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Transfection of the cloned human excision repair gene *ERCC-1* to UV-sensitive CHO mutants only corrects the repair defect in complementation group-2 mutants

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Summary

The human DNA-excision repair gene *ERCC-1* is cloned by its ability to correct the excision-repair defect of the ultraviolet light- and mitomycin-C-sensitive CHO mutant cell line 43–3B. This mutant is assigned to complementation group 2 of the excision-repair-deficient CHO mutants. In order to establish whether the correction by *ERCC-1* is confined to CHO mutants of one complementation group, the cloned repair gene, present on cosmid 43–34, was transfected to representative cell lines of the 6 complementation groups that have been identified to date. Following transfection, mycophenolic acid was used to select for transferants expressing the dominant marker gene *Ecogpt*, also present on cosmid 43–34. Cotransfer of the *ERCC-1* gene was shown by Southern blot analysis of DNA from pooled (500–2000 independent colonies) transformants of each mutant. UV survival and UV-induced UDS showed that only mutants belonging to complementation group 2 and no mutants of other groups were corrected by the *ERCC-1* gene. This demonstrates that *ERCC-1* does not provide an aspecific bypass of excision-repair defects in CHO mutants and supports the assumption that the complementation analysis is based on mutations in different repair genes.

During the last decade a large number of ultraviolet light (UV)-sensitive Chinese hamster ovary (CHO) cell lines has been isolated that are deficient in DNA-excision repair (Thompson et al., 1981; Wood and Burki, 1982; Stefanini et al., 1982). Genetic characterization performed by fusing cells from different mutant cell lines revealed the presence of at least 6 complementation groups (Thompson et al., 1981, 1987a; Thompson and Carrano, 1983). These mutants are phenotypically comparable with cell strains isolated from DNA-excision-repair-deficient xeroderma pigmentosum (XP) patients. These XP cells have been classified in 9 complementation groups (De Weerd-Kastelein et al., 1972; Fischer et al., 1985). Although the cell fusion data are far from complete, none of the

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tested XP and Chinese hamster excision-repair mutants belong to the same group (Stefanini et al., 1985; Thompson et al., 1985a).

The UV sensitivity of CHO mutants belonging to complementation groups 1, 2 and 5 has been corrected to nearly wild-type levels in genomic transfections with human DNA (Rubin et al., 1983; MacInnes et al., 1984; Westerveld et al., 1984; Weber et al., 1987). The human *ERCC-1* gene that corrects the repair defect of the complementation group-2 43–3B cell line has been molecularly cloned (Westerveld et al., 1984; Van Duin et al., 1986). Complementation group-2 mutants display an extreme sensitivity to the drug mitomycin-C (MMC) and have also an increased sensitivity to 4-nitroquinoline-1-oxide and *N*-acetoxy-2-acetyl-aminofluorene and alkylating agents. *ERCC-1* converts all these characteristics of group-2 mutants to wild-type levels. Moreover, the UV-induced mutation frequency at the Na^+/K^+ ATPase locus and the rate of cyclobutane pyrimidine dimer removal were also returned to normal (Zdzienicka et al., 1987).

It is generally assumed that intergenic complementation accounts for the classification of the UV-sensitive CHO mutants in different complementation groups. However, it should be noted that intragenic complementation or aspecific bypass of repair defects after cell fusion in the complementation assay cannot be excluded. To investigate the specificity of the cloned *ERCC-1* gene for group-2 mutants, we have examined whether *ERCC-1* can correct the repair defect in the other CHO complementation groups. Therefore, the cloned *ERCC-1* gene was transfected to representative cell lines of all 6 CHO complementation groups. UV survival and UV-induced repair synthesis data of the *ERCC-1*-containing transformants revealed that only CHO mutants belonging to complementation group 2 are transformed to wild-type.

Materials and methods

Cell lines and culture conditions

The wild-type CHO cell lines CHO-9 and AA8 have been described by Burki et al. (1980) and Thompson et al. (1980), respectively. The UV-sensitive mutants of CHO-9 and AA8 and corresponding complementation-group assignments are listed in Table 1. The cells were routinely cultured in a 1:1 mixture of Ham's F10 and Dulbecco's ME medium (DMEM) supplemented with antibiotics and 3% fetal and 7% newborn calf serum.

TABLE 1

UV-SENSITIVE CHO MUTANTS AND CORRESPONDING COMPLEMENTATION GROUPS THAT WERE USED FOR cos 43–34 TRANSFECTION EXPERIMENTS

Mutant	Complementation group	Parental line	Reference [a]
UV5	1	AA8	1
UV4, UV20	2	AA8	1
43–3B	2	CHO-9	2
UV24	3	AA8	1
UV41, UV47	4	AA8	1
UV135	5	AA8	3
UV61	6	AA8	4

[a] 1 = Thompson et al., 1981; 2 = Wood and Burki, 1982; 3 = Thompson et al., 1982; 4 = Thompson, 1987a.

DNA transfection and selection of transferants

One day before DNA transfection 5×10^5–1×10^6 recipient cells were seeded in 100-mm Petri dishes and cultured in a humidified incubator (37 °C, 5% CO_2). The transfection was carried out using the calcium-phosphate precipitation method (Graham and Van der Eb, 1973). Cosmid 43–34 (Fig. 1) (Westerveld et al., 1984) used in the transfection, harbors the 15-kb human excision-repair gene *ERCC-1* and in addition the dominant marker genes *agpt*, encoding G418 resistance, and *Ecogpt*, which allows selection with mycophenolic acid (MPA). To each Petri dish 1 μg cosmid 43–34 + 10 μg 43–3B carrier DNA was supplied. Following overnight exposure to the precipitate, the cells were treated with dimethylsulfoxide (10% for 30 min) and cultured for 24 h in non-selective medium to allow expression of the transfected DNA. Selection for the *Ecogpt* marker was performed in modified MPA medium containing F10/DMEM 1:1 and antibiotics, 10% fetal calf serum, aminopterin (0.2 μg/ml), thymidine (5 μg/ml), xanthine (10 μg/ml), hypoxanthine (15 μg/ml), mycophenolic acid (25 μg/ml) and deoxycytidine (2.3 μg/ml) (Mulligan and Berg, 1980;

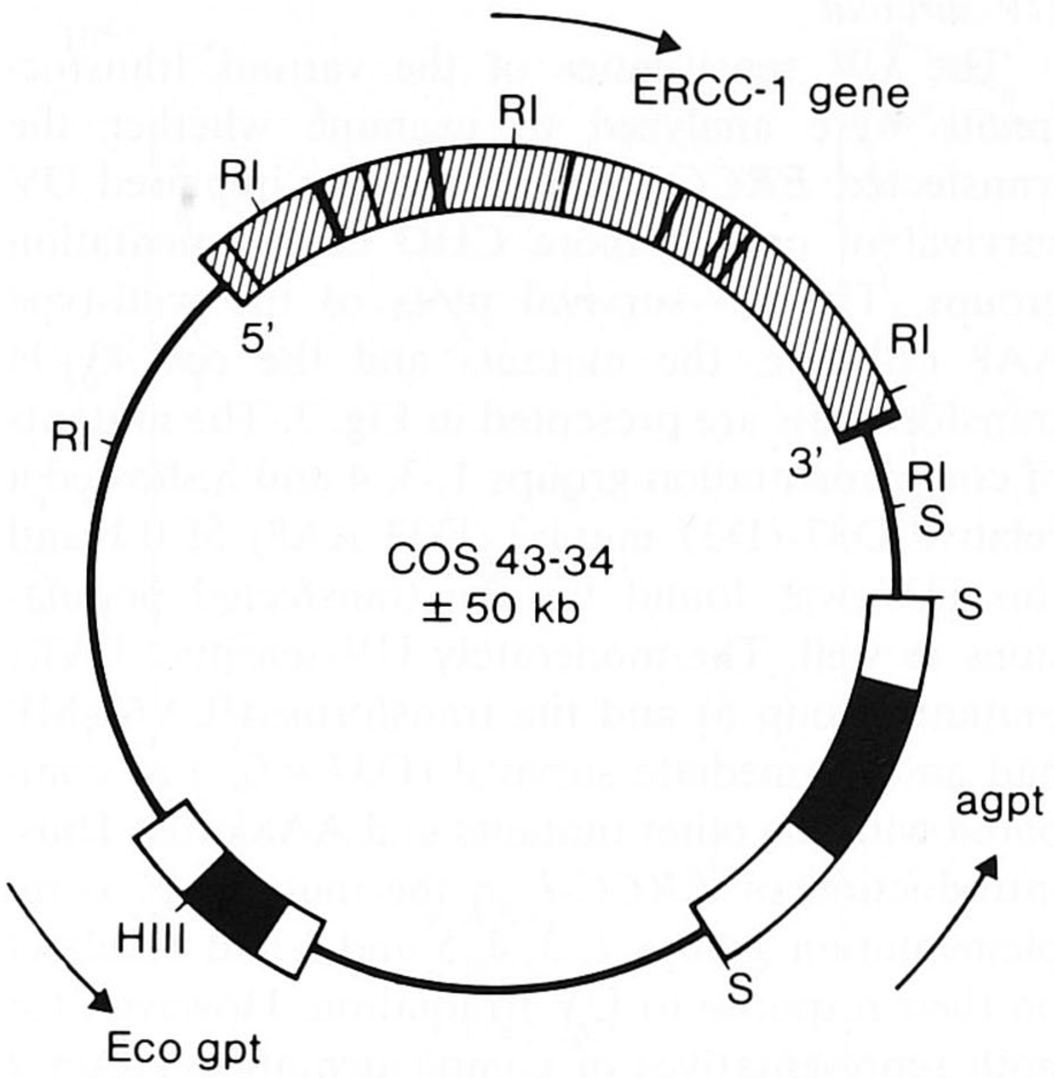

Fig. 1. Schematical presentation of cosmid 43–34 harboring approximately 42 kb of genomic DNA of a secondary 43–3B transformant (Westerveld et al., 1984). The cosmid vector pTCF (Grosveld et al., 1982) is flanked by SalI sites and contains the *agpt* gene. Furthermore the *Ecogpt* gene (on plasmid pSV3*gpt*H) and the human *ERCC-1* gene are located on the cosmid insert. Shaded boxes and small black boxes represent introns and exons of the *ERCC-1* gene, respectively (van Duin, in preparation). Arrows indicate transcriptional orientation. Abbreviations: S: SalI; RI: EcoRI; HIII: HindIII (not all restriction sites are shown).

Westerveld et al., 1984). The selection medium was refreshed every 3–4 days. After 2 weeks MPA-resistant colonies were trypsinized and grown into mass cultures. Within 1 week unscheduled DNA synthesis and UV survival were determined. The transformed cells were cultured for another 2 weeks before genomic DNA was isolated.

UV survival

Exponentially growing cultures were trypsinized and 200–4000 cells were plated onto 60-mm dishes and left to attach for 12 h. Subsequently cells were rinsed with phosphate-buffered saline (PBS) and exposed to UV light with a 254-nm low-pressure mercury, germicidal Philips TUV lamp with a fluence rate of 0.6 J/m^2. After cultivation in non-selective medium for 7 days clones were fixed and stained with Coomassie brilliant blue. For each dose 3–6 dishes were used. The relative survival was plotted versus the UV dose.

Unscheduled DNA synthesis (UDS)

Two days after seeding in medium without MPA, the cells were exposed to UV light (16 J/m^2) and incubated in thymidine-free, Ham's F10 medium supplemented with [^{3}H]thymidine (10 μCi/ml; specific activity 50 Ci/mmole) and 5% dialyzed fetal calf serum. After Bouin fixation the preparations were processed for autoradiography (Kodak AR10 stripping film), exposed for 1 week at 4°C, developed and stained with Giemsa solution. For each preparation the number of grains per fixed square of 25–50 nuclei was counted.

Southern blot analysis

Genomic DNA was isolated as described by Jeffreys et al. (1977), digested to completion with *EcoRI* and electrophoresed in 0.7% agarose gels. After transfer of the size-fractionated DNA to nitrocellulose (Southern, 1975) the filter was hybridized with ^{32}P-labelled nick-translated probes (Rigby et al., 1977). The hybridization was visualized by autoradiography.

Results

Cosmid 43–34, harboring the *ERCC-1* gene and the dominant markers *Ecogpt* and *agpt* (Fig. 1), was transfected to representative mutants of the various UV-sensitive CHO complementation groups. After transfection, a selection was carried out in MPA-containing medium for transferants with a functional *Ecogpt*. The mutants had a transfection frequency of approximately 100 MPA-resistant clones per μg cosmid 43–34 DNA per 10^6 cells. The MPA-resistant clones of each transfected mutant were pooled and grown into mass populations consisting of 500–2000 independent transferants. DNA was isolated from the mass populations and characterized by Southern blot analysis using *Ecogpt* and *ERCC-1* probes. The various transfected populations and the original CHO mutants were analysed by UV survival and UDS.

Southern blot analysis

DNA from the pooled transformants was analyzed by Southern blotting. *EcoRI*-digested

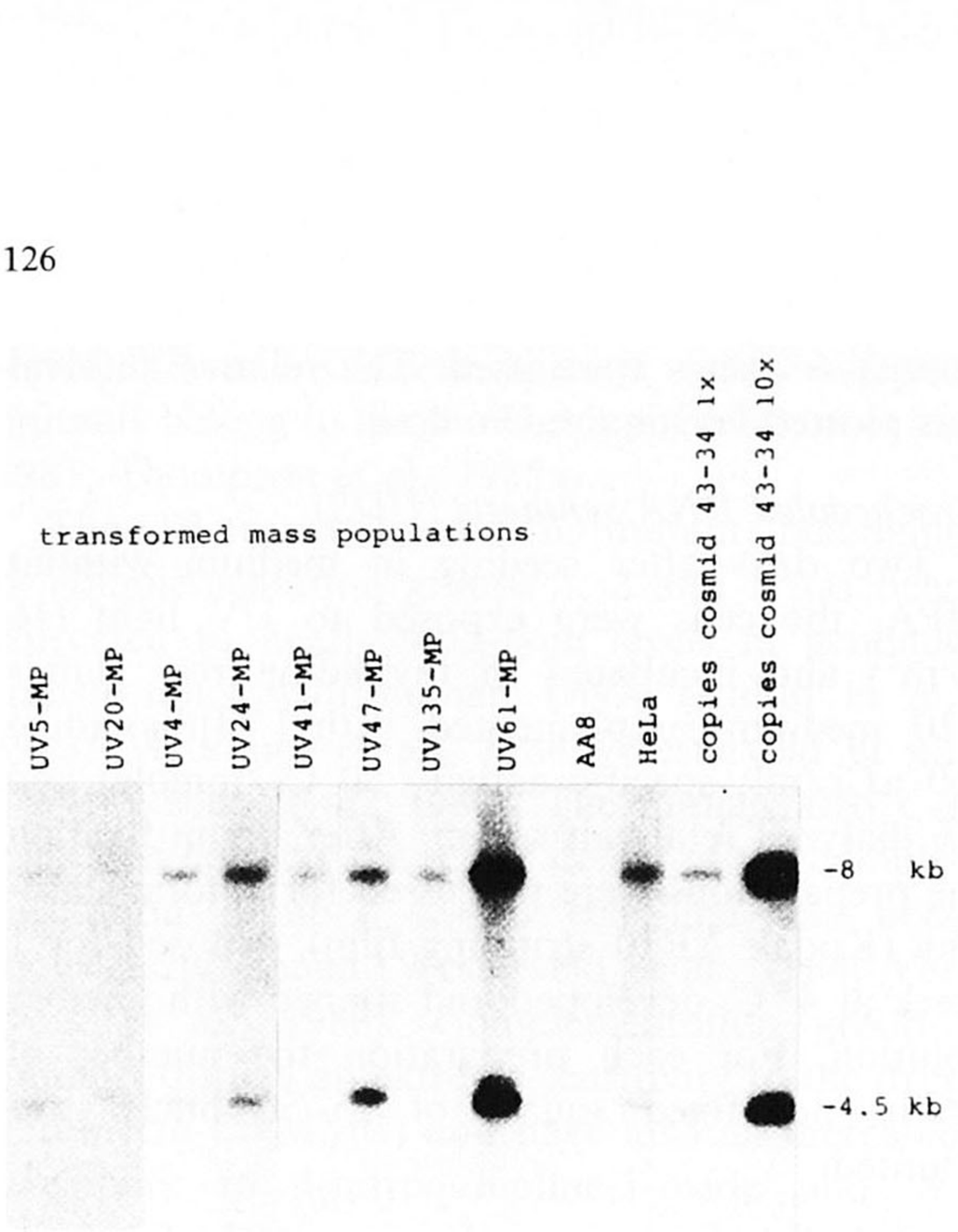

Fig. 2. Southern blot analysis of EcoRI-digested DNA of cos 43–34-transformed mass populations (MP), HeLa (human) and CHO AA8 cells probed with complete human *ERCC-1* cDNA. The last 2 lanes on the right harbor 1 and 10 copies of EcoRI-digested cosmid 43–34 per diploid genome, respectively. EcoRI digestion of cosmid 43–34 results in 3 fragments that hybridize with a complete *ERCC-1* cDNA probe: two 4.5-kb fragments and one 8-kb fragment (see also Fig. 1).

DNA was size-fractionated by agarose-gel electrophoresis, transferred to nitrocellulose and the blot was hybridized with a ^{32}P-labeled *Ecogpt* and a complete *ERCC-1* cDNA probe (Van Duin et al., 1986). The results of the *ERCC-1* hybridization are presented in Fig. 2. The 1.0-kb cDNA probe recognizes an 8-kb and 2 4.5-kb fragments of the human *ERCC-1* gene in control HeLa DNA, whereas the hybridization conditions did not allow detection of the Chinese hamster *ERCC-1* gene in AA8 cells (see also Fig. 1). The number of cosmid 43–34 copies that was integrated by transformants was estimated from the hybridization signal with HeLa DNA and the titration of 1 and 10 cosmid copies per diploid genome. On average the transformed mass populations harbored 1–5 cosmid molecules per cell. UV5 and UV20 transformants displayed the lowest and the UV61-MP the highest hybridization signal. UV61-MP contains in the order of 5–10 copies per cell. A similar conclusion could be drawn from the hybridization experiments with the *Ecogpt* probe (data not shown).

UV survival

The UV sensitivities of the various transformants were analyzed to examine whether the transfected *ERCC-1* can correct the impaired UV survival of one or more CHO complementation groups. The UV-survival plots of the wild-type AA8 cell line, the mutants and the cos 43–34 transformants are presented in Fig. 3. The mutants of complementation groups 1, 3, 4 and 5 showed a relative D37 (D37 mutant/D37 AA8) of 0.1 and this D37 was found for the transfected populations as well. The moderately UV-sensitive UV61 mutant (group 6) and the transformed UV61-MP had an intermediate survival (D37 = 0.3) as compared with the other mutants and AA8 cells. Thus, introduction of *ERCC-1* in the mutants of complementation groups 1, 3, 4, 5 and 6 had no effect on their response to UV irradiation. However, for both representatives of complementation group 2 (UV4 and UV20), the UV sensitivities of the transformed populations varied from those of the corresponding mutants. The survival curves of both populations were biphasic (see Fig. 3). About 65% of the UV4-MP and 10% of the UV20-MP cells behaved AA8-like with a relative D37 (D37 transformants/D37 AA8) value of 1. The UV survival of the sensitive fractions, about 35% of the UV4-MP and 90% of the UV20-MP cells, was similar to that of the mutant cells. For both fractions a relative D37 of 0.1 was calculated.

Unscheduled DNA synthesis

The capacity of cos 43–34 transformants to remove UV-induced DNA damage was measured by the incorporation of [^{3}H]thymidine as the result of UDS. The results, expressed as grains per fixed square of 25–50 nuclei, are presented in Table 2. In 5 of the mutant cell lines, UV4, 5, 20, 24 and 41, the UDS levels range from 5 to 10% of that found in wild-type cells. UV47 (group 4) and UV135 (group 5) exhibited about 30% of the wild-type AA8 activity, while the moderate UV-sensitive UV61 (group 6) cell line showed a UDS level of 60% compared to the AA8. The transformants of complementation groups 1, 3, 4, 5 and 6 did show UDS activities comparable with the original mutant cell line. Restoration to wild-type levels was found in transformants of complementation group 2. However, not all cells displayed

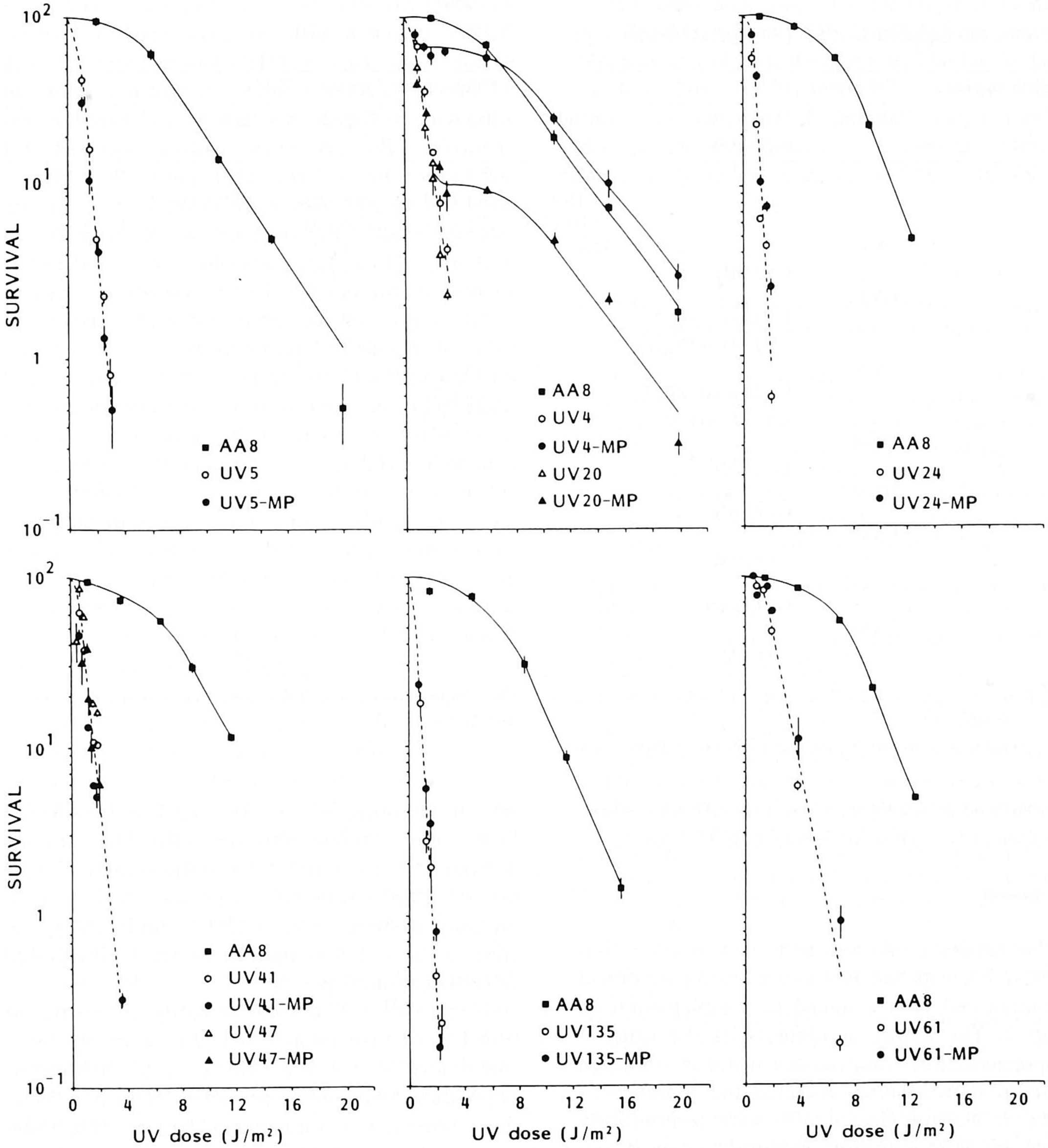

Fig. 3. UV-survival curves of wild-type (AA8), mutants (UV5; UV4; UV20; UV24, UV41; UV47; UV135; UV61) and transfected mass populations (MP): UV5-MP; UV4-MP; UV20-MP; UV24-MP; UV41-MP; UV47-MP; UV135-MP; UV61-MP. Error bars in the data points represent the SEM (standard error of the mean).

UDS activities identical to the wild-type level. In UV20-MP about 10% of the cells exhibited wild-type UDS levels and 90% of the cells had a mutant phenotype. Also UV4 transferants could be divided in 2 classes. About 65% of the UV4-MP cells showed wild-type UDS levels and about 35% were of the mutant type. These results are in accordance with the UV-survival data and ap-

TABLE 2

UV-INDUCED UNSCHEDULED DNA SYNTHESIS

Complementation group	Cell line			Grain counts [a] (mean ± SEM)			
	Mutant	Mass population	Wild type	Exp. 1	Exp. 2	Exp. 3	Exp. 4
			AA8	26.4 ± 0.6			28 ± 1.1
			CHO9	19.1 ± 0.5	18.6 ± 0.6	29.0 ± 2.0	
			HeLa	37.9 ± 0.7	33.0 ± 0.6		43 ± 2.2
1	UV5				2.4 ± 0.3		
		UV5-MP			2.4 ± 0.3		
2	UV4				1.8 ± 0.2		
		UV4-MP (35%) [b]			1.9 ± 0.3		
		UV4-MP (65%) [b]			25.7 ± 0.6		
	UV20			0.9 ± 0.2			
		UV20-MP (92%) [b]		1.6 ± 0.3			
		UV20-MP (8%) [b]		25.1 ± 0.6			
3	UV24					1.5 ± 0.3	
		UV24-MP				2.6 ± 0.4	
4	UV41						2.1 ± 0.4
		UV41-MP					1.9 ± 0.5
	UV47						7.1 ± 0.8
		UV47-MP					8 ± 1.3
5	UV135						11 ± 2.2
		UV135-MP					8.2 ± 0.8
6	UV61					19 ± 1.1	
		UV61-MP				18 ± 1.1	

[a] The number of grains is given as mean ± SEM per fixed square of non-S-phase nucleus and for each preparation 25–50 nuclei were characterized.

[b] Percentage is determined by screening 200 non-S-phase nuclei.

parently due to the fact that not all MPA-resistant transformants harbor an active *ERCC-1* gene.

Discussion

The results presented here demonstrate that *ERCC-1* corrects the DNA-excision-repair defect of mutant cell lines assigned to complementation group 2. The defect in mutants of the other 5 complementation groups is not restored, although Southern blot analyses revealed the presence of *ERCC-1*. The transfected cells were continuously grown in MPA-selection medium, so each cell should contain at least one functional *Ecogpt* copy. The mean copy number per cell for *Ecogpt* as well as *ERCC-1* sequences varied from 5–10 in UV61-MP to 1–5 in the other transformants. Recently we showed that the average amount of stably integrated DNA in the genome of transfected cells is species- and cell-line-specific (Hoeijmakers et al., 1987; unpublished results). In general human cells incorporate 20- to 100-fold less transfected DNA than Chinese hamster cells. The mutants derived from the CHO AA8 subline studied in the present paper integrate considerably less than mutants isolated from CHO-9, underlining the conclusion that the amount of stably integrated DNA is cell-line-specific.

In case of UV20 transformants an inefficient transfer of a functional *ERCC-1* gene was achieved since only 8% of the cells in the transformed population were repair-proficient. The possibility that potential complementation of the other mutants by the *ERCC-1* gene is masked due to inefficient gene transfer seems unlikely, since Southern blot analysis revealed that all cell lines had integrated 1–5 *ERCC-1* copies (Fig. 2) and that UV61 had incorporated even more transfected DNA than UV4 and UV20.

The *ERCC-1* gene has been mapped on the long arm of human chromosome 19 (Rubin et al., 1985; Van Duin et al., 1986). Using cell-fusion

experiments Thompson et al. (1987b, personal communication) have recently assigned *ERCC* genes complementing CHO group-1, -3, -4 and -5 mutants to human chromosomes 19, 2, 16 and 13, respectively. The chromosomal assignment of the UV61-complementing gene is still unknown. Hence, it appears that CHO complementation groups 1 and 2 are corrected by a human gene on chromosome 19. Weber et al. (1987) have recently succeeded in the molecular cloning of a gene that confers UV resistance to UV-5 mutants (group 1). Molecular characterization of this gene, designated *ERCC-2*, revealed that it is clearly different from *ERCC-1* (Weber et al., 1987) indicating that 2 genes involved in excision repair are located on human chromosome 19. In this respect it is interesting to note that a DNA-repair gene associated with sister-chromatid exchange has also been assigned to human chromosome 19 (Siciliano et al., 1986). The conclusion of our transfection results, that *ERCC-1* can only correct the repair defect in CHO group-2 mutants is completely in accord with the chromosomal assignment data obtained by Thompson et al. (1987b).

Aspecific bypass of DNA-excision-repair defects has been observed after introduction of the T4 or *Micrococcus luteus* endonuclease in cell lines of all XP-complementation groups (Tanaka et al., 1977; De Jonge et al., 1985) and CHO mutants of group 1 (Valerie et al., 1985). The specificity of *ERCC-1* for group-2 mutants and the assignments of other *ERCC* genes to different human chromosomes render it unlikely that bypass activities account for the complementation analysis of UV-sensitive CHO mutants. Our results rather support the assumption that mutations in different repair genes underlie the classification of UV-sensitive CHO cell lines in different complementation groups and that *ERCC-1* is the mutated gene in CHO group-2 mutants.

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