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A Novel UV-Sensitivity Mutation Induces Nucleotide Excision Repair Phenotype and Shows Epistatic Relationships with UvsF and UvsB Groups in *Aspergillus nidulans*

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DNA damage response has a central role in the maintenance of genomic integrity while mutations in related genes may result in a range of disorders, including neoplasic formations. The *uvsZ1* characterized in this report is a novel *uvs* mutation in *Aspergillus nidulans*, resulting in a nucleotide excision repair (NER) phenotype: UV-sensitivity before DNA synthesis (quiescent cells), high UV-induced mutation frequency and probable absence of involvement with mitotic and meiotic recombinations. The mutation is recessive and non-allelic to the previously characterized *uvsA101* mutation, also located on the *paba-y* interval on chromosome I. *uvsZ1* showed wild-type sensitivity to MMS, which suggests non-involvement of this mutation with BER. Epitasis tests showed that the *uvsZ* gene product is probably involved in the same repair pathways as UVSB or UVSH proteins. Although mutations in these proteins result in an NER phenotype, UVSB is related with cell cycle control and UVSH is associated with the post-replicational repair pathway. The epistatic interaction among *uvsZ1* and *uvsB413* and *uvsH77* mutations indicates that different repair systems may be related with the common steps of DNA damage response in *Aspergillus nidulans*.

Key words: *uvs* mutation, DNA repair, UV light, alkylating agents, *Aspergillus nidulans*

Terrestrial life as known at present has only been possible by developing a range of protective mechanisms against chemical and physical agents, including UV light, that may result in mutagenesis and the killing of cells.

Several types of DNA repair mechanisms have been described in prokaryote and eukaryote cells, correcting a high spectrum of lesions introduced in the DNA molecule. These mechanisms are part of the DNA damage response, a complex system that ensures the maintenance of genomic integrity. DNA damage response consists of checkpoint systems and extensive repair mechanisms that deal directly with DNA damage (11). There are three well-characterized basic repair mechanisms: excision repair, which acts mostly in non-dividing cells and post replicational and error-prone repair which functions mainly during and after DNA replication. The error-prone repair results in an increase of mutation frequencies, since survival is ensured at the cost of mutagenic change (6).

Among these basic repair mechanisms, the excision pathways have a central role as the cell's main defense against DNA damage, due to their wide underlying specificity, universatility and accuracy (2). Base excision repair (BER) removes little adducts, such as alkyl radicals, in the DNA molecule. Nucleotide excision repair (NER) is able to repair "bulky" lesions such as pyrimidine dimmers caused by UV light (12, 28). Defects in proteins involved in NER can lead to inherited disorders such as Xeroderma pigmentosum, Cochaynes syndrome and cancer (1). Studies with UV-sensitive mutants in many organisms have been a help in the understanding of repair pathways and of syndromes associated with deficiencies in the DNA repair mechanisms.

Excision repair mutants sensitive to UV light were first studied in prokaryotes, mainly in *Escherichia coli* and, during the last decade, in eukaryotes. In *Saccharomyces cerevisiae* a large number of radiation sensitive mutants (*rad*) have been identified as being involved in NER (17, 20).

In the filamentous fungi *Aspergillus nidulans*, the UV-sensitive mutants have been classified into four epistatic groups: UvsB, UvsC, UvsF and UvsI (5, 15). The UvsC epistatic group, including *uvsA*, *uvsC* and *uvsE* genes, has been mentioned as participating in the post replicational repair process. Recent cloning showed homology between the *uvsC* gene product and the *E. coli* RecA protein, involved in the recombinational repair pathways (10, 27). The UvsI group, consisting of the *uvsI* gene only, is

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involved in mutagenic repair of specific DNA sequences (1, 6, 10).

Although NER is found in all living organisms, surprisingly no NER defective mutant has been found in *A. nidulans*. The UvsF group, that includes *uvsF*, *uvsH* and *uvsJ* genes, shows the same properties as NER mutants in *E.coli* and in *S.cerevisiae*. They have high UV-sensitivity in non-dividing cells, increased frequencies of UV-induced mutation and spontaneous mitotic crossing-over in homozygous diploids. (16, 30). However, posterior molecular analyses showed homology between UvsF protein and RCF1, the large subunit of the DNA replication factor C of *E.coli*. This fact suggests that perhaps UvsF has no relationship with NER but with post replicational pathway repair (10, 17).

Previous reports have related genes of the UvsB epistatic group (*uvsB* and *uvsD* genes) and NER. However, recent observations suggest that these genes are likely to control cell cycle checkpoint responses to DNA damage and incomplete replication. The UVSB protein is a member of the conserved family of ATM-related kinases, acting in the inhibition of septum formation, in the regulation of DNA-repair genes expression and in induced mutagenesis in the presence of DNA damage (8, 11, 14).

The characterization of a new *uvs* mutation in *A. nidulans*, named *uvsZ1*, is reported in this paper. The mutant strain (Z1) was derived from master strain UT448 after treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). It has mitotic instability caused by a duplicated segment of chromosome II transposed to chromosome I [DP (II, I)] and by the *uvsZ1* mutation mapped between *pabaA* and *yA* genes (3, 4, 31). The mutant showed the same characteristics as NER mutants of *E. coli* and *S. cerevisiae*, namely high UV-sensitivity in non-dividing cells and high frequencies of UV-induced mutation. Since the Z1 mutant strain was able to repair alkyl radicals inserted in DNA molecules, this suggests that it is not defective in BER.

Materials and Methods

Aspergillus nidulans strains and media

The *A. nidulans* strains used are described in Table 1. Complete medium (CM) and minimal medium (MM) were described previously (21, 26) and Selective medium (SM) was supplemented with MM according to the requirements of each strain. Solid medium contained 1.5% agar. Compact colonies were obtained in SM plus Triton X-100 (0.01%) (TSM). SM plus p-fluoro-phenylalanine (FPA) was previously described (2). Incubation occurred at 37°C.

Genetic techniques

The general methodology followed previous reports (21). The diploid strains were prepared by Roper's method (23). Heterokaryons were prepared in liquid MM plus 2.0% CM. Cleistothecia were obtained from heterokaryons after 21 days of incubation in sealed plates containing solid supplemented MM according to the requirements of the crossed strains. Distinct *uvs* mutants were combined into heterozygous crosses to obtain double *uvs* mutant strains.

Table 1. Genotype of *Aspergillus nidulanss* trains

Strain	Genotype	Origin
Z1	*riboA1, pabaA124, bioA1, uvsZ1 (IR), wA2, DP (II-I)*	Zucchi, 1990.
A561	*pabaA6, yA2, adE8, uvsB413 (IVC)*	FGSC
A572	*anA1, bioA1, pyroA4, uvsE182 (VR)*	FGSC
A579	*uvsA101 (IR), adD3*	FGSC
A837	*pabaA1, uvsH77 (IV), pyroA4, choA1, chaA1*	FGSC
A838	*pabaA1, AcrA1, uvsI501 (III), choA1, riboB2, chaA1*	FGSC
A757	*methA17, yA2, pyroA4*	FGSC
A495	*lysB5, nicA2, pA2*	FGSC
A441	*proA1, pabaA1, yA2*	FGSC
Z325	*pabaA124, bioA1, uvsZ1 (IR), lysB5, nicA2, pA2*	(Z1XA495)
UT448	*riboA1, pabaA124, bioA1, wA2*	Utrecht Stock

pro, ribo, paba, bio, meth, lys, nic, ad, pyro, and cho are requirements for proline, riboflavin, *p*-aminobenzoic acid, biotin, methionine, lysine, nicotinic acid, adenine, pyridoxine and choline respectively. y (yellow), *w* (white), *p* (pale), and *cha* (chartreuse) are conidial color markers. *Acr* determines resistance to Acriflavine and *uvs* indicates sensitivity to UV radiation. Gene symbols are used according to suggestion by Clutterbuck (1994). FGSC: Fungal Genetic Stock Center.

Determination of mutagen sensitivity

Conidia were collected with Tween 80 (0.001%) and NaCl (0.85%). The suspension was filtered, washed by centrifugation and stored at 5°C in NaCl (0.85%) before treatments. The density of the suspension was determined by haemocytomer counts. Germinant conidia were pre-incubated for 6 h before mutagen exposure.

In order to test for UV sensitivity, conidia were spread on TSM media and irradiated. The UV dose rate reached 1.4 ergs. sec^{-1}. Results represent the mean ± SEM of 4 experiments carried out in dark or red light to exclude photoreactivation.

In order to test for methyl methanesulfonate (MMS), MMS (Aldrich Chemical Co.) was added (0.5-2.0 µl) directly to conidial suspension and incubated at 30°C for 2 h. After incubation the treated suspension was centrifuged and washed twice in phosphate buffer (0.5 M, pH 7.6) containing 5% sodium thiosulfate to remove the mutagen (6). Conidia were plated onto TSM media to determine the survival rate (15).

Measurements of mutation frequencies

Conidia were germinated for 6 h in liquid SM plus 0.15% agar to avoid clumping. The number of conidia per plate was 1.09×10^5 for the uvs^+ and 1.25×10^5 for the *uvsZ1*. Germinant and quiescent conidia were plated on FPA medium and irradiated with UV (2). 15 plates were used for uvs^+ and *uvsZ1* strains at each irradiation time. Muta-

tion frequency was calculated according to Babudri *et al.* (15).

Determination of spontaneous mitotic and meiotic crossing-over frequencies

The effect of *uvsZ1* mutation in the intergenic mitotic recombination was evaluated by using UT448//A495 (*uvs*$^+$*//uvs*$^+$), A495//Z1 (*uvs*$^+$*//uvsZ1*) and Z1//Z325 (*uvsZ1 / /uvsZ1*) diploid strains. The procedures to measure mitotic recombination followed Franzoni *et al.* (9). The Z325 strain is a F1 segregant of the Z1 × A495 cross and bears an *uvsZ1* mutation in its genome (data not shown).

The intergenic meiotic recombination was analyzed in UT448× A495, A495× Z1 and Z1× Z325 crosses. Z1× A441 cross was performed to analyze the intragenic recombination. The frequencies of meiotic recombination (FR) were then determined in percentages (total number of recombinants × 100/total number of meiotic segregants). Data were compared by using contingency table 2 × 2 (Yates corrected x^2) at $p<0.05$.

Results

Recessiveness of the uvsZ1 mutation

The allelic relationship between *uvsZ1* and its counterpart wild-type allele was determined by the comparison of UV sensitivity of the homozygous UT448//A757 (*uvs*$^+$*//uvs*$^+$) wild-type and the heterozygous Z1//A757 (*uvsZ1//uvs*$^+$) diploid strains. The *uvs*$^+$*//uvs*$^+$ and the *uvs*$^+$*//uvsZ1* strains showed the same survival response to UV, demonstrating the recessiveness of the mutant allele. The Z1//Z325 (*uvsZ1// uvsZ1*) diploid strain showed high sensitivity when compared with *uvs*$^+$*//uvs*$^+$ and *uvs*$^+$*//uvs* diploid strains (Fig. 1).

Differentiation between uvsZ1 and uvsA101 alleles

Two recessive *uvs* mutations, *uvsZ1* and *uvsA101*, both

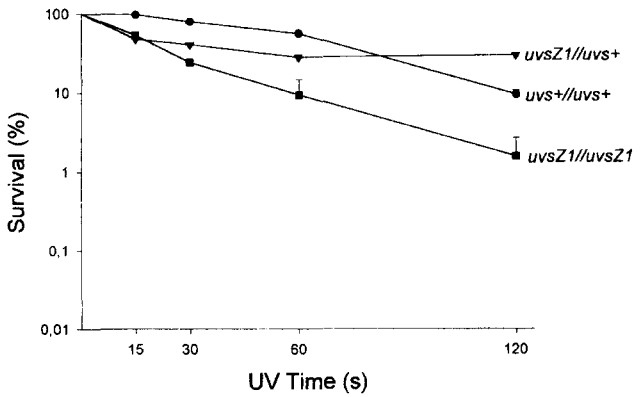

Fig. 1. Dominance-recessiveness of *uvsZ1* with respect to sensitivity to UV. This was determined by the analyses of the survival response of germinating conidia of diploid heterozygous *uvsZ1//uvs*$^+$ as compared with the homozygous *uvs*$^+$*//uvs*$^+$ and *uvsZ1//uvsZ1* diploid strains.

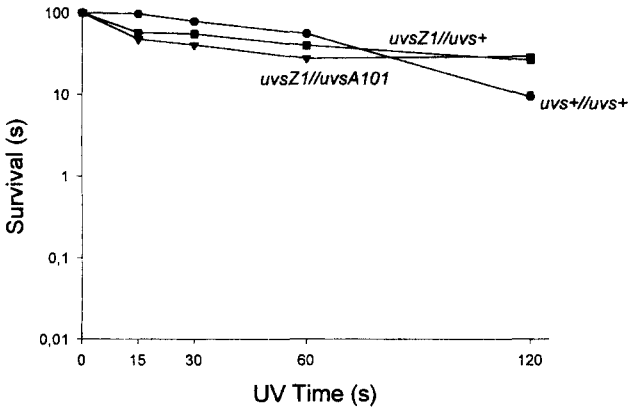

Fig. 2. Unallelic character of the *uvsZ1* mutation related with *uvsA101* mutation. This was determined by analysis of the survival response of germinating conidia of diploid heterozygous *uvsZ1//uvs*$^+$ as compared with the homologous *uvs*$^+$*//uvs*$^+$ and *uvsZ1//uvsZ1* diploid strains.

mapped on the right arm of chromosome I, were tested for allelism. Survival curves after UV treatment of germinating conidia for heterozygous diploid strains are represented in Fig. 2. Results show that Z1//A579 (*uvsZ1//uvsA101*), A757 //Z1 (*uvs*$^+$*//uvsZ1*) and UT448//A757 (*uvs*$^+$*//uvs*$^+$) diploid strains have the same survival response to UV and define the *uvsZ* as a new *uvs* gene.

The map distance between *uvsZ1* and *uvsA101* mutations, obtained from Z1 × A579 sexual cross, was 8.3 cM apart in chromosome I (Fig. 3). Differentiation among the four types of UV-sensitivities was obtained by UV-irradiation of parental strains and their progeny and by comparison between their UV-phenotypes. Segregants that showed higher UV-sensitivities than those in parental strains (double-mutants) and those that showed UV-resistance were considered recombinants (Fig. 3). The presence of double mutants in this cross confirms that *uvsZ* and *uvsA* are different genes located in the same linkage interval of chromosome I (Fig. 4).

In contrast to *uvsA101* mutation, the *uvsZ1* mutation conferred higher UV-sensitivity in quiescent conidia than in germinating conidia (Fig. 5).

UV mutagenesis

The mutator phenotype of the *uvsZ1* mutant to UV-treat-

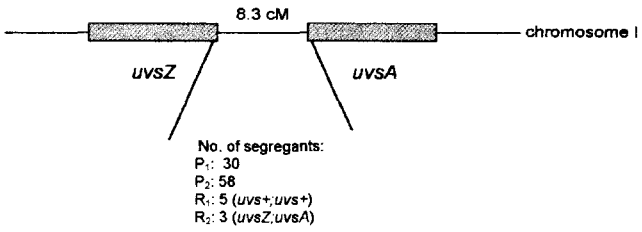

Fig. 3. Map distance between *uvsZ* and *uvsA* genes in chromosome I obtained from the Z1 × A579 cross. P_1, parental *uvsZ1* class; P_2, parental *uvsA101* class; R_1 and R_2, recombinant classes.

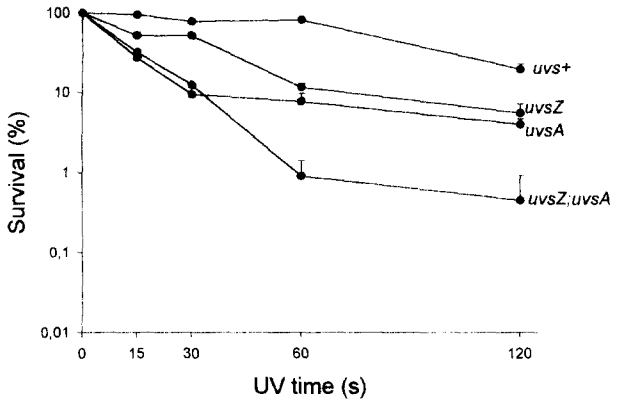

Fig. 4. UV-survival of *uvsZ, uvsA* double mutant strain compared to *uvs*$^+$, *uvsZ1*, and *uvsA101* single mutants without pre-incubation (quiescent conidia).

ment shows that there is no involvement of *uvsZ1* mutation in error-prone repair, since non-repaired lesions by an inefficient UVSZ protein induced mutagenesis (17, 15) (Figs. 6a and 6b). On the other hand, the lethality observed in *uvsZ1* quiescent conidia in UV-exposition higher than 45 s (data not shown) suggests that UVSZ protein has an important function in the DNA damage response at the G0 phase of the cell cycle (Fig. 6a). This may explain the hypermutator behavior of *uvsZ1* quiescent conidia in low UV-doses, which show an opposite effect in the UV-exposition of germinating *uvsZ1* conidia.

MMS sensitivity

The *uvsZ1* mutant and the wild-type strain showed the same sensitivity to MMS. This suggests that *uvsZ1* mutant is capable of removing the methyl adducts in the DNA molecule and indicates the lack of involvement of *uvsZ1* mutation and BER pathways. The *uvsA101* mutant with a MMS wild-type sensitivity (5) was used as the negative control and *uvsH77* mutant was used as the positive control (19) (Fig. 7).

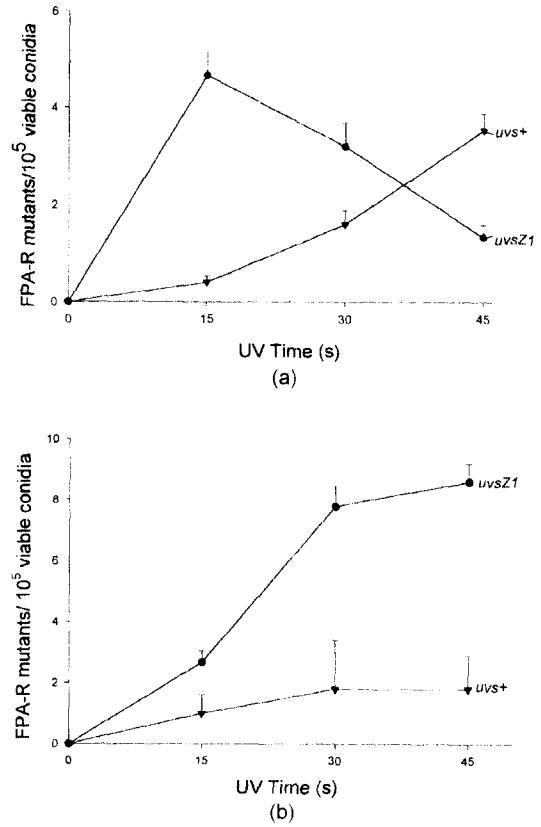

Fig. 6. Frequencies of UV-mutation to FPA-resistant in *uvsZ* and *uvs*$^+$ conidia in (a) quiescent conidia and (b) germinating conidia (6 h of the pre-incubation). The frequencies of spontaneous mutation have been subtracted. They were below 4.6×10^{-6} in the *uvsZ1* strain. No spontaneous mutant was recovered from the *uvs*$^+$ strain. The level of mutagenesis is expressed as the number of FPA-resistant colonies/10^5 viable colonies plated.

Measurement of the mitotic and meiotic crossing-overs

The *uvsZ1* homozygous (Z1//Z325) and heterozygous (Z1 //A495) diploid strains were constructed to study the effect of *uvsZ1* mutation on the mitotic crossing-over.

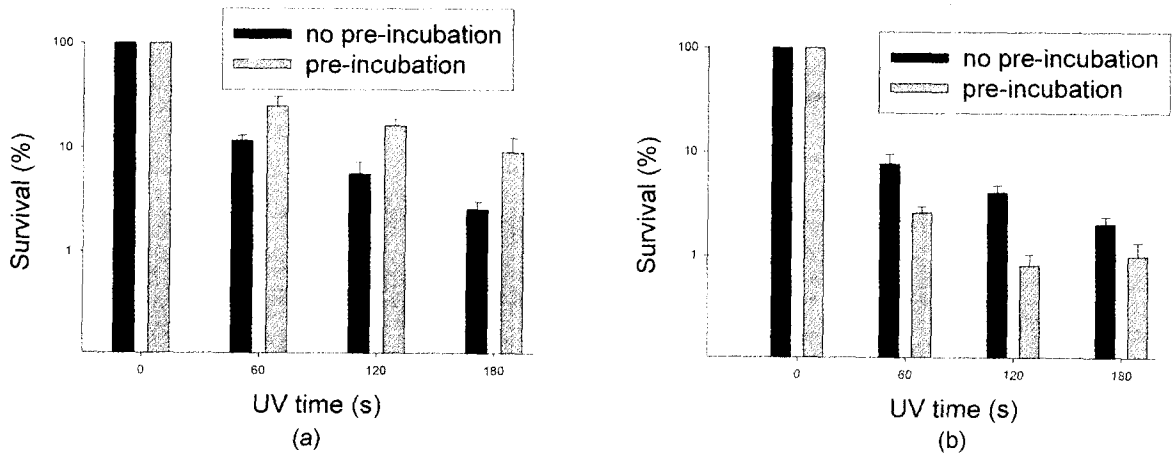

Fig. 5. UV-survival of both *uvsZ1* (a) and *uvsA101* (b) mutants with 0 (quiescent conidia) and 6 h of pre-incubation (germinating conidia).

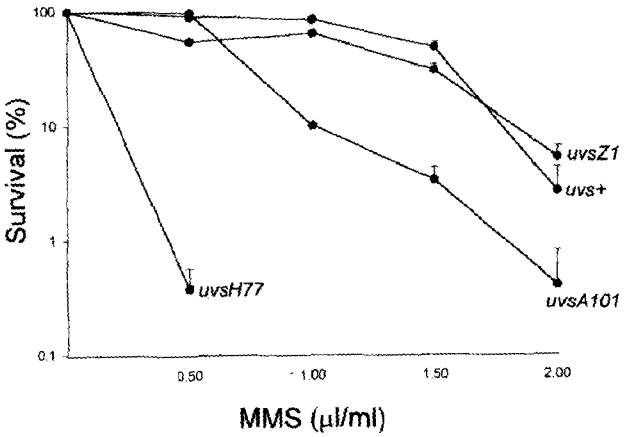

Fig. 7. MMS sensitivity of *uvs*$^+$, *uvsZ1*, *uvsA101* and *uvsH77* mutant strains.

Mitotic recombination frequencies were not significantly high in these diploids when compared with those of the *uvs*$^+$//*uvs*$^+$ diploid strain. Analysis of meiotic crossing-over was impaired by the absence of fertility in the homozygous cross Z1 × Z325 (*uvsZ1* × *uvsZ1*). Thus the meiotic inter- and intragenic crossing-overs were analyzed only in heterozygous crosses for *uvsZ1* mutation. The Z1 × A441 cross (*pabaA124* × *pabaA1*) showed an absence of *paba*+ recombinant segregants, while the Z1 × A495 cross showed normal recombinant frequency for the interval *lysB5* and *nicA2*. These results suggest that *uvsZ1* does not affect the meiotic intergenic or intragenic crossing-overs (data not shown).

Epistatic grouping of uvsZ1 mutant

The *uvsZ1* mutant was combined with different *uvs* mutations belonging to the epistatic groups UvsB (*uvsB413*), UvsC (*uvsE182*), UvsF (*uvsH77*) and UvsI (*uvsI501*). Such double-mutant strains were analyzed for epistasis by survival curves after UV treatment.

In germinating conidia the *uvsZ1;uvsE182* double mutant showed at least additive effects (Fig. 8a). This argues against epistasis between *uvsZ1* and UvsC epistatic groups. However, when quiescent cells were treated with UV, no synergistic interaction was found in the two pairs of mutations (results not shown), since *uvsE* mutants only showed UV sensitivity after pre-incubation (8). Similar findings have already been commented on by Kafer and Mayor (15).

With regard to the *uvsI* test, double mutants were built, combining *uvsI501* and *uvsZ1* mutations. Such double mutant strains demonstrated lack of epistasis for *uvsI501*

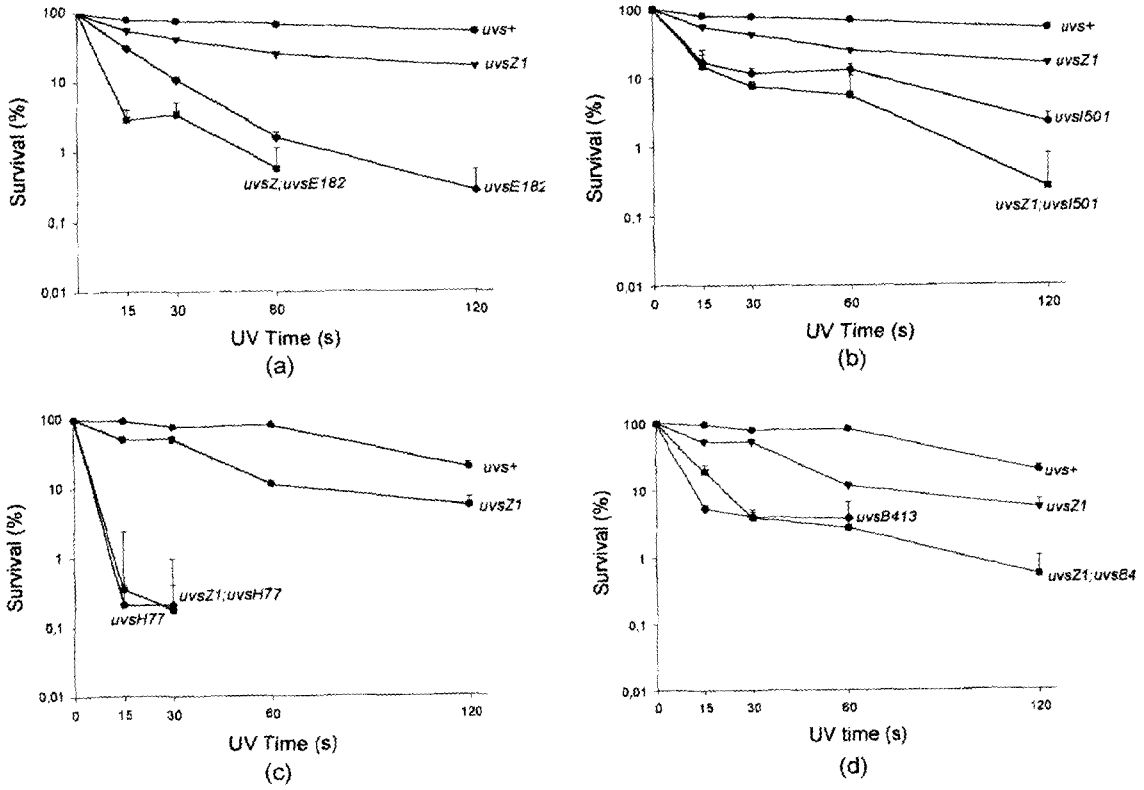

Fig. 8. Survival of single *uvs* mutants strains, compared to double mutants combining the *uvsZ1* mutation with members of the four epistatic gr UvsB (*uvsB413*), UvsC (*uvsE182*), UvsF (*uvsH77*) and UvsI (*uvsI501*). a-b, UV irradiation of germinating conidia; c-d, UV irradiation of qui conidia.

and *uvsZ1* mutations, since additive interaction was found after UV exposure (Fig. 8b).

The survival curves showed epistatic relationships among the *uvsZ1* mutation and UvsF and UvsB epistatic groups. The *uvsZ1; uvsB413* and *uvsZ1; uvsH77* double mutants were no more UV-sensitive than the more extreme of their single mutant strains (Fig. 8c and 8d respectively).

Discussion

DNA repair responses have been intensely studied especially after the discovery of the involvement of DNA repair genes with human cancer (7). These mechanisms have been investigated in several organisms, ranging from prokaryotes to humans. This paper characterizes a novel DNA repair mutation in *A. nidulans*. This mutation, named *uvsZ1*, was found to be recessive and was mapped on the interval between *pabaA* and *yA* genes in chromosome I (4).

The first aim of this investigation was to distinguish between *uvsZ1* and *uvsA101* genes, previously mapped in the same linkage interval. Complementation tests showed wild-type sensitivity to UV of the *uvsZ1//uvsA101* diploid. This indicated that *uvsZ1* and *uvsA101* are not allelic mutations. Indeed, the distance between these two *uvs* genes was roughly 8.3 cM apart in chromosome I. Further, *uvsZ1* mutation causes major UV-sensitivity in quiescent cells, contrary to *uvsA101* mutation (5).

The *uvsZ1; uvsA101* double mutant exhibited high UV sensitivity when compared with *uvsZ1* and *uvsA101* single mutants and these results confirm the non-allelic character of *uvsZ1* and *uvsA101* mutations.

Although the mitotic intergenic recombination was measured in a small map interval, preliminary results showed that *uvsZ1* mutation seemed to have no effect on the mitotic crossing-over. With regard to the sexual cycle, the *uvsZ1* × *uvsZ1* cross was infertile, impairing the analysis of the meiotic recombination. Several *uvs* mutations, such as *uvsF, uvsB and uvsD*, also promote deficiency in the sexual cycle in homozygous conditions (8, 15).

uvsZ1 mutant is able to remove the damage caused by alkylanting agents, such as MMS. This may exclude the participation of *uvsZ* gene in the BER pathways (12). However, the *uvsZ1* mutation confers a leaky UV-sensitivity phenotype only in quiescent cells. It may be possible that the functional *uvsZ* gene is related with the removal of "bulk" lesions in the DNA molecule before DNA synthesis (18).

Besides, *uvsZ1* quiescent conidia showed lethality in high UV-doses and hypermutagenic behavior in low UV-doses in a mutagenic assay. In a previous report, lethality in mutagenesis tests was also reported in the highest sensitivity phase of *uvsC114* and *uvsE182* mutants (germinating conidia) because of their high UV-sensitivity (15). Such findings may suggest that UVSZ protein has an important role as a response to DNA damage in the G0 phase of the cell cycle and may be related with NER since, in quiescent cells, only NER and error-prone repair correct UV-induced lesions. Moreover, NER *rad* mutants in *S. cerevisiae* show high level of UV-induced mutations in quiescent cells (15, 22). In spite of this, *uvs* mutations of *A. nidulans*, such as *uvsF201*, have shown an increase of UV-sensibility and UV-induced mutation in quiescent cells but are not involved with NER (15). Therefore, additional assays must be carried out to check the *uvsZ* gene and NER relationships.

In the epistasis test *uvsZ1* mutation showed an epistatic relationship with *uvsH77* and *uvsB413* mutations. In fact, the latter's familiarity has been found. In a previous report, *uvsB* and *uvsH* genes were considered the same, because of their similar phenotypes. In spite of the NER phenotype of these mutants (*uvsH77* and *uvsB413*), they have not been in fact assigned to NER defects. Indeed, UvsF members (*uvsF* and *uvsH* genes) seem to be involved with the post replicational repair pathways (13) and UvsB group (*uvsB* and *uvsD* genes) is involved with checkpoint control, induced mutagenesis and regulation of DNA-repair gene expression (11). The epistatic relationships of the *uvsZ1* with *uvsH77* and *uvsB413* mutations suggest that their DNA damage responses may be associated. These findings may represent a common enzymatic step in different DNA repair pathways or the same enzymatic action in distinct repair pathways, such as the role of DNA polymerase, required in almost all DNA repair mechanisms (28). DNA polymerases β, δ and ε are all involved in various forms of DNA-repair. Base excision-repair involves DNA polymerase β and δ or ε in yeast, *Saccharomyces cerevisiae*. Nucleotide excision-repair uses DNA polymerase δ or ε to resynthesize the base removed during repair of pyrimidine and other bulky adducts in DNA. Similarly, it seems that mismatch-repair of replication errors involves DNA polymerases δ or ε to replace the altered bases removed during the repair process (18, 28). Besides the excision repair, DNA polymerase δ is also involved in post replicational repair in error-free recombinational bypass process of the UV-damaged DNA in yeast (25).

The DNA damage responses consist of extensive repair systems that deal directly with DNA damage, as well as checkpoint surveillance systems in complex and overlying pathways (11). These mechanisms are so complex that in the case of *A. nidulans* it has been really difficult to understand the precise role of the *uvs* genes in the DNA damage response. Answers to this subject are still to be given.

uvsZ1 mutation showed normal frequencies of mitotic and meiotic crossing-overs and epistatic relationship with two different epistatic groups. On the other hand, the *uvsZ1* mutant exhibited NER phenotype: (i) UV-sensitivity before

DNA synthesis, (ii) increase of UV-induced mutagenesis and (iii) absence of sensitivity to alkylanting agent. These observations were not found in other *A. nidulans uvs* mutant and further studies will be necessary to provide information about the interaction of the cell cycle control, post replicational and excision repair pathways in the *uvsZ1* mutant.

Acknowledgments

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