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Susceptibility of Xeroderma Pigmentosum Cells to Transformation by Murine and Feline Sarcoma Viruses

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SUMMARY

Among various strains of skin fibroblasts tested, two strains derived from xeroderma pigmentosum (XP) patients (ages 19 and 25) with neurological complications and two strains obtained from heterozygotes (ages 54 and 18) showed relatively higher susceptibility than normal age-matched controls to transformation by feline sarcoma virus (FSV). Only one strain from a normal individual also showed a high susceptibility. Generally, there was a parallelism in susceptibilities to FSV and Kirsten murine sarcoma virus (KiMSV). However, cells from normal individuals of 46 years or older exhibited high ratios of FSV:KiMSV titers which were due to their lower susceptibility to KiMSV. Cells from two XP patients (ages 25 and 22) and a heterozygote (age 18), who were in a younger age group, manifested such a differential susceptibility to FSV and KiMSV. There was a correlation between the relative sensitivity of XP cells to the cytotoxic effect of 4-nitroquinoline 1-oxide and killing effect of UV light. Pretreatment of fibroblasts from three XP patients by a subtoxic dose of 4-nitroquinoline 1-oxide 24 hr before viral infection facilitated transformation by KiMSV and FSV, whereas no such effect was observed with three normal cell strains similarly treated.

INTRODUCTION

XP[1] is an autosomal recessive disease in which there is an unusually high sensitivity to sunlight and a greatly increased incidence of carcinomas of the skin, sometimes associated with abnormalities of other organs, including the central nervous system (11, 17-19). Studies of XP cells indicated that the initial step of excision-repair of UV-induced pyrimidine dimers in DNA is defective (6-8). XP cells are known to be less efficient than normal cells in their ability to reactivate UV-inactivated SV40 (2), adenovirus (10), herpesvirus (14, 16), vaccinia virus (30), and double-stranded RNA of encephalomyocarditis virus (29).

However, lack of DNA repair is not necessarily the basic cause of all XP skin cancers. XP variants with normal DNA repair have been reported (19). It is possible that other defects or inherent characteristics of XP cells unrelated to UV sensitivity may be causally related to oncogenesis. Cells derived from patients afflicted with Fanconi's anemia and Down's syndrome exhibit a greater susceptibility to transformation by SV40, compared with normal cells (3, 27). An increased frequency of transformation by SV40 was observed in a strain of XP cells, compared with cells from the patient's mother (28). Other workers observed no increased susceptibility to transformation by SV40 in other strains of XP cells (15).

The present investigation was undertaken to define the susceptibility of XP cells to transformation by oncogenic RNA viruses, KiMSV, and FSV, which are known to have the capacity to transform human fibroblasts (4, 13, 21). Cells derived from normal, age-matched subjects and heterozygous family members of XP patients were used as controls. Cells from patients with another genetic disease, LNS, were also included for comparative study. Furthermore, these cells were pretreated with 4NQO, which exerts UV-like cytotoxic effects and induces DNA repair synthesis (23-26), to investigate its effect on their susceptibility to transformation by these viruses.

MATERIALS AND METHODS

Cells. Vials of frozen samples of cultured fibroblasts were obtained from the American Type Culture Collection (Rockville, Md.). These were derived from low-passage cultures of skin biopsies from apparently normal individuals, patients with LNS, XP, or heterozygotic family members of XP. For details of the origin of these cells, see Ref. 5. The frozen cells were recovered and maintained in McCoy's Medium 5A supplemented with 10% fetal bovine serum and 100 units penicillin, 100 μg streptomycin, and 5 μg Fungizone per ml. Monolayer cultures of these cells in plastic flasks (Falcon Plastics, Oxnard, Calif.) were split at the ratio of 1:2 every 7 to 10 days. Cells passaged not more than 5 to 10 times after receipt were used for focus assays.

Viruses. A stock of KiMSV was prepared from the cell-free supernatant fluid of a culture of NRK cells transformed by, and actively producing, the virus. The cells, which were originally developed by Dr. W. Klement (13), were obtained from Dr. J. S. Rhim, Microbiological Associates, Inc., Bethesda, Md. This stock was distributed in vials and stored at −80°. Its titer was constant, on repeated titration over a period of 6 months, and was 5×10^5 FFU/ml on NRK cells. Almost an

[1] The abbreviations used are: XP, xeroderma pigmentosum; SV40, simian virus 40; KiMSV, Kirsten murine sarcoma virus; FSV, feline sarcoma virus; LNS, Lesch-Nyhan syndrome; 4NQO, 4-nitroquinoline 1-oxide; FFU, focus-forming units; MEM, Eagle's minimal essential medium.

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equal amount of helper Kirsten murine leukemia virus was present in this stock as titrated by XC plaque assay (20) on NIH Swiss mouse embryo cell cultures.

A stock of Snyder-Theilen strain of FSV (22) grown in feline embryo cell cultures was obtained from Dr. J. S. Rhim. This was stored at −80° and had the titer of 2×10^4 FFU/ml, plus 2 logs higher titer of feline leukemia virus as titrated by complement-fixing antigen-induction (infectivity) assay on feline embryo cells.

Focus Assays. Cells dispersed with trypsin were suspended in McCoy's Medium 5A supplemented with 10% fetal bovine serum and antibiotics, and plated in 5-cm disposable plastic Petri dishes (2×10^5 cells/plate). After overnight incubation at 37° in a CO_2 incubator, the cells were treated with DEAE-dextran, 25 μg/ml, for 1 hr at 37°. The solution was removed and the cells were rinsed once with medium. Appropriate dilutions of viruses (usually at 0.5-log intervals) were seeded in duplicate plates (0.4 ml/plate) and allowed to adsorb for 2 hr at 37°. The plates were replenished with the medium every 3 or 4 days, and transformed cell foci were counted at the end of 14 days for KiMSV, and at 10 days for FSV.

The average number of FFU in duplicate plates was taken as the titer and was corrected by multiplication with the dilution factor to give FFU/ml. Usually, there was a good agreement between the values obtained with the 2 plates of each dilution, and the difference did not exceed 20% of the average values. Reproducibility of FFU titers on these cell strains was tested by repeated titrations at different passage levels. The variation in titers was usually within the limit of 0.5 log. In such experiments, the viability and passage levels of cell strains may introduce an additional variable, but the simultaneous titration of KiMSV and FSV would provide an internal control on this variability. A lowered viability of cells would result in simultaneous decrease in FFU titers for KiMSV and FSV.

UV Irradiation of Cells. Trypsinized cell suspensions were washed and resuspended at a concentration of 2×10^4/ml in McCoy's Medium 5A containing 10% fetal bovine serum. A number of Falcon plastic Petri dishes (10 cm in diameter), each containing 10 ml of the cell suspension, were irradiated with UV emitted from a Sylvania G15T8 UV lamp which gave at least 95% of energy at 2537 Å. Irradiation was done at a distance of 55 cm at an incident dose of 10 ergs/sq mm/sec. Immediately before and after irradiation for various lengths of time, appropriate dilutions of these cells were plated on Falcon plastic dishes (5 cm in diameter) containing 4 ml medium. The cells attached on the plates were checked on Days 1 and 7, during which period dying cells manifested a disintegrating cellular morphology, while the living cells showed a healthy morphology with distinctive cell contour and occasional cell divisions.

The number of individual attached cells that did not divide, plus the number of small colonies consisting of an island of a few cells, represented the number of surviving cells that would have given rise to larger colonies after a longer incubation period.

4NQO Treatment of Cells. 4NQO (K & K Laboratories, Plainview, N. Y.) was dissolved in ethanol to make a 10^{-2} M solution. This stock solution was further diluted with MEM without serum to give desired concentrations. Corresponding concentrations of ethanol were used as control. For observation of cytotoxicity, 10^5 cells plated 1 day previously in Falcon plastic dishes (5 cm in diameter) were washed twice with MEM and then were treated with 1 ml of diluted 4NQO at 37° for 1 hr. The cells were washed twice with MEM after removal of 4NQO, and then McCoy's Medium 5A with 10% fetal bovine serum was added. The cell growth was scored at the end of 7 days from − to +++, depending on the confluency; +++, ++, +, and − representing confluent, moderate, slight, and no growth, respectively. For susceptibility testing of 4NQO-treated cells to transformation by KiMSV and FSV, subconfluent growths of cells in flasks were washed and treated as described above with a noncytotoxic concentration ($10^{-6.5}$ M) of 4NQO. Control cells received a corresponding concentration of ethanol. The washed, treated cells were trypsinized and seeded on plates (3×10^5 in 4 ml medium). After overnight incubation, these plates were tested for focus-forming efficiency by KiMSV and FSV, according to the method described above.

RESULTS

Differential Susceptibility to Transformation by KiMSV and FSV. Skin fibroblasts derived from apparently normal individuals of various ages, from the fetus to the 92-year-old, were tested for their susceptibility to transformation by KiMSV and FSV. As presented in Table 1, the titers of transforming activity in FFU/ml of an FSV stock were fairly uniform for these cells, except that C5 strain showed exceptionally high, and C6 and C15 strains, exceptionally low titers. The titers of the KiMSV stock were generally lower than those of FSV and were especially low for those cell strains derived from persons whose ages were 46 years or older. The C5 strain again showed a relatively high titer to KiMSV transformation. Consequently, the ratios of titers (FSV:KiMSV), were greater with cells derived from individuals whose ages were 46 years or older (ratio, 240 to 560), whereas those obtained with younger ages were lower (ratio, 7 to 76).

A group of skin fibroblast strains derived from patients with LNS, ages 7 to 14, were tested similarly (Table 2) and gave ratios of titers that fit into the pattern of the younger age groups mentioned above.

The results with skin fibroblasts derived from XP patients (ages 12 to 27) were more variable (Table 3). Two strains (X1 and X2), derived from XP patients (ages 19 and 25) with neurological complications (De Sanctis-Cacchione syndrome), exhibited exceptionally high titers of FSV (7.5 and 5.5×10^4 FFU/ml, respectively) and moderate and low titers (4.1×10^3 and 1.1×10^2 FFU/ml, respectively) of KiMSV. Consequently, the FSV:KiMSV titer ratio was low for X1 and high for X2. The age-matched controls (C3 and C1, ages 15 and 29) showed FSV titers of 1.7 and 1.6×10^4 FFU/ml, which were 3.4- to 4.7-fold less than those of X1 and X2. These controls showed KiMSV titers (2.4×10^3 and 3.2×10^2 FFU/ml) that were not significantly different from those of XP series in general. Strain X3 (age 22) showed an exceptionally low titer (1.8×10^1 FFU/ml) of KiMSV, compared with C3 and C1, resulting in a high FSV:KiMSV ratio (833). All other strains of XP origin (X4 through X7, ages 27, 12,

Table 1
Susceptibility of skin fibroblasts derived from apparently normal individuals to transformation by KiMSV and FSV

Cell designation		Donor		Titer (FFU/ml)		
CRL no.	Code	Age	Sex	KiMSV	FSV	Ratio of titers (FSV:KiMSV)
1105	C1	29 yr	M	3.2×10^2	1.6×10^4	67
1106	C2	Fetus	?	2.5×10^2	1.9×10^4	76
1119	C3	15 yr	M	2.4×10^3	1.7×10^4	7
1121	C4	3 yr	M	2.0×10^3	1.7×10^4	9
1125	C5	13 yr	F	1.1×10^4	1.5×10^5	14
1141	C6	3 yr	M	1.0×10^2	7.5×10^2	8
1146	C7	6 mo.	M	1.9×10^3	1.8×10^4	10
1147	C8	9 yr	F	NT[a]	1.5×10^4	
1101	C10	43 yr	M	5.0×10^2	1.7×10^4	34
1102	C11	46 yr	M	2.5×10^1	6.2×10^3	248
1126	C12	73 yr	M	7.5×10^1	2.7×10^4	360
1120	C13	84 yr	M	6.8×10^1	3.8×10^4	560
1116	C15	92 yr	M	7.5	1.8×10^3	240

[a] NT, not tested.

Table 2
Susceptibility of skin fibroblasts derived from patients with LNS to transformation by KiMSV and FSV

Cell designation		Donor		Titer (FFU/ml)		
CRL no.	Code	Age	Sex	KiMSV	FSV	Ratio of titers (FSV:KiMSV)
1111	L1	9	M	2.3×10^3	2.1×10^4	9
1112	L2	7	M	4.0×10^2	2.5×10^3	6
1113	L3	12	M	1.3×10^1	NT	
1110	L4	14	M	2.6×10^2	1.1×10^4	42

[a] NT, not tested.

Table 3
Susceptibility of skin fibroblasts derived from XP patients to transformation by KiMSV and FSV

Cell designation		Donor			Titer (FFU/ml)		Ratio of titers (FSV: KiMSV)
CRL no.	Code	Age	Sex	Additional information	KiMSV	FSV	
1157	X1	19	F	XP with neurological complications; sister of X2	4.1×10^3	7.5×10^4	18
1160	X2	25	F	XP with neurological complications; sister of X1	1.1×10^2	5.5×10^4	500
1166	X3	22	M	XP	1.8×10^1	1.5×10^4	833
1170	X4	27	F	XP	1.1×10^3	3.0×10^4	27
1158	X5	12	M	XP; brother of X3, and identical twin to X6	5.0×10^2	2.3×10^4	46
1161	X6	12	M	XP; brother of X3, and identical twin to X5	3.6×10^2	8.0×10^3	22
1162	X7	27	M	XP; normal UV induced [^{3}H]- thymidine uptake into lymphocytes and skin fibroblasts	1.1×10^3	6.3×10^3	6

12, and 27) showed titers and FSV:KiMSV ratios within the normal range, compared with those obtained with age-matched controls (C3, C1, L3, and L4). (C5, age 13, was excluded from comparison because it gave exceptionally high titers, as described above.)

The results of titration with fibroblast strains derived from individuals presumably heterozygotes for XP are summarized in Table 4. Strain X8, which was derived from the 60-year-old mother of X1 and X2, showed a pattern of susceptibility to KiMSV and FSV in terms of FSV:KiMSV ratios (287) similar to those obtained with age-matched controls (C11 and C12, ages 46 and 73). Strain X9, which originated from the 54-year-old mother of X3, showed a pattern of susceptibility similar to those obtained with younger age groups of normal individuals. By contrast, Strain X10, which was derived from the 54-year-old father of X3, showed a remarkably high FSV:KiMSV ratio because of its exceptionally high and low susceptibility to FSV and KiMSV, respectively. Strain X11, although derived from the young (18-year-old) brother of X3, also manifested an exceptionally high susceptibility to FSV with a moderate degree of susceptibility to KiMSV, resulting in a relatively high FSV:KiMSV ratio, com-

Table 4

Susceptibility of skin fibroblasts derived from individuals presumably heterozygotes for XP to transformation by KiMSV and FSV

Cell designation		Donor			Titer (FFU/ml)		Ratio of titers (FSV:KiMSV)
CRL no.	Code	Age	Sex	Additional information	KiMSV	FSV	
1159	X8	60	F	Mother of X1 and X2	1.5×10^1	4.3×10^3	287
1165	X9	54	F	Mother of X3	2.0×10^3	2.4×10^4	12
1167	X10	54	M	Father of X3	2.3×10^1	5.0×10^4	2174
1168	X11	18	M	Brother of X3	4.5×10^2	8.7×10^4	193

Table 5

Cytotoxic effect of 4NQO on skin fibroblasts derived from a normal individual and 4 XP patients

Cell designation		Cytotoxic effect at following 4NQO concentration						
CRL no.	Code	0 M	$10^{-7.5}$ M	10^{-7} M	$10^{-6.5}$ M	10^{-6} M	$10^{-5.5}$ M	10^{-5} M
1119	C3	+++[a]	+++	+++	+++	++	+	–
1157	X1	+++	+++	++	+	–	–	–
1160	X2	+++	+++	++	+	–	–	–
1166	X3	+++	+++	+++	++	+	–	–
1158	X5	+++	+++	+++	++	+	–	–

[a] +++, confluent growth; ++, moderate growth; +, slight growth; –, no growth.

pared with those observed with the age-matched normal controls (C3 and C1).

Sensitivity to UV Irradiation and Treatment with 4NQO. As illustrated in Chart 1, with UV, survival curves of 4 strains of fibroblast (X1, X2, X3, and X5) derived from XP patients were compared with that of Strain C3 as a representative of control cells obtained from normal individuals. Under the conditions of the experiments, X1 and X2 showed very high sensitivities to UV, compared with other strains. The UV sensitivity of X3 and X5 was somewhat higher than that of C3. The 37% survival doses for X1, X2, X3, X5, and C3 were 24, 15, 84, 78, and 132 ergs/sq mm, respectively.

Since a strain of XP fibroblasts was reported by Takebe *et al.* (25) to be highly sensitive to the cytotoxic effect of 4NQO, compared with a strain of normal fibroblasts, an experiment was conducted to compare the sensitivity of the above strains of XP origin with that of a control strain. As shown in Table 5, the minimal concentrations of 4NQO to inhibit cell growth following 1 hr of treatment at 37° were 10^{-6} M for X1 and X2, $10^{-5.5}$ M for X3 and X5, and 10^{-5} M for C3. Thus, these different grades of sensitivity to 4NQO correlated well with the degrees of sensitivity to UV irradiation.

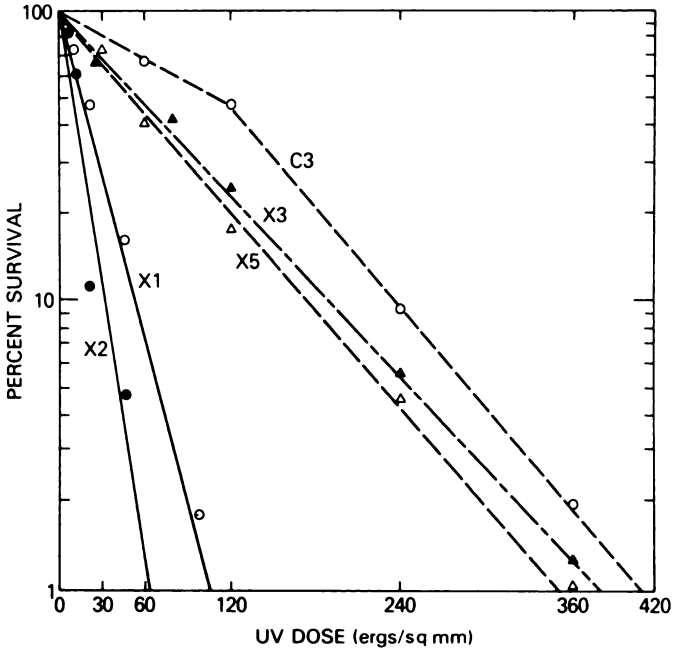

Chart 1. Survival curves for UV-irradiated normal (C3) and XP (X1, X2, X3, and X5) cells. Trypsinized and washed cell suspensions (2×10^4/ml) in McCoy's Medium 5A containing 10% fetal bovine serum were irradiated with UV at an incident dose of 10 ergs/sq mm/sec. Immediately before and after irradiation for various lengths of time, appropriate dilutions of these cells were plated on plastic dishes (5 cm in diameter) containing 4 ml medium. After 7 days of cultivation, the number of attached, living cells in each plate was counted.

Facilitation of Viral Transformation by Pretreatment of Fibroblasts with 4NQO. Since 4NQO is known for its mutagenic action and since the above experiments demonstrated relatively greater sensitivities to 4NQO of XP cells, compared with those of control cells, it was of interest to test the effects of 4NQO pretreatment of these cells on their ability to be transformed by these RNA tumor viruses. The data summarized in Table 6 were obtained when duplicate plate cultures of XP and control cell strains (X3, X5, and C3 in Experiment 1; X4, C4, and C5 in Experiment 2) were prepared from flask cultures pretreated with a noncytotoxic concentration ($10^{-6.5}$ M) of 4NQO, and were tested for focus formation by inoculation with appropriate dilutions of KiMSV and FSV. In each experiment, there was about 3- or 4-fold increase in FFU counts with the X3, X5, and X4 cells pretreated with 4NQO, compared with the untreated control. No such facilitation of viral transformation was observed with C3, C4, or C5 cells pretreated with the same concentration of 4NQO.

The relative degrees of sensitivity (interstrain differences) of various cell strains presented in Table 6 remained almost the same as those reported in Tables 1 and 3. Therefore, the intrastrain differences in titers observed after 4NQO treatment of XP cells must not be regarded as random variations. Therefore, it may be concluded that, under appropriate conditions such as those used in the present experi-

Table 6
Facilitating effect of 4NQO pretreatment on transformation of XP fibroblasts by KiMSV and FSV

Experiment	Cell designation		Treatment	FFU/plate	
	CRL no.	Code		KiMSV	FSV
1	1166	X3	4NQO, $10^{-6.5}$ M	NT[a]	60, 68
			Control	NT	20, 27
	1158	X5	4NQO, $10^{-6.5}$ M	25, 20	112, 107
			Control	7, 4	40, 38
	1119	C3	4NQO, $10^{-6.5}$ M	8, 9	10, 11
			Control	14, 13	16, 18
2	1170	X4	4NQO, $10^{-6.5}$ M	NT	210, 265
			Control	NT	93, 69
	1121	C4	4NQO, $10^{-6.5}$ M	NT	66, 58
			Control	NT	44, 52
	1125	C5	4NQO, $10^{-6.5}$ M	NT	285, 280
			Control	NT	290, 282

[a] NT, not tested.

ments, the sensitivity of these XP cells was altered by pretreatment with 4NQO in such a way that the viral transformation process was facilitated.

DISCUSSION

It is evident from the above results that there are various degrees of susceptibility of human fibroblast strains to transformation by KiMSV and FSV. A low susceptibility to KiMSV accompanied by a moderate degree of susceptibility to FSV, which resulted in a higher ratio of FSV:KiMSV titers, was observed with cell strains derived from normal individuals at the age of 46 or older. In a study of *in vitro* transformation of skin fibroblasts by SV40, it was noted that those derived from normal individuals over 70 as well as those obtained from patients afflicted with Fanconi's anemia and Down's syndrome, showed a high susceptibility to SV40 transformation (26). The significance of such a contrasting manifestation of age as a factor in susceptibility of skin fibroblasts to transformation by oncogenic DNA and RNA viruses is not clear.

A markedly high susceptibility to transformation by FSV was observed with X1 and X2, which were derived from XP patients with neurological complications (De Sanctis-Cacchione syndrome). Two strains (X10 and X11) from the presumably heterozygous individuals showed also a high susceptibility to FSV transformation. However, such a high susceptibility was observed in only 1 strain (C5) among those derived from control individuals, including those with LNS. Since these tests were performed under normal conditions of cultivation, these results are not directly associated with faulty DNA repair synthesis resulting from UV irradiation. It is not known whether the higher susceptibility to FSV transformation in some of these cells is due to increased efficiency in adsorption, penetration, and uncoating, or intracellular replication and integration of the FSV genome. In the case of SV40, the differences in susceptibility of various human fibroblasts disappeared when infectious DNA was used for transformation (1).

It is of interest that 2 strains from XP patients (X2 and X3) and a strain from a heterozygote (X11) showed high FSV:KiMSV ratios characteristic of older age groups although their ages were 25, 22, and 18, respectively. The genetic factors or physiological conditions of the cell cultures affecting their susceptibility to transformation by KiMSV appear to be different from those determining their susceptibility to transformation by FSV.

Although the cause for skin carcinogenesis in XP patients is not clear, the present observation that pretreatment of XP cell strains with a subtoxic dose of 4NQO enhanced their susceptibility to transformation by KiMSV and FSV is interesting in view of the report by Stich *et al.* (24), who found that a marked increase in chromosome aberrations was induced in the XP cells (but not in normal cells) after a single dose (10^{-7} M) of 4NQO, and that this change was maximal at 24 hr after treatment. This coincided with the time when 4NQO-treated cells were infected with KiMSV and FSV in the present experiments. It is tempting to link the enhanced susceptibility to viral transformation with the chromosome aberrations effected by 4NQO in XP cells. These findings are compatible with the hypothesis that "faulty DNA repairs and subsequent errors in post-UV semiconservative DNA replication may increase the frequency of malignant change through mutation, oncogenic viral integration, or activation of oncogenes" (12). Repeated attempts to demonstrate activation of type C viruses by treatment of these cells (X1 through X4 and C3 through C8) with 5-iododeoxyuridine have been unsuccessful (K. S. S. Chang, unpublished observation). However, induction by UV of the expression of oncogenes without complete expression of type C viral genome is conceivable. In the present experiments, no cell transformation was observed by 4NQO treatment alone. The questions whether the activity of 4NQO for facilitation of viral transformation is specific for XP cells and whether the faulty DNA repair synthesis or chromosome aberrations are directly related to the enhancement of viral transformation need further investigation.

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