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Transient correction of excision repair defects in fibroblasts of 9 xeroderma pigmentosum complementation groups by microinjection of crude human cell extracts

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Summary

Crude extracts from human cells were microinjected into the cytoplasm of cultured fibroblasts from 9 excision-deficient xeroderma pigmentosum (XP) complementation groups. The level of UV-induced unscheduled DNA synthesis (UDS) was measured to determine the effect of the extract on the repair capacity of the injected cells. With a sensitive UDS assay procedure a (transient) increase in UV-induced UDS level was found in fibroblasts from all complementation groups after injection of extracts from repair-proficient (HeLa) or complementing XP cells (except in the case of XP-G), but not after introduction of extracts from cells belonging to the same complementation group. This indicates that the phenotypic correction is exerted by complementation-group-specific factors in the extract, a conclusion that is in agreement with the observation that different levels of correction are found for different complementation groups. The XP-G-correcting factor was shown to be sensitive to proteolytic degradation, suggesting that it is a protein like the XP-A factor.

Patients suffering from xeroderma pigmentosum (XP) exhibit severe sensitivity of the skin to sun exposure and predisposition to neoplasia in the exposed areas (see Kraemer, 1983, for review on various aspects of XP). The primary defect in most XP patients is thought to reside in initial steps of the excision repair of ultraviolet light (UV)-induced DNA lesions (Cleaver, 1968; Tanaka et al., 1975, 1977; de Jonge et al., 1985). Cell hybridization studies have revealed a considerable genetic heterogeneity within the XP syndrome: thus far 9 excision-deficient complementation groups (designated A to I) have been identified (de Weerd-Kastelein et al., 1972; Fischer et al., 1985). If these groups represent mutations in different genes, it means that at least 9 polypeptides are required early in the excision process. Despite extensive research none of the genes or gene products deficient in XP have been isolated. In order to study function and properties of individual components affected in XP we have developed a repair assay system which consists of the introduction of crude extracts from human cells into living XP fibroblasts of different complementation groups using glass microneedles (de Jonge et al., 1983). Increase of the level of UV-induced unscheduled DNA synthesis (UDS) of the injected cells is used to monitor activities in the extract that transiently correct the repair defect. In this way we have

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detected a protein that specifically corrects the XP-A repair deficiency (de Jonge et al., 1983). Here we report the result of a systematic search for correcting activities of the other 8 excision-deficient XP complementation groups.

Materials and methods

Cell lines, culture conditions and cell fusion

Relevant information on the various cell lines used in this study is summarized in Table 1. The primary fibroblasts listed were cultured in Ham's F10 medium, supplemented with newborn and fetal calf serum (7.5% each) and antibiotics (penicillin 100 U and streptomycin 100 μg/ml). The HeLa S3 cell line as well as the simian virus 40 (SV40)-transformed XP cells were cultured in a 1 : 1 mixture of Dulbecco's modified Eagle's medium and Ham's F10 medium, containing 3% fetal and 7% newborn calf serum and antibiotics. Homopolykaryons to be injected were generated by fusion of cells of one cell strain using inactivated Sendai virus as described by the Weerd-Kastelein et al. (1972). The fused cell population was seeded onto 0.6 cm $\times$ 0.8 cm pieces of a microscope slide with a 2-mm grid and cultured for at least 3 days prior to microinjection. The use of homopolykaryons for microinjection facilitates reidentification of the injected cells. Furthermore, since polykaryons older than 3 days do not enter S phase anymore, the possibility that labeling due to S-phase replication is confused with UDS, is eliminated (de Jonge et al., 1983).

Preparation of extracts, microinjection and assay for UDS

Preparation of crude cell extracts and microinjection were performed as detailed before (de Jonge et al., 1983). After injection cells were irradiated with a saturating dose of UV (15 J/m^2) and assayed for UDS. To increase the sensitivity of the UDS assay and to reduce the exposure times some modifications were introduced in the UDS proce-

TABLE 1

RELEVANT INFORMATION ON THE CELL LINES USED

Cell line designation		XP complementation group	References
(A) Primary fibroblasts			
XP25RO		A	Kraemer et al. (1975)
XP11BE		B	Kraemer et al. (1975)
XP21RO		C	Kleijer et al. (1973)
XP1BR		D	W. Keijzer (unpubl. res.)
XP2RO		E	de Weerd-Kastelein et al. (1974)
XP126LO		F	W. Keijzer (unpubl. res.)
XP2BI		G	Keijzer et al. (1979)
XP3BR		G	Arlett et al. (1980)
XPCS2		H	Moshell et al. (1983)
XP3MA		I	Fischer et al. (1985)
C5RO		Human wild type	
(B) SV40-transformed cells			
XP12RO	SV40	A	[a]
XP4RO	SV40	C	[b]
XP8CAC	SV2	C	[c]
XP2YO	SV	F	Yage and Takebe (1983)
XP3BR	SV40 cl.15	G	[b]

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dure used before. These include the following:

(1) The serum (13% fetal calf serum) in the culture medium for the UDS incubation was dialyzed to remove free nucleic acid precursors and to increase the real specific activity (s.a.) of the labeled deoxyribonucleosides in the medium.

(2) ^{3}H-Labeled TdR (10 μCi/ml) of high s.a. was used (40–100 Ci/mmole, instead of 20 Ci/mmole, Amersham).

(3) FUdR was added to the UDS solution (at a concentration of 1 μM) to inhibit the endogeneous de novo synthesis of TdR.

(4) In some experiments the period of labeling with radioactive deoxyribonucleosides was extended from 2 to 4 h.

The combined use of these modifications resulted in a 6–10-fold increase in the number of autoradiographic grains above nuclei of repair-proficient fibroblasts compared to the original UDS procedure.

Experiments using proteinase K

Proteinase K (pretreated for 2 h at 37°C to destroy any contaminating DNAase or RNAase activity) or bovine serum albumin (BSA) was covalently linked to cyanogen bromide-activated Sepharose beads and incubated with aliquots of a HeLa cell extract as described previously (de Jonge et al., 1983). The effect of proteinase K on the enzymatic activity of glucose 6-phosphate dehydrogenase (G6PD) in the extract was quantitatively determined following the method of Jongkind (1967).

Results

Correction of the repair defects of XP-B through I by microinjection of cell extracts

In a previous report (de Jonge et al., 1983) we have demonstrated that injection of a HeLa crude cell extract induced a strong increase of the UDS of XP-A cells. Under the same conditions no significant enhancement of UDS was found in injected homopolykaryons from a XP-C, D and F cell line. This could be due to lack of (active) correcting factors in the extract, or to the fact that our microinjection assay was not sufficiently sensitive. Therefore a number of modifications (specified in Materials and Methods) were introduced in the UDS assay procedure with the aim to improve the limit of detection. This resulted in a 6–10-fold increase in the level of UDS labeling of UV-irradiated normal fibroblasts. Furthermore — when possible — within each complementation group a cell line was selected with a low level of residual UDS activity and with good growth characteristics. Finally, in the preparation of crude cell extracts dilution was minimized as much as possible to obtain very concentrated extracts. The beneficial effect of these modifications is indicated by the finding that correction of the XP-A defect upon microinjection of a HeLa extract amounted to the level of repair-competent fibroblasts (Table 2).

To investigate whether additional components involved in excision repair could be detected in crude cell extracts the same method was applied to the other 8 excision-deficient XP complementation groups. The effect on the UV-induced UDS upon injection of various extracts is summarized in Table 2. Fig. 1 shows corresponding pictures of homopolykaryons of XP complementation groups B and H after injection of extracts from HeLa or complementing XP cells and assay for UDS. In all cases the average number of grains above nuclei of homopolykaryons injected with extracts prepared from repair-proficient cells was higher than the mean grain count of non-injected neighboring cells. The increase is in each case dependent on injection of extract since it was not found when the extract was replaced by buffer (data not shown). Furthermore, when the UV irradiation was omitted the number of autoradiographic grains was not above background, indicating that the incorporation of [^{3}H]TdR is due to UV-induced UDS and not to stimulation of the injected cells to progression into S phase by protein(s) in the extract or to other causes. Also extracts prepared from (SV40-transformed) cells from XP complementation groups A, C, F and G were able to stimulate UV-induced UDS in multinucleated cells from heterologous groups (with the exception of XP-E (not tested) and XP-G in which no correction could be registered after injection of an XP-C extract). In contrast, the same extracts were unable to enhance UDS in homopolykaryons from their own complementation group (Table 2). This strongly suggests that the (partial) recovery of UDS is caused by

TABLE 2

EFFECT OF INJECTION OF CRUDE HUMAN CELL EXTRACTS ON THE UV-INDUCED UDS OF HOMOPOLYKARYONS OF VARIOUS XP COMPLEMENTATION GROUPS

Injected cell line [a]	Extract injected [a]	UV irradiation (15 J/m^2)	UDS (grains/nucleus) [b] (% of wild type ± S.E.M.)	
			Non-injected [c]	Injected
XP25RO (A)	HeLa	+	2 ± 1	102 ± 7
XP25RO (A)	HeLa	−	1 ± 1	1 ± 1
XP25RO (A)	XP12RO SV40 (A)	+	2 ± 1	3 ± 1
XP25RO (A)	XP8CAC SV2 (C)	+	5 ± 1	60 ± 1
XP25RO (A)	XP3BR SV40 cl.15 (G)	+	1 ± 1	22 ± 2
XP11BE (B)	HeLa	+	3 ± 1	13 ± 1
XP11BE (B)	HeLa	−	0 ± 1	0 ± 1
XP11BE (B)	XP12RO SV40 (A)	+	5 ± 1	15 ± 2
XP11BE (B)	XP4RO SV40 (C)	+	3 ± 1	13 ± 1
XP21RO (C)	HeLa	+	13 ± 1	20 ± 1
XP21RO (C)	HeLa	−	0 ± 1	0 ± 1
XP21RO (C)	XP12RO SV40 (A)	+	13 ± 1	18 ± 1
XP21RO (C)	XP4RO (C)	+	13 ± 1	14 ± 2
XP1BR (D)	HeLa	+	17 ± 1	33 ± 2
XP1BR (D)	HeLa	−	0 ± 1	1 ± 1
XP1BR (D)	XP12RO SV40 (A)	+	15 ± 1	26 ± 2
XP1BR (D)	XP4RO SV40 (C)	+	17 ± 1	28 ± 2
XP2RO (E)	HeLa	+	47 ± 2	75 ± 3
XP2RO (E)	HeLa	−	1 ± 1	1 ± 1
XP126LO(F)	HeLa	+	16 ± 1	49 ± 3
XP126LO(F)	HeLa	−	0 ± 1	1 ± 1
XP126LO(F)	XP12RO SV40 (A)	+	16 ± 1	46 ± 3
XP126LO(F)	XP4RO SV40 (C)	+	16 ± 1	45 ± 3
XP126LO(F)	XP2YO SV (F)	+	14 ± 1	13 ± 1
XP2BI (G) [d]	HeLa	+	6 ± 1	33 ± 3
XP2BI (G) [d]	HeLa	−	1 ± 1	1 ± 1
XP2BI (G) [d]	XP4RO SV40 (C)	+	6 ± 1	5 ± 1
XP2BI (G) [d]	XP3BR SV40 cl.15 (G)	+	7 ± 1	5 ± 1
XPCS2 (H)	HeLa	+	33 ± 2	60 ± 1
XPCS2 (H)	HeLa	−	1 ± 1	2 ± 1
XPCS2 (H)	XP12RO SV40 (A)	+	33 ± 2	51 ± 3
XPCS2 (H)	XP4RO SV40 (C)	+	39 ± 2	63 ± 2
XP3MA (I)	HeLa	+	14 ± 1	30 ± 3
XP3MA (I)	HeLa	−	1 ± 1	1 ± 1
XP3MA (I)	XP4RO SV40 (C)	+	14 ± 1	29 ± 2
XP3MA (I)	XP3BR SV40 cl.15 (G)	+	14 ± 1	23 ± 2

[a] Between brackets XP complementation group.

[b] In each experiment the grains above more than 35 nuclei of homopolykaryons were counted, the average number of grains/nucleus was calculated and expressed as % of the mean number of grains/nucleus of repair-proficient fibroblasts (C5RO), assayed in parallel under the same conditions. The UDS level of these control cells varied between individual experiments, but was always higher than 100 grains/nucleus.

[c] Residual UDS activity.

[d] Incubation time for UDS assay: 4 h.

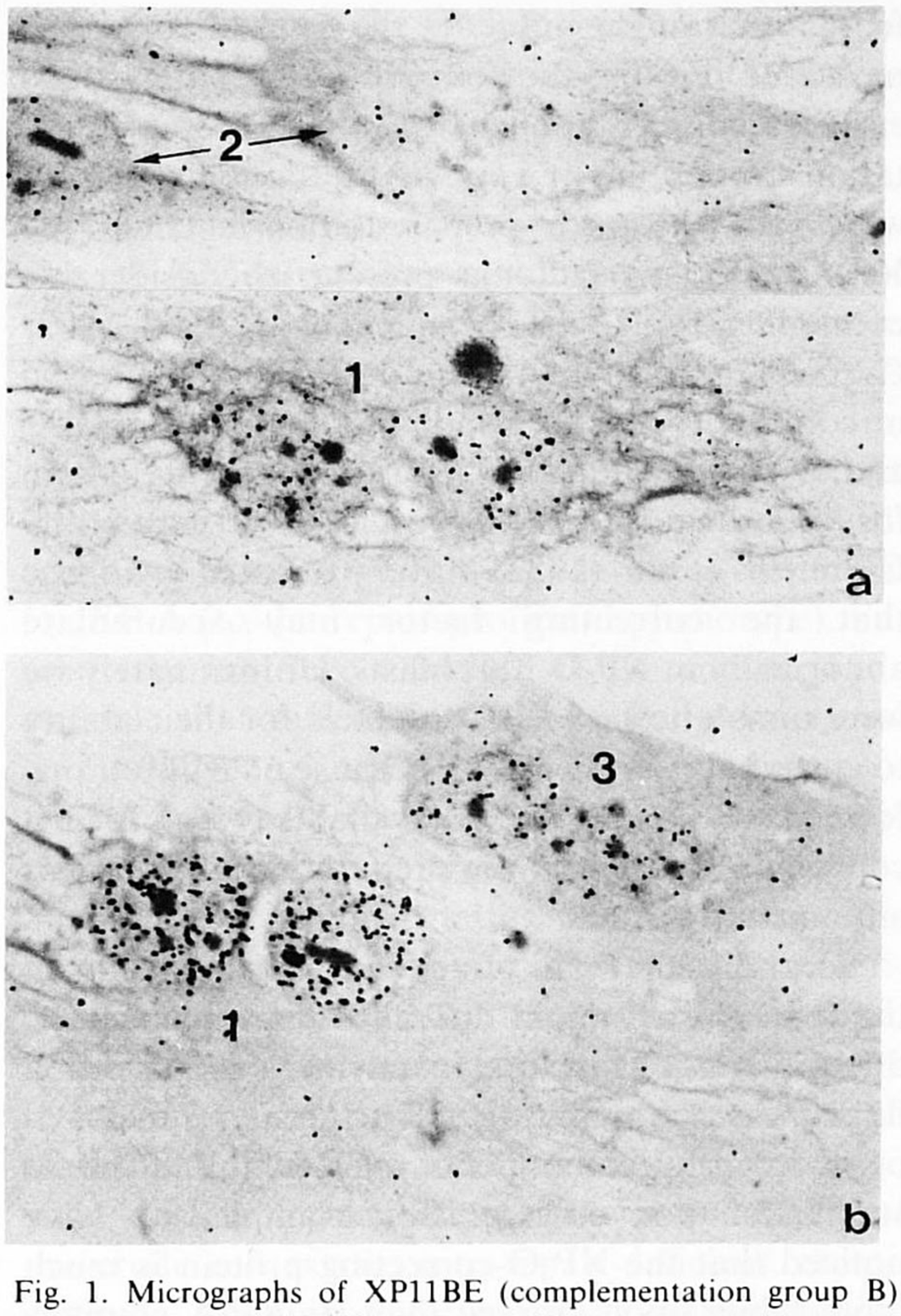

Fig. 1. Micrographs of XP11BE (complementation group B) (micrograph a) and XPCS2 (group H) (micrograph b) homopolykaryons microinjected with HeLa extract followed by UV irradiation and UDS assay. 1, injected homodikaryon; 2, non-injected monokaryon; 3, non-injected homodikaryon.

repair components in the extracts that are deficient in heterologous XP complementation groups.

As shown in Table 2, the stimulation of UDS varied between different cell lines and complementation groups. In some fibroblast lines normal to near normal UDS levels were reached (e.g. XP25RO(XP-A), XP2RO(XP-E) and XPCS2(XP-H)), whereas the increase in e.g. XP21RO(XP-C) was only very small.

The effect of proteinase K treatment on the XP-G correcting factor

To determine whether the XP-G-correcting component is sensitive to proteolytic degradation (like the XP-A-correcting factor), a HeLa cell extract was incubated prior to injection with proteinase K covalently attached to CNBr-activated cellulose beads. Aliquots of the same extract incubated without beads or in the presence of BSA beads served as controls. After incubation the proteinase K or BSA cellulose grains were removed by centrifugation and the G6PD activity in the extract was measured to verify the action of the proteolytic enzyme. As shown in Table 3 incubation of the extract with proteinase K beads led to a substantial reduction of G6PD activity, whereas the enzyme activity was largely unaffected in the control samples. Similarly the XP-G-correcting activity was not detectable after the proteinase K treatment. Since incubation alone, or in the presence of BSA beads, had only a marginal effect on the XP-G correction we conclude that the factor(s) responsible for the restoration of the repair capacity of this complementation group is sensitive to proteolytic action.

TABLE 3

THE EFFECT OF TREATMENT WITH PROTEINASE K ON THE XP3BR (XP-G)-CORRECTING ACTIVITY IN HeLa EXTRACTS

Treatment of extract [a]	UDS (grains/nucleus) (% of wild type ± S.E.M.) [b]	Enzymatic activity of G6PD [c] (%)
No incubation	24 ± 2	100
Proteinase K beads [d]	3 ± 1	15
BSA beads	20 ± 1	77
Incubation without beads	20 ± 1	100

[a] Sepharose beads with covalently attached proteinase K or BSA were incubated with aliquots of a HeLa extract. After removal of the beads by centrifugation, the supernatant was injected into XP3BR (XP-G) homopolykaryons and the level of UDS was determined.

[b] Incubation time for UDS assay: 4 h.

[c] The enzymatic activity of glucose 6-phosphate dehydrogenase (G6PD) in the extract was assayed according to Jongkind (1967). The activity of untreated HeLa extract was set at 100%.

[d] The extract treated with proteinase K beads did not induce a significant reduction in the UDS of repair-competent control fibroblasts (C5RO).

Discussion

The application of a sensitive microinjection assay procedure, has allowed the detection of activities in crude HeLa cell extracts, that restore the repair capacity in all 9 excision-deficient XP complementation groups, as indicated by a (transient) increase in UV-induced UDS. Although for most groups only one cell line was tested we believe that the results are representative for the entire complementation group. This is supported by our finding that similar results were obtained with two cell lines from XP-A (de Jonge et al., 1983) and from XP-G (this report). In all cases tested (except XP-G) heterologous (but not homologous) cell extracts were able to induce repair synthesis, demonstrating that the temporal correction is specific for each complementation group and not caused by a general bypass mechanism. In XP-G fibroblasts, up to now no detectable correction was found after injection of an XP-C extract. The same extract was able to induce significant increase in UDS in injected XP-B, D, F, H and I fibroblasts. It is possible that the XP-C cell line used for extract preparation contains considerably lower amounts of the XP-G-correcting factor. However, other explanations (e.g. inactivation of the XP-G-correcting component during extract preparation or storage) cannot be ruled out (see below). Further experiments are required to decide between these possibilities.

In this and in a previous report (de Jonge et al., 1983) we have shown that the correction of the XP-A and XP-G defects are due to proteins. It remains to be determined whether the restoration of the other complementation groups is also exerted by polypeptides. Our finding that the XP-A- and -G-correcting factors are proteins is in agreement with the observation of Legerski et al. (1984), that restoration of repair capacity in these complementation groups can also be achieved by microinjection of messenger RNA.

The results presented in Table 2 display a strong variation in the level of correction (scored as UDS) obtained between different cells and complementation groups. Although part of this variation can be attributed to the semi-quantitative type of results inherent to the microinjection procedure (e.g. variations in volumes injected) there are additional factors that might influence the level of correction measured. Firstly, the concentration of the different correcting components of the XP complementation groups might vary in the donor cell from which the extract is prepared. For instance, the XP-A-correcting factor is present in considerable excess in various cells (Giannelli et al., 1973, 1982; Giannelli and Pawsey, 1976; de Jonge et al., 1983), in contrast to the corresponding factors for XP-C and D (Giannelli et al., 1982). Concerning XP-C, for which we find the lowest level of correction, Giannelli et al. (1982) have presented evidence that the correcting factor may accumulate abnormally in XP-D fibroblasts. Unfortunately we were unable to test XP-D extracts for their ability to correct the XP-C defect, because no SV40-transformed XP-D cell lines are available, which form a convenient source for the preparation of sufficient amounts of extract.

Secondly, the yield of active correcting factor in the final extract might differ for different factors, due to variations in loss, inactivation or inhibition during extract preparation. Furthermore, the various correcting components may exhibit different stabilities upon storage. For example, we have noticed that the XP-G-correcting protein is much more labile upon storage than its XP-A counterpart.

Thirdly, from hybridization and cybridization experiments (involving fusion of whole cells or isolated cytoplasts from wild-type or heterologous complementation groups with XP fibroblasts) it is apparent that striking differences exist in the rate of complementation (Pawsey et al., 1979; Matsukuma et al., 1981; Keijzer et al., 1982; Giannelli et al., 1982). In XP-A the repair-proficient level of UDS is reached very rapidly after fusion or injection (probably within 30 min, de Jonge et al., 1983), whereas for XP-C and D the same process takes respectively about 16 and more than 24 h (Giannelli et al., 1982; Keijzer et al., 1982). Time intervals in between these two extremes are found for XP-B, F and G (W. Keijzer, unpublished observations). As suggested by Giannelli et al. (1982) one of the reasons for the slow kinetics of complementation observed in XP-C and D could be that the exchange of the introduced correcting factors in the cytoplasm with their defective homologues in the nucleus occurs at a very slow rate.

Transport through the nuclear membrane could be the rate-limiting step in the complementation or e.g. assembly of the proficient factor into a (defective) repair complex.

As mentioned above, temporary complementation of XP defects has also been observed after microinjection of poly(A)$^+$RNA. Correction to near normal UDS values was reported for XP-A and G (Legerski et al., 1984). In contrast, no measurable increase in UDS was detected for an XP-D and F cell line, with the same method. With crude cell extracts we find high levels of correction for XP-A (to the repair-proficient phenotype), but relatively low levels for XP-G, D and F. It is possible that differences in the steady-state level and turnover of mRNA and corresponding proteins exist, which result in different levels of correction with these two types of gene products.

Finally, it is worth noting that the phenotypic complementation observed for all 9 excision-deficient XP complementation groups presented here, is exerted by extracts prepared from non-UV-irradiated cells. Apparently the constitutive level of the gene products involved is high enough to yield detectable correction upon introduction of the crude cell extract into repair-deficient, recipient cells. The microinjection assay system applied in this study, provides a useful tool to the purification and further characterization of these proteins.

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