit thorough investigations of the underlying causes of melanoma initiation and progression.

Among the lesions induced by UV, cyclobutane pyrimidine dimers (CPD; 80–90%) and [6-4] pyrimidine-pyrimidone photoproducts ([6-4] PP; 10–20%) are most abundant, although both can be accurately removed from the genome by nucleotide excision repair (henceforth termed "excision repair"). This well-characterized repair system responds to a variety of environmental and chemotherapeutic agents that form bulky adducts in DNA and, in humans, is the sole mechanism for removal of CPDs and [6-4] PPs from DNA (5). Impor-}

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CDKN2A locus (17–19). Therefore, alterations of p53-dependent pathways have the potential to influence melanoma progression.

In contrast, although there is some evidence linking a polymorphism in the excision repair gene XPD and susceptibility to cutaneous melanoma (20), there is little available data indicating that altered expression of excision repair genes contributes to melanoma, and indeed, a recent microarray analysis of mRNA expression profiles in metastatic melanomas did not find changes in excision repair genes (21). Although analyses of mRNA transcript and protein expression profiles have the potential to be informative, it may be more relevant to test for functional excision repair capacity to make proper correlations of DNA repair and carcinogenesis. Along these lines, although early work initially indicated that melanoma cells did not show enhanced repair rates (22), other work suggested that subclones of a metastatic melanoma line did indeed show elevated repair rates in comparison with nonmelanoma cells, and this repair correlated with increased survival after UV (23). An additional study similarly concluded that DNA repair capacity in mouse melanoma cell lines correlated with metastatic potential (24). However, more recent in situ work indicated that cutaneous melanoma patients show normal repair kinetics (25). It is therefore unclear whether excision repair capacity is altered in melanoma cells relative to normal melanocytes or whether genetic background (B-RAF/N-RAS/p53 status) or metastatic potential is directly correlated with excision repair capacity.

In this study, we used normal human melanocytes (NHM) and a variety of melanoma cell lines to characterize excision repair capacity as a function of genetic and metastatic states. Our results show that in nearly all melanoma cell lines tested, excision repair occurred as efficiently as in NHMs, irrespective of mutations in the N-RAS and B-RAF oncogenes. In addition, we found no change in excision repair capacity in a highly metastatic melanoma cell line (A375SM) compared with its parental melanoma cell line (A375P), which has a low metastatic potential. Lastly, we observed that melanoma cell lines containing functional p53 repair UV photoproducts more efficiently than cells with inactive p53 but that this difference seems to be not due to enhanced levels of the UV photoproduct binding protein DDB2.

Materials and Methods

Cell lines

Description of the sources, culture method, and UV irradiation of the melanoma cell lines is provided in Supplementary Table S1. All of the cell lines used in our study are authenticated by microarray analysis as described previously (13). Secondary cultures of NHMs were derived as reported previously (26). Briefly, these cells (NHM16 and NHM21) were grown in Medium 254 (Life Technologies) containing human melanocyte growth supplement (HMGS-1; Life Technologies) at 37°C in a cell culture incubator with 5% CO2. A375P and A375SM cell lines were a gift from Dr. Richard O. Hynes (Massachusetts Institute of Technology, Cambridge, MA).

UV irradiation

Culture medium was removed from exponentially growing cells and set aside, and then cells were washed once with warm PBS before placement under a GE germicidal lamp emitting primarily 254-nm UV light (UV-C) connected with a digital timer. After receiving the indicated dose of UV (typically 5–20 J/m², as indicated), culture medium was added back to the cells, which were subsequently placed back into the cell culture incubator for the indicated length of time. A UV-C sensor (UV Products) was used to calibrate the fluence rate of the incident light.

Immunoslot blot assay for measurement of CPD and [6-4] PP repair in vivo

Repair of CPDs and [6-4] PPs by immunoslot blot was performed essentially as reported previously (27).

Fluorescence microscopy

Immunofluorescence microscopy was performed as described previously (28). Briefly, cells were cultured in 35-mm glass-bottom dishes (MatTek) for 24 hours before UV irradiation (10 J/m²). Cells harvested at various time points after irradiation were fixed with 4% formalin and further treated with ice-cold detergent (0.5% Triton X-100) for 5 minutes. After denaturation of DNA with 2 mol/L HCl for 30 minutes at room temperature, CPDs were detected with the mouse monoclonal anti-CPD antibody (Kamiya Biomedical) and Alexa Fluor 488 goat anti-mouse IgG conjugate (Invitrogen). Nuclear DNA was counterstained with propidium iodide, and CPD signals were observed with a Leica inverted DMIRB fluorescence microscope.

Measurement of [6-4] PP repair activity in cell-free extracts

Preparation of radiolabeled substrate and the in vitro excision repair assay was essentially as previously described (27, 29). Cell-free extracts for use in the excision assay were prepared as reported (30).

Immunoblot analyses

Protein lysates from exponentially growing cultures of cells were harvested and analyzed by SDS-PAGE and immunoblotting as described elsewhere (26). The following antibodies were used to detect the respective proteins: XPA, XPC, RPA70, TFIH (p62 subunit, XBP), p53, and actin (Santa Cruz Biotechnology); p21, DDB2, and GAPDH (Cell Signaling Technology, Inc.); RPA34 (Calbiochem); and XPF and XPG (Abcam).

siRNA transfection

Exponentially growing cells of SK-Mel-103 or SK-Mel-187 were transfected with either p53 siRNA (Santa Cruz Biotechnology) or nontargeting siRNA (Dharmacon) using Lipofectamine RNAiMAX (Invitrogen) transfection reagent. Cells were UV irradiated 48 hours after transfection and then harvested at the indicated time points to assay for CPD repair.
Electrophoretic mobility shift assay for UV-DDB binding activity

UV-DDB binding activity was performed using cell-free extracts from both SK-Mel-103 and SK-Mel-187 cell lines as reported previously (30–33). Briefly, 5 fmol of 136-bp dsDNA containing a [6-4] PP were incubated with the indicated amount of proteins or cell-free extract in 12.5 μL of reaction mixtures. After a 30-minute incubation at 30°C, glycerol was added to ~8%, and reaction mixtures were resolved using 5% native PAGE at room temperature with a constant current (25 mA). DNA binding was visualized by autoradiography and quantified using ImageQuant 5.2 software (Molecular Dynamics). Recombinant UV-DDB protein was used as a positive control for DDB binding activity (31).

Matrigel invasion assay

Cellular invasion assays were performed using 8.0-μm pore size Biocoat Matrigel Invasion chambers (BD Biosciences) as described by the manufacturer. Each data point represents the average of three independent experiments and error bars represent the SD of the mean.

Results

Measurement of [6-4] PP repair in vitro

Epidemiologic evidence suggests a strong correlation between exposure to UV from the sun and development of melanoma in humans (22, 34, 35), and we therefore sought to investigate whether the capacity to repair UV photoproducts differs between NHMs and melanoma cell lines. Our initial approach used an in vitro, cell-free excision assay to measure excision repair. Our laboratory has used this assay extensively to study the mechanism of nucleotide excision repair and to measure repair capacity in mammalian cell lines and tissues (29, 36). The assay involves incubation of an internally 32P-labeled oligonucleotide containing a site-specific [6-4] PP in cell-free extract and then electrophoresis of the purified DNA on a denaturing gel, which allows visualization and quantitation of the small 24- to 32-nucleotide-long oligomers that are generated during the repair reaction (Fig. 1A). Although the assay has been used with extracts from a variety of mammalian cell types and tissues, it has not previously been applied to measure repair in melanocytes or melanoma cells, a physiologically relevant and medically important target of UV-induced DNA damage.

Our initial studies focused on two NHM lines (NHM16 and NHM21) and two cell lines each from melanoma cells containing normal or mutant forms of the B-RAF and N-RAS oncogenes [wild-type (WT): SK-Mel-187 and RPMI8322; N-RAS: SK-Mel-103 and VMM39; B-RAF: A2058 and A375]. Using cell-free extracts prepared from the indicated cell lines, we observed variable amounts of [6-4] PP removal among the different melanoma lines (Fig. 1B), ranging from ~1% in the RPMI8322 line and up to ~12.5% in A375 cells (Fig. 1C). This variation is consistent with previous reports showing that human melanomas show a high degree of interindividual variability in excision repair in situ (25). Importantly, immunoblot analyses of these extracts showed no clear correlation between excision repair capacity and expression level of any specific excision repair protein (Supplementary Fig. S1).

Interestingly, we observed very little excision activity in the extracts from the NHMs. To better understand this lack of excision repair activity with this assay, we supplemented extracts from excision-competent A375 and Chinese hamster ovary (CHO) cells, which do not contain detectable level of melanin (Supplementary Table S2), with either NHM16 or NHM21 extract. As shown in Supplementary Fig. S2A, both NHM extracts inhibited the excision activity of A375 and CHO extracts, indicating the presence of an inhibitory factor.
in the NHM extract. We considered that the presence of melanin in the NHM extracts might interfere with the *in vitro* excision activity. To test for the effect of melanin, we titrated CHO cell-free extract with increasing amounts of synthetic melanin and observed a concentration-dependent inhibition of excision repair (Supplementary Fig. S2B). This inhibition was not specific to excision repair, however, as the ability of restriction enzymes to digest the substrate was also inhibited by melanin (Supplementary Fig. S2C), indicating that melanin may nonspecifically bind to DNA and inhibit the action of multiple nucleases. We conclude, however, that although the excision assay is a convenient and reliable tool for measuring repair capacity in many cell lines, including melanoma cells, it cannot be used for all cell types, such as melanocytes.

**Measurement of [6-4] PP repair *in vivo***

We next used an immunoslot blot assay to monitor removal of [6-4] PPs in NHMs and melanoma cell lines. This assay involves the immobilization of genomic DNA from cells at various times after UV irradiation onto a nitrocellulose membrane and then immunoblotting with antibodies that specifically recognize either CPDs or [6-4] PPs (37). As shown in Fig. 2A, we observed a time-dependent reduction in anti-[6-4] PP antibody reactivity in genomic DNA from both the NHMs and the melanoma cell lines, at rates near those previously reported for other cell types (38), with typically 50% to 80% of [6-4] PPs removed within 2 hours in the various cell lines (Fig. 2B). Importantly, we observed very similar [6-4] PP signals in the UV-irradiated melanocytes and melanoma cells before repair, indicating that similar numbers of photoproducts were induced by UV. Cell lines lacking or containing mutations in the *B-RAF* and *N-RAS* oncogenes repaired [6-4] PPs at similar rates, indicating that mutation of these oncogenes does not significantly affect excision repair. Interestingly, when we compared the relative amount of [6-4] PP repair in the immunoslot blot assay (Fig. 2A and B) with repair in the *in vitro* excision assay (Fig. 1) among the six melanoma cell lines tested, we observed a strong correlation ($R^2 = 0.91$) between the two assays (Fig. 2C), indicating that the two approaches are reliable measures of [6-4] PP repair capacity.

**Measurement of CPD repair *in vivo***

We next measured CPD repair in the same set of cell lines. CPDs constitute the majority of UV photoproducts in DNA.
and are recognized and repaired by the excision repair machinery more slowly than for [6-4] PPs and inefficiently in the in vitro excision assay, making quantitative comparison of CPD repair with the excision assay difficult. Therefore, we solely relied on the slot blot assay for in vivo repair. As displayed and quantified in Fig. 3A, with the exception of RPMI8332 cells, which repaired CPDs very inefficiently, all the other cell lines removed 40% to 80% of CPDs within 12 hours. Importantly, the two NHM lines showed very similar CPD repair kinetics with three of these melanoma lines, indicating that melanocytes and melanoma cells repair UV photoproducts with similar kinetics. The RPMI8332 melanoma line, which repaired [6-4] PPs least efficiently in both the in vitro excision assay (Fig. 1) and the in vivo slot blot assay (Fig. 2), seemed to lack any CPD repair capacity, with only ∼4% of CPDs removed within 12 hours (Fig. 3A). To confirm this inefficient repair phenotype, we used immunofluorescence microscopy to detect CPD formation and removal in the repair-deficient RPMI8332 line and the repair-proficient line SK-Mel-187. Very little CPD removal was observed in RPMI8332 cells by immunofluorescence (Fig. 3B), consistent with the results of the immunoslot blot assay.

Because we observed a significant difference in CPD repair in RPMI8332 and SK-Mel-187 cells, both of which are WT for both B-RAF and N-RAS, we decided to measure CPD removal in six additional melanoma lines with WT forms of these genes. As shown in Fig. 3C, all six lines displayed CPD removal rates comparable with SK-Mel-187 and the other cell lines and were unlike that seen in the RPMI8332 cells. Although the cause of the inefficient CPD and [6-4] PP removal in RPMI8332 cells is not known, we conclude that the repair deficiency is not characteristic of melanoma cells that are WT for both B-Raf and N-Ras. Interestingly, RPMI8332 cells were also significantly more sensitive to UV than the other cell lines in a colony formation assay (Supplementary Fig. S3). This line has high level of chromosomal instability and some unusual growth properties as the cells undergo massive cell death on reaching confluency, suggesting that inefficient repair is secondary to gross dysregulation of many pathways.

**p53 contributes to CPD repair efficiency in melanoma cells**

Although the tumor suppressor p53 has been shown to contribute to CPD repair rates and UV survival in human skin fibroblasts and other cell types (14, 38), other work has indicated no effect of p53 deficiency on UV photoproduct repair in keratinocytes (39). We therefore sought to examine
Figure 4. Analysis of p53 and DDB2 functionality and in melanoma cells and melanocytes. A, Western blot analyses were performed with extracts from the indicated cell lines harvested at various times after UV irradiation (12.5 J/m²) to monitor p53 functionality, as determined by induction of p21 and DDB2 protein expression. B, based on p53 functionality determined in A, CPD repair measurements for the individual cell lines (Fig. 3) were pooled and reanalyzed as a function of p53 status. Columns, average of CPD repair for the seven p53 mutant cell lines (RPMI was excluded) and four p53 WT cell lines; bars, SD. Asterisks indicate a statistically significant difference (P < 0.01, two-tailed Student's t test) in CPD repair between p53 mutant and WT cell lines. C, knockdown of p53 in SK-Mel-103 cells inhibits CPD repair. SK-Mel-103 (p53 WT) and SK-Mel-187 (p53 mutant) cells were transfected with nontargeting or p53 siRNAs and exposed to UV, and CPD repair was measured at the indicated time points. D, electrophoretic mobility shift assay of UV-DDB binding to damaged DNA. Cell-free extract from SK-Mel-103 (p53 WT) and SK-Mel-187 (p53 mutant) cells was incubated with radiolabeled [6-4] PP substrate DNA, and complexes were separated on a 5% nondenaturing gel. Purified UV-DDB complex was used as a positive control and CHO-AA8 extract as a negative control. The cell-free extract protein concentrations ranged from 0.5, 1.0, 2.0, or 4.0 μg per reaction. The experiment was repeated thrice, and the average percent binding is indicated.
p53 functionality in normal melanocytes and melanoma cell lines to determine whether p53 status may influence CPD repair in melanoma. Because p53 mutation status has only been characterized in a subset of these lines (13, 40), we tested p53 functionality by immunoblotting extracts from nonirradiated or UV-irradiated cells for UV-induced expression of p53 and its transactivation targets p21 and DDB2. As shown in Fig. 4A, p53 functionality varied among the different cell lines but exhibited normal responses in the normal melanocytes and in four of the melanoma lines (SK-Mel-103, A375, SK-Mel-5, and Mel-537). With this information, we then reexamined the CPD repair data for the melanoma cell lines presented in Fig. 3 by combining the repair data among the cell lines based on p53 status. Interestingly, we observed significantly more CPD repair in cells with WT, functional p53 compared with cells with mutant or inactive p53 (Fig. 4B). Although less pronounced, [6-4] PP repair also correlated with p53 functionality (Supplementary Fig. S4). To confirm the positive role for p53 in excision repair, we transfected p53-positive SK-Mel-103 and p53-inactive SK-Mel-187 cells with either a nontargeting control siRNA or a siRNA targeting p53 and then measured CPD repair. Consistent with the pooled cell line data shown in Fig. 4B, knockdown of p53 in SK-Mel-103 cells, which did not have measurable effect on DDB2 level (Supplementary Fig. S5), resulted in less CPD removal near the level observed in p53-inactive SK-Mel-187 cells (Fig. 4C). Based on these results, we conclude that p53 contributes to UV photoproduct removal in human melanoma cell lines.

A role for p53 in excision repair has been reported to be due to transcriptional induction of the XPE gene encoding the DDB2 protein (41), which in the form of UV-DDB (DDB1-DDB2 heterodimer) directly binds to UV photoproducts. We therefore used an electrophoretic mobility shift assay (32, 33) to examine UV-DDB functionality in SK-Mel-103 and SK-Mel-187 cell extracts. As shown in Fig. 4D, we observed similar levels of binding to an oligonucleotide containing a [6-4] PP in both extracts, but not in extract from CHO cells, in which the XPE (DDB2) gene is transcriptionally repressed (14). The levels of UV-DDB activities in SK-Mel-103 and SK-Mel-187 were similar 6 hours after UV but slightly higher in SK-Mel-103 24 hours after UV (Supplementary Fig. S6), by which time all of the CPDs were removed in both cell lines. Thus, we conclude that although p53 contributes to the removal of UV lesions in DNA, UV-DDB does not seem to be a major contributor through which p53 promotes repair in melanoma cells.

Excision repair in highly metastatic melanoma cells

We next wished to address whether metastatic state in melanoma contributes to the efficiency of nucleotide excision repair because a previous report indicated that UV photoproduct removal occurred more rapidly in highly metastatic murine melanoma cells (24). However, because the repair assay used in that study did not directly measure repair of UV-damaged genomic DNA, we reexamined whether excision repair capacity is altered in melanoma cells of different metastatic states by comparing [6-4] PP and CPD removal in A375 cells and a derivative line with a higher metastatic potential (A375SM). As previously reported (42), we confirmed that A375SM cells are more invasive than its parental A375 line (A375P; Fig. 5A). We then examined the protein expression levels of excision repair factors and found no significant difference between the two lines (Fig. 5B). Consistent with the similar expression levels, both A375P and A375SM cells repaired [6-4] PPs and CPDs at similar rates (Fig. 5C). We conclude from these results that metastatic state does not necessarily alter nucleotide excision repair capacity in melanoma cell lines.

Discussion

Melanoma is the most deadly form of skin cancer and in industrialized countries is rapidly growing in prevalence (43). Based on the high rates of melanoma in patients with XP, most of whom lack one of the essential excision repair factors, the development or progression of melanoma may be associated with a reduced capacity for excision repair. However, here, we show that excision repair capacity in NHMs is very similar to that in melanoma cells (Figs. 2 and 3),
irrespective of B-RAF and N-RAS status, suggesting that altered repair capacity may not be a predominant cause of melanoma initiation or progression.

Tumors from metastatic melanoma patients are characterized by significant resistance to DNA-damaging agents, such as cisplatin, decarbazine, and melphalan (23), suggesting a broad underlying resistance to the effects of DNA damage. Although one report indicated that mouse melanoma cells with high metastatic potential exhibited elevated excision repair capacity (24), the study used an indirect measure of DNA repair. By monitoring the direct removal of CPDs and [6-4] PPs from genomic DNA in human A375 cells and a supermetastatic derivative cell line (A375SM), here, we observed no difference in nucleotide excision repair efficiency (Fig. 5). We conclude that metastatic potential and excision repair capacity are not directly related to one another.

In contrast, our results do show that the functionality of the tumor suppressor p53 is an important determinant of UV photoproduct repair efficiency in melanoma cells (Fig. 4; Table 1). These results are consistent with a variety of data from other cell types, including normal human fibroblasts (38, 39), although, importantly, our results provide the first evidence that p53 status affects excision repair specifically in melanoma cells. Although only 1% of primary melanomas and 5% of metastatic melanomas show mutations in the p53 gene (15, 16, 44), the common loss of ARF function in metastatic melanomas with deletion of the CDKN2A locus (17–19) suggests that p53-dependent processes may contribute to melanoma development. Because p53 regulates many components of the cellular response to DNA damage induced by UV irradiation, including DNA repair, cell cycle checkpoint, and apoptosis, it is not clear how its many diverse functions ultimately control cell fate in melanoma. Similarly, although our data do not indicate that p53 regulation of DDB2 influences excision repair in melanoma cells, DDB2 may contribute to other aspects of the UV response in melanocytes or melanoma, such as cell survival and apoptosis (45, 46).

Inefficient UV photoproduct repair has also been shown in cells with mutations in the melanocortin 1 receptor (MC1R), which acts upstream in the microphthalmia-associated transcription factor (MITF) signaling pathway of eumelanin biosynthesis (47), and in cells with deletion of the CDKN2A locus that encodes the tumor suppressor genes p16 and ARF (48). Although the repair-deficient RPMI8332 cell line shows reduced expression of MITF and loss of p16, many of the other melanoma cell lines we examined also show reduced MITF levels (Mel505, SK-Mel-187, and PMWK) or p16 loss (SK-Mel-103; refs. 13, 26), indicating that other factors are responsible for the lack of excision repair in RPMI8332 cells.

In summary, 11 of 12 melanoma cell lines displayed normal rates of repair of UV-induced DNA photoproducts in comparison with normal melanocytes, indicating that functional inactivation of the excision repair pathway is uncommon in sporadic melanoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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