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THE ROLE OF INDUCIBLE DNA REPAIR IN W-REACTIVATION AND RELATED --ETC(U)
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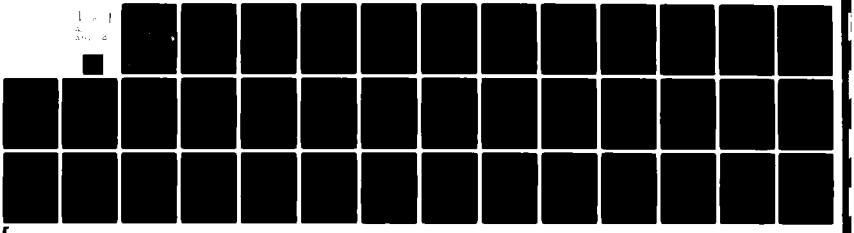

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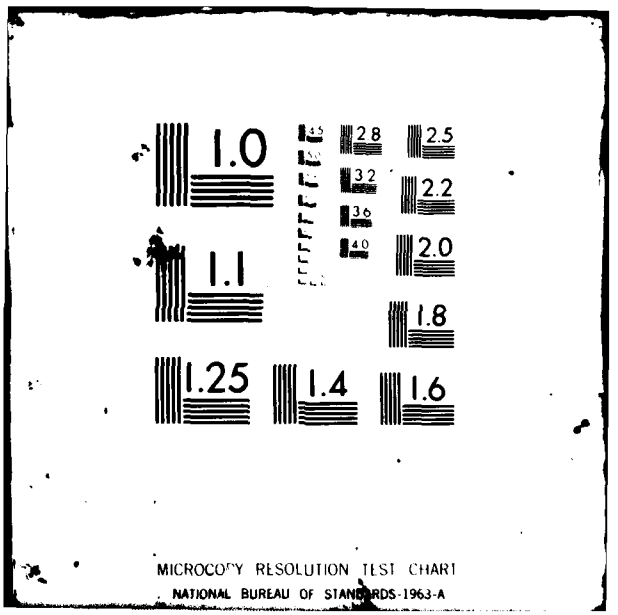
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Most of the UV-induced photoproducts in the DNA of bacteria and their viruses are repaired by "error-proof" repair mechanisms such as photoreactivation, "short-patch" excision repair, and recombinational repair. Single-strand gaps resulting from replication of DNA, which contains pyrimidine dimers, can be repaired by ultraviolet (UV)-inducible, recA+ lex+-dependent "error-prone" repair ("SOS" repair) which leads to mutations in the bacteria and its phages. Other UV-induced, recA+ lex+-dependent functions, such as prophage induction, filamentous growth, and W-reactivation, are coordinately regulated with the

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error-prone repair functions. An increasing amount of experimental evidence suggests that misincorporation of bases could result from an inducible factor which affects the proofreading activities of DNA polymerase, allowing it to fill postreplicative daughter strand gaps across from non-coding UV photoproducts. Mutagenic W-reactivation illustrates the role of UV-inducible, recA+ lex+-dependent functions in the error-prone DNA repair of bacteria and their viruses.

The Role of Inducible DNA Repair in W-reactivation and Related Phenomena[1]

Gregory B. Knudson

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Running head: W-REACTIVATION

[1]The views of the author do not purport to reflect the positions of the Department of the Army or the Department of Defense.

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A. Introduction

Most of the UV-induced photoproducts in the DNA of bacteria and their viruses are repaired by "error-proof" repair mechanisms such as photoreactivation, "short-patch" excision repair, and recombinational repair. Single-strand gaps resulting from replication of DNA, which contains pyrimidine dimers, can be repaired by ultraviolet (UV)-inducible, *recA*$^+$ *lex*$^+$-dependent "error-prone" repair ("SOS" repair) which leads to mutations in the bacteria and its phages. Other UV-induced, *recA*$^+$ *lex*$^+$-dependent functions, such as prophage induction, filamentous growth, and W-reactivation, are coordinately regulated with the error-prone repair functions. An increasing amount of experimental evidence suggests that misincorporation of bases could result from an inducible factor which affects the proofreading activities of DNA polymerase, allowing it to fill postreplicative daughter strand gaps across from non-coding UV photoproducts. Mutagenic W-reactivation illustrates the role of UV-inducible, *recA*$^+$ *lex*$^+$-dependent functions in the error-prone DNA repair of bacteria and their viruses.

B. Enzymatic Repair Systems in Bacteria and their Viruses

Ultraviolet irradiation of bacteria damages the DNA by forming intrastrand pyrimidine dimers (Setlow and Carrier 1966) and other lesions which distort the DNA duplex (Marmur and Grossman 1961) which may utimately lead to cell death or to mutations through error-prone repair. In UV-irradiated *Escherichia coli* about six pyrimidine dimers are formed per genome per erg per mm^2 (Witkin 1969c). Bacteria can remove these UV-induced distortions

in the DNA double helix by several enzyme repair systems, including photoreactivation, "short-patch" and "long-patch" excision repair (dark repair), pre- and postreplicative recombinational repair, and inducible error-prone ("SOS") repair. Some bacteriophages possess genes for enzymatic dark repair operating to minimize the damaging effects of UV-induced lesions in their DNA (Hayes 1974) thereby protecting the integrity of their genetic material. Ultraviolet-induced lesions in the DNA of infecting phages that do not have their own DNA repair systems may be repaired by the bacterial host systems. Thus the lethal effects of dimers in the phage DNA can be overcome by (a) their monomerization through enzymatic photoreactivation (Dulbecco 1950); (b) the physical removal by an excision-repair system, as in "host cell reactivation;" (c) genetic recombination, as in "prophage reactivation" and "multiplicity reactivation" (Luria 1952; Bernstein 1981); or (d) the inducible error-prone repair system, as in "Weigle-reactivation" (UV-reactivation).

The most important biological effect of UV irradiation is the photochemical formation of thymine dimers in the DNA double helix. Kelner (1949) first observed that the killing and mutagenic effects of ultraviolet light can be prevented by exposing UV-irradiated E. coli to visible light. Wulff and Rupert (1962) demonstrated that photoreactivation results from the error-free monomerization of pyrimidine dimers in situ by a photoreactivating

enzyme which is activated by visibile light. The ability to hydrolyze thymine dimers photochemically can be lost by a single *phr*$^-$ gene mutation (Setlow and Setlow 1963; Hanawalt 1968). This enzyme, isolated from the photoreactivable species *E. coli* or *Saccharomyces cerevisiae*, can restore about 10% of the transforming activity to UV-inactivated transforming DNA in the presence of visible light of wavelength 300-400 mμ (Rupert 1961). *Bacillus subtilis*, *Pneumococcus*, and *Haemophilus* lack this enzyme and are not photoreactivable (Hayes 1974).

Garen and Zinder (1955) found that some UV-irradiated bacteriophages could be reactivated by the nonirradiated host bacteria. This mode of UV repair, later named host cell reactivation (HCR), was shown to result from excision of the regions containing pyrimidine dimers in the phage followed by repair synthesis (Boyce and Howard-Flanders 1964; Setlow and Carrier 1964; Devoret et al. 1975). In host cell reactivation, three widely separated genes on the chromosome of *E. coli* K12, *uvrA*$^+$, *uvrB*$^+$, and *urvC*$^+$ (Van de Putte et al. 1965; Mattern et al. 1965), control the repair of UV lesions in the infecting phage genome or in the bacterial DNA resulting from the excision of pyrimidine dimers. A mutation in any one of these three unlinked loci (*uvrA*, *B*, or *C*) shows a ten- to twenty-fold increase in sensitivity to UV (Lewin 1974) and cannot repair UV damage to infecting phages (Hcr$^-$) or their own genomes due to their inability to excise pyrimidine dimers from

DNA (Howard-Flanders et al. 1966). The Uvr^- strains retain most of their resistance to X-rays and other ionizing radiation and show normal recombination (Hayes 1974). Excision repair of DNA exposed to UV has been described at the biochemical level as the excision of single stranded oligonucleotides which include the dimer and a small number of bases on either side of it (Howard-Flanders and Boyce 1966) followed by gap enlargement and repair synthesis utilizing the bases opposite the excised segment as a template and then sealing the backbone by a DNA ligase (Kushner et al. 1971) This "short-patch" excision repair eliminates photodimers by bacterial Uvr^+ functions before DNA replication and does not seem to be mutagenic (Defais et al. 1971). "Long-patch" excision repair, which requires the $\underline{recA}^+$ $\underline{lex}^+$ genotype, introduces errors in the repair of excision gaps at a low frequency.

C. W-reactivation and W-mutagenesis

UV-reactivation is one of several interacting reactions on primary DNA damage. Weigle (1953) experimentally defined "UV-restoration" as the increased survival of UV-irradiated phage λ when plated on E. coli host cells stimulated by slight UV-irradiation before phage infection or by UV-irradiation of the phage-bacterium complexes after adsorption of the UV-inactivated phage. "UV-reactivation" (UVR) has come to refer to the higher survival of UV-irradiated bacteriophage in general when it infects host cells that have been exposed to a low dose of UV

irradiation before infection, as compared with infection of nonirradiated host cells. Among the reactivated phages, a fairly large proportion are mutants. This high rate of mutation among the reactivated phage is referred to as "UV-mutagenesis." Since ultraviolet light is not the only agent that can induce this kind of reaction, the terms "W-reactivation" (Weigle-reactivation) and "W-mutagenesis" (Weigle-mutagenesis) are used in place of the older terms "UV-reactivation" and "UV-mutagenesis" to describe the more general phenomena of error-prone repair of phage lesions that occur when host bacteria are stimulated by exposure to a mutagen prior to phage infection (Radman 1974).

W-reactivation was first observed as the increased survival of UV-irradiated phage λ when infecting UV-irradiated E. coli, as compared with infection of nonirradiated E. coli (Weigle 1953). The W-reactivation process has been demonstrated in several other E. coli bacteriophages including T3 (Weigle and Dulbecco 1953); P22 (Garen and Zinder 1955); T1 (Garen and Zinder 1955; Tessman 1956); P1 (Kerr and Hart 1973); P2 (Bertani 1960); HP1 (Harm and Rupert 1963); and T7 (McKee and Hart 1975); and in several bacteriophage containing single-stranded DNA including S13 (Tessmand and Ozaki 1960); ϕR (Ono and Shimazu 1966); and ϕX174 (Das Gupta and Poddar 1975). W-reactivation was also demonstrated with other UV-irradiated phages including AR-1 and SP-50 plated on UV-irradiated B. subtilis (Azizbekyan and Galitskaya

1975); phage 81A in Streptococcus faecalis X14 (Miehl et al. 1980); phage P22 in Salmonella typhimurium TA92 (Walker 1978); and phages PS20 and 368ϕ in Serratia marcescens (pKM101; R68.45) (Knudson 1977).

W-reactivation of UV-irradiated phage λ can be initiated not only by exposure of the E. coli host cells to UV, but also by their exposure to nitrogen mustard (Weigle 1953); X-rays (Weigle 1953; Ono and Shimazu 1966); mitomycin C (Otsuji and Okubo 1960); or to nonlethal periods of thymine starvation (Hart and Ellison 1970). W-reactivation of UV-irradiated phage λ also occurs on E. coli with DNA ligase deficiency (Morse and Pauling 1975) or with the presence of the tif$^-$ mutation (Castellazzi et al. 1972a). Phage damage by agents other than UV-irradiation also show W-reactivation, such as gamma radiation (Bresler et al. 1978), nitrous acid (Ono and Shimazu 1966), hydroxylamine (Vizdalova 1969), nitrogen mustard (Kerr and Hart 1972), and 5-bromouracil incorporation before UV-irradiation (Kneser et al. 1965; Kerr and Hart 1972).

The variety of DNA lesions which can be W-reactivated indicates that the process must be of a generalized nature, depending on elimination of the damage rather than its reversal. Treatments that promote W-reactivation of phage λ in nonlysogenic E. coli, such as UV-irradiation, thymineless death, or thermal shift of tif$^-$ mutants, also promote

lysogenic induction in lysogenic bacteria (Hart and Ellison 1970; Castellazzi et al. 1972a).

Several possible mechanisms for W-reactivation have been postulated. Harm (1963) reported that W-reactivation is not a specific repair process but an enhancement of host cell reactivation. He showed that in the "completely" HCR-deficient strain of E. coli K12s (hcr^-), which inhibits the excision of pyrimidine dimers from both bacterial and phage DNA mediated by host-cell enzymes, no W-reactivation is found. W-reactivation took place in systems which showed HCR and was absent in those where no HCR was observed. In support of this hypothesis, Mattern et al. (1965) and Ogawa et al. (1968) reported that the UV-sensitive Hcr^- strains (mutants in uvrA, B, or C) of E. coli lack the capacity for both host cell reactivation and W-reactivation. However, in contradiction to Harm's (1963) hypothesis, Kneser et al. (1965) and Kneser (1968) reported that even when HCR was efficiently restricted by using the nonhost cell-reactivating strain of E. coli K12s (hcr^-) as the host, appreciable W-reactivation of λ phage was observed. Harm (1966) defended his hypothesis that increased phage survival under W-reactivation conditions is due to enhanced efficiency of HCR by showing that Hcr^- bacteria still exhibit "residual" HCR. So the W-reactivation of phage λ observed in E. coli K12s (hcr^-) was said to be due to "residual" HCR but not "ordinary" HCR (Kneser 1968). This "residual" HCR which allows W-reactivation in an E.

coli hcr⁻ strain may be coded for by the gene uvrD (Ogawa et al. 1968), while hcr⁻ mutants at the uvrA, B, and C loci block "ordinary" HCR (Rupert and Harm 1966). Since three known types of excision-deficient mutants of E. coli K12 (uvrA, B, and C) exhibit W-reactivation of λ phage with approximately the same efficiency of W-reactivation in the excision-proficient and -deficient strains, Radman and Devoret (1971) and Defais et al. (1971) suggested that W-reactivation does not involve excision repair of pyrimidine dimers in phage DNA. Boyle and Setlow (1970) also reported that W-reactivation of λ phage does not involve HCR and that it is achieved by different mechanisms of repair. W-reactivation of λ phage in uvr⁻ mutants strongly depends on the UV dose given to both the phage and to the host cells (Defais et al. 1971), which is probably why W-reactivation in excision-deficient mutants was not detected in earlier investigations. Defais et al. (1971) further suggested that the uvr⁺ functions of excision repair, which is an accurate repair mechanism (Witkin 1969a,b), are not required for W-mutagenesis of λ phage. The single-stranded DNA phage ϕR fails to be reactivated by the HCR mechanism of E. coli but is competent for W-reactivation (Ono and Shimazu 1966), which further suggests that W-reactivation and host cell reactivation are due to independent mechanisms.

In UV-irradiated E. coli, both excision and resynthesis are carried out by DNA polymerase I (Hanawalt and Setlow

1975). Ogawa (1970) reported that the polA$^-_1$ mutant of E. coli K12, which is deficient in DNA polymerase activity and has increased UV-sensitivity, lacks W-reactivation ability for UV-irradiated λ phage. Paterson et al. (1971) also reported that polA$^-_1$ mutants are almost totally deficient in W-reactivation. However, Caillet-Fauquet and Defais (1972) showed that maximum W-reactivation occurs in polA$^-$ mutants, as in uvrA$^-$ mutants, at lower UV doses than in the wild type cells. Ogawa (1970) and Paterson et al. (1971) did not observe W-reactivation in the polA$^-$ mutants due to the high doses of UV used on both λ and the host cells.

Defais et al. (1971) suggested that the UV-induced repair system resulting in W-reactivation and W-mutagenesis acts directly on unexcised dimers in λ DNA. This was consistent with the finding of Tomilin and Mosevitskaya (1975) which showed that the UV-endonuclease from Micrococcus luteus strongly decreases W-reactivation and mutagenic (error-prone) repair of UV-irradiated λ DNA. Roulland-Dussoix (1967) and Boyle and Setlow (1970), suggested that W-reactivation results from the protection of the UV-damaged phage DNA against attack by nucleases which are directed against UV-damaged bacterial DNA. W-reactivation could occur because UV-damaged host DNA acts as a substrate for the excision enzymes competing for their action with dimers in the λ phage DNA and shifting the balance in favor of phage repair. Harm and Rupert (1963) also

interpreted W-reactivation to be the result of competiton between irradiated bacterial DNA and phage DNA for a nuclease specific for UV damage. However, this hypothesis does not explain how the remaining pyrimidine dimers in the λ phage DNA are eliminated or bypassed. Kneser, et al. (1965) criticized the nuclease-protection theory on the grounds that W-reactivation of phage can occur when HCR is inhibited in *uvr*$^-$ strains.

Mutants of *E. coli* K12 which have a Rec$^-$ phenotype are defective in genetic recombiantion, highly sensitive to UV and X-irradiation and map at three separate loci (Clark and Margulies 1965; Barbour and Clark 1970). The radiation-sensitive, recombination deficient *recA*$^-$ mutants degrade an abnormally large amount of their genome when exposed to UV light, earning them the name "reckless" mutants (Howard-Flanders and Theriot 1966). The closely linked, radiation-sensitive, recombination deficient *recB*$^-$ and *recC*$^-$ "cautious" mutants degrade their DNA much less after UV-irradiation (Lewin 1974). The *recB*$^+$ and *recC*$^+$ gene products may be nucleases which are responsible for much of the DNA breakdown following UV-irradiation, while the *recA*$^+$ gene product may limit the process in some way.

Bacterial *recA*$^+$ function is necessary for W-reactivation of UV-damaged phage λ (Ogawa et al. 1968; Shimada et al. 1968). The *recA*$^+$ gene function is also required for W-mutagenesis (the increased frequency of mutations in the

surviving phage from W-reactivation) and is eliminated by a single recA$^-$ mutation (Miura and Tomizawa 1968). Both W-reactivation and W-mutagenesis of phage λ are independent of recB$^+$ and recC$^+$ gene products (Kerr and Hart 1972). McKee and Hart (1975) showed that the recA$^+$ function is needed for W-reactivation of T7; Das Gupta and Poddar (1975) reported that the recA$^+$ gene is essential for W-reactivation of the single stranded DNA phage ϕX174. W-reactivation and W-mutagenesis of phage λ also require the bacterial lex$^+$ gene function (Defais et al. 1971) in E. coli K12 and the analogous exr$^+$ gene function in E. coli B (Witkin 1967a). W-reactivation does occur in the absence of recA$^+$ and exr$^+$ alleles when phage λ is damaged by nitrous acid, hydroxylamine, or nitrogen mustard, rather than by UV (Kerr and Hart 1972). The recA$^+$ and exr$^+$ gene products may be necessary to stabilize or modify UV lesions in phage DNA, but not other kinds of lesions before W-reactivation can take place, rather than being directly involved in the basic repair process itself. UV-induction of the prophage λ (Donch et al. 1970; Castellazzi et al. 1972b; Mount et al. 1976) also require the recA$^+$ and lex$^+$ functions. Host cell reactivation is also less effective in recA$^-$ mutants (Echols and Gingery 1968), suggesting that some common pathways are involved in these phenomena.

As replication proceeds in UV-damaged bacterial DNA, unrepaired pyrimidine dimers cause the formation of daughter

strand gaps in the newly formed DNA strand opposite each unrepaired lesion (Howard-Flanders et al. 1966, 1968; Rupp and Howard-Flanders 1968). These discontinuities in the newly replicated molecule, which are lethal if not repaired, cannot be filled by repair replication since they are located opposite a non-coding lesion. Postreplication repair of gaps opposite unexcised pyrimidine dimers can proceed by a recA$^+$-dependent recombinational process between complementary daughter strands in which the intact region of one daughter strand serves as a template for repair of the gap in the other to restore the original DNA structure (Rupp et al. 1971). According to Witkin (1969c), UV-induced mutagenesis results from errors due to inaccurate post-replicative repair dependent upon the lex$^+$ function.

In prereplicative recombinational repair, which involves recombination of two DNA duplexes, there is no need for DNA synthesis since all the DNA strands needed for recombination are already present. Prereplicative recombinational repair is a nonmutagenic (error-free) process.

In prophage reactivation, first described by Jacob and Wollman (1953), the survival of UV-irradiated phage λ is greater when plated on a bacterium carrying a homologous prophage than on a host nonlysogenic or lysogenic with a nonhomologous prophage. Prophage reactivation also occurs

in phage P2 and phage P22 (Yamamoto 1967). This type of repair is due to prereplicative recombination between the homologous DNA of the UV-damaged phage and the intact resident prophage (Yamamoto 1967), so there is no need for any extensive DNA synthesis. This process is not mutagenic and is strongly decreased in a host carrying recA$^-$ mutations, but is not influenced by the presence or absence of the lex$^+$ function (Blanco and Devoret 1973).

Garen and Zinder (1955) proposed the hypothesis that in W-reactivation, UV-irradiation of E. coli stimulates recombinational repair between the homologous regions of UV-damaged phage DNA and intact bacterial DNA, resulting in increased viability of the irradiated phage. This hypothesis could explain the requirement of recombination functions for UV-reactivation (Weigle 1966). Hart and Ellison (1970) proposed that W-reactivation and prophage reactivation of phage λ occur by related mechanisms since UV- and nitrous acid-damaged phage are reactivated by both processes. Furthermore, both processes are eliminated by recA$^-$ mutants in the host bacterium while neither process is appreciably affected by hcr alleles. W-mutagenesis could be the result of inaccurate recombination or imperfect homology between the phage and bacterial DNA (Tessman 1956; Stent 1958).

Other experimental results do not support the idea that W-reactivation occurs as a result of prereplicative recombination between homologous parts of the UV-irradiated

phage and bacterial chromosomes (Ogawa and Tomizawa 1973). Radman and Devoret (1971) reported that the absence of attachment regions in the host and λ chromosomes does not effect W-reactivation. Blanco and Devoret (1973) showed that W-reactivation of phage λ does not require, and is not enhanced by, the presence of large pieces of DNA which are homologous to the infecting phage DNA. The independence of W-reactivation and prereplicative recombination is further demonstrated by the fact that UV-reactivation requires the lex$^+$ function (Defais et al. 1971) and is highly mutagenic, while prophage reactivation is unaffected by mutations in lex and is not mutagenic (Blanco and Devoret 1973). In contrast to prereplicative recombinational repair, W-reactivation is unaffected by the recB and recC genes and the need for the recA$^+$ and lex$^+$ gene products in W-reactivation is dependent on the nature of the lesion in the DNA (Kerr and Hart 1972). W-reactivation occurs in the single stranded DNA phage S13, ϕR, and ϕX174, which seems to exclude the possibility that W-reactivation is due to a pre-replicative recombinational repair mechanism between two DNA duplexes, as in prophage reactivation. The "recombination" hypothesis as the mechanism of W-reactivation presumes a high degree of homology between the bacterial and the phage DNA. However, in the DNA of phage AR9, which is subject to W-reactivation in B. subtilis, the thymine has been replaced by hydroxymethyluracil. Furthermore, the compositions of the DNA bases of the phage and bacteria

differ substantially [G + C = 27.7 and 44.8, respectively (Azizbekyan and Galitskaya 1975)]. These results indicate that prophage reactivation and W-reactivation are engendered by two different mechanisms.

Although UV-reactivation and UV-mutability of λ phage are correlated, in that they are both blocked by recA$^-$ and lex$^-$ mutations, are both UV-induced, and show comparable kinetics as a function of UV dose given to the host cells and to the phage (Defais et al. 1971; Wackernagel and Winkler 1971), there is evidence that they are separate, non-interdependent phenomena. Kerr and Hart (1972) showed that when phage λ is damaged by nitrous acid, hydroxylamine, or nitrogen mustard, rather than by UV, W-reactivation does occur in recA$^-$ and exr$^-$ mutants. However, W-mutagenesis of λ phage, which normally accompanies W-reactivation, does not occur in the recA$^-$ or exr$^-$ bacteria (Kerr and Hart 1972). This demonstrates that W-mutagenesis of λ phage is not an essential feature of the W-reactivation process itself. Although W-reactivation is independent of the recA$^+$ and exr$^+$ alleles, W-mutagenesis is not, and like UV-induced error-prone repair mutagenesis of bacteria, it does not occur in recA$^-$ or exr$^-$ mutants. Morse and Pauling (1975) have shown that W-mutagenesis in E. coli is not essential component of W-reactivation because phage mutagenesis, but not reactivation, is inhibited by 3 μg/ml of chloramphenicol. Mount et al. (1976) reported that phage λ is W-reactivated in the tsl$^-$ recA$^-$ mutant strain of E. coli with about

one-half the efficiency of that in the wild type strain, but with no corresponding mutagenesis of the phage. This suggests that there is a UV-inducible error-free pathway of DNA repair in E. coli that is independent of the UV-inducible error-prone repair of phage lesions.

George et al. (1974) demonstrated indirect W-reactivation of phage λ and its mutagenesis by introducing UV-damaged DNA into a nonirradiated F^- recipient host cell through conjugation with a UV-irradiated Hfr (high-frequency recombination) or F-lac$^+$ donor prior to infection with UV-irradiated phage. George et al. (1974) found that chromosomal or episomal UV-damaged DNA is effective in inducing indirect W-reactivation even in Uvr^- strains, in which there is no excision of pyrimidine dimers.

D. Direct and Indirect Prophage Induction

The lysogenic state of prophage λ is maintained by a cytoplasmic protein repressor which is specified by the c_1 region of the λ phage genome (Ptashne 1967). Lwoff et al. (1950) first demonstrated that treating bacteria with small doses of UV can induce the prophage to enter the vegetative state, multiply, and lyse the bacteria (direct induction). Jacob and Wollman (1959) showed that X-rays and nitrogen mustard were also effective inducing agents. Treatment of E. coli K12 lysogenic for phage λ with mitomycin C or deprivation of thymine, which inhibits bacterial DNA synthesis, also induces

prophage λ to enter the vegetative state (Korn and Weissbach 1962). These treatments which result in prophage induction must involve the inactivation of the prophage repressor system, perhaps by the formation of an "inducer" which inactivates the repressor.

Indirect induction, first described by Borek and Ryan (1958), occurs when an $F^+\lambda^-$ donor E. coli K12 is irradiated with UV and crossed with a non-irradiated F^- cell lysogenic for λ. The indirect induction of prophage λ is mediated through the UV-irradiated sex factor. However, unlike indirect W-reactivation, indirect induction does not occur when UV damaged chromosomal DNA from an Hfr λ^- cell is introduced by conjugation into an $F^- \lambda^+$ recipient (Devoret and George 1967). Indirect induction can also result from the conjugal transfer of UV damaged F', such as F-lac^+ and F-gal^+, into F^- lysogenic recipients (George and Devoret 1971). Monk (1969) reported that indirect induction of prophage λ in a lysogenic recipient cell can be brought about by conjugation with a UV-irradiated donor cell carrying the transmissible Col I factor (colicinogen) or RTF (resistant transfer factors). Infection with irradiated phage P1, which is maintained in an autonomous state (Ikeda and Tomizawa 1968) also brings about indirect induction of λ lysogens (Rosner et al. 1968). The replicons Col I, RTF, the sex factors F and F', and the phage P1, all of which can mediate indirect induction of a lysogen, have in common the

ability to replicate coordinately with the bacterial chomosome without integrating into the bacterial chromosome.

Recombination-deficient mutants (*recA*$^-$) of *E. coli* K12 which are lysogenic for λ phage are not inducible by UV irradiation (Fuerst and Simonovitch 1965; Hertman and Luria 1967). Indirect induction, mediated by irradiated F or P1, does not occur in *recA*$^-$ mutants which are lysogenic for λ (Brooks and Clark 1967; Rosner et al 1968). When the *rec*$^+$ gene is introduced into *E. coli* K12 *rec*$^-$ (λ$^+$) by transduction with phage P1, it is then capable of producing λ phage after UV induction (Hertman and Luria 1967). This shows that the failure of UV to induce λ in the *rec*$^-$ lysogens is due to an inability to lift repression rather than to damaged prophage. Direct UV-induction of λ, like W-reactivation, also requires the *lex*$^+$ gene in *E. coli* K12 (Castellazzi et al. 1972b) or the equivalent *exr*$^+$ gene in *E. coli* B (Donch et al. 1970).

E. Plasmid Mediated UV-Protection and Mutagenesis

Plasmid mediated resistance to killing by UV-irradiation (UV-protection) with an increase in mutagenesis has been reported in *S. typhimurium* and *E. coli* containing Col I (Howarth 1965, 1966), R46 (Mortelmans and Stocker 1976) and its derivative pKM101 (Walker 1977) and R-Utrecht (MacPhee 1973); in *E. coli* (Monti-Bragadin et al. 1978; Siccardi 1969) and *Pseudomonas aeruginosa* (Krishnapillai 1975; Lehrbach et al. 1977, 1978) containing R factors

and sex factors; in S. faecalis (Miehl et al. 1980); and in S. marcescens containing plasmids pKM101 and R68.45 (Knudson 1977). Plasmid R46 mediated UV-protection and enhanced UV-mutagenesis are absolutely dependent on the recA$^+$ genotype in E. coli and S. typhimurium (Mortelmans and Stocker 1976) and dependent on the host lex$^+$ function in some strains of E. coli (Waleh and Stocker 1979). The ability of plasmid pKM101 to enhance mutagenesis and DNA repair is recA$^+$ lex$^+$-dependent in E. coli (Walker 1977) and recA$^+$ dependent in S. typhimurium (McCann et al. 1975). Plasmid R46 and pKM101 mediated W-reactivation of UV-irradiated phage λ in E. coli (Walker 1977) and phage P22 in S. typhimurium (Walker 1978) has also been observed. The evidence suggests that these plasmids amplify the activity of the inducible error-prone repair system of the host.

F. Inducible "SOS"-Repair Functions

W-reactivation, W-mutagenesis, direct and indirect induction of prophage λ, cell filamentation and UV-mutagenesis of bacteria are all related phenomena with common pathways (Sedgwick 1975a,b). None of these phenomena are expressed constitutively but all are induced by UV. W-reactivation and W-mutagenesis of irradiated bacteriophage, induction of phage λ, and UV-mutagenesis of bacteria resulting from error-prone repair are dependent on recA$^+$ and lex$^+$ (equivalent to exr$^+$) gene functions (Miura and Tomizawa 1968; Mount et al. 1976). Filamentous growth in lon

strains, which is strikingly parallel to prophage induction (Witkin 1967b), has the same requirement for *recA*$^+$ (Green et al. 1969) and *lex*$^+$ functions (Donch et al. 1968). Long filaments can also be induced indirectly by mating UV-irradiated Col I donor cells with nonlysogenic (λ^-) recipients (Kirby et al. 1967; Monk 1969). All of these UV-inducible, *recA*$^+$ *lex*$^+$-requiring functions are expressed spontaneously in *E. coli* K12 *tif* mutants following a shift to 42°C for 45 min (Castellazzi et al. 1972 a; Witkin 1974). These effects are abolished if chloramphenicol is present during incubation at the elevated temperature, just as in the case of prophage induction (Witkin 1975).

Protein and RNA synthesis is essential for W-reactivation (Ono and Shimazu 1966). Protein synthesis is also necessary for UV-mutagenesis (Witkin 1956) and for UV-induction of prophage λ (Tomizawa and Ogawa 1967). UV-inducible, *recA*$^+$ *lex*$^+$-requiring functions might be coordinately induced in response to the inhibition of DNA synthesis, while RNA and protein synthesis continues (Witkin and George 1973; Witkin 1974, 1975). Monk and Kinross (1975) showed that the arrest of DNA synthesis is essential for λ induction. *E. coli lig*$^-$ mutants produce defective DNA ligase, which is an enzyme that closes single-strand nicks in the DNA duplex resulting from UV-irradiation (Bonura and Smith 1975). DNA ligase deficiency which results in the inhibition of DNA synthesis (Pauling and Hamm 1969) leads to the stimulation of prophage induction

(Gottesman et al. 1973), W-reactivation, and W-mutagenesis by depressing the error-prone repair pathway (Morse and Pauling 1975).

Radman (1974) has called this $\underline{recA}^+$ $\underline{lex}^+$-dependent error-prone repair pathway, which is inducible by DNA lesions which temporarily block DNA replication, "SOS" repair. We know that in E. coli this repair pathway is (a) UV-inducible, (b) requires the $\underline{recA}^+$ and $\underline{lex}^+$ functions, (c) requires protein synthesis without DNA synthesis, (d) is error-prone, (e) involves a repair mechanism different from pre- or postreplicative recombinational repair or excision repair processes, and (f) is common to the phenomena of W-reactivation, W-mutagenesis, UV-induction of λ, cell filamentation, and UV-mutagenesis of bacteria (Devoret 1973). Witkin (1974, 1976) suggested that all of the UV-inducible $\underline{recA}^+$ $\underline{lex}^+$-dependent functions express the activity of newly derepressed genes, governed by repressors which respond to a common effector produced by a common induction pathway. The inactivation of a repressor has been demonstrated in prophage induction. Inhibition of DNA synthesis by UV lesions may initiate the induction pathway. The UV-inducible product may inhibit the 3'-5'-exonuclease "proofreading" activity of DNA polymerase. A DNA polymerase with relaxed template dependence could polymerize DNA past noninstructive UV photoproducts, while filling postreplicative daughter strand gaps, with a high probability of inserting "wrong" bases.

The ability to recover from injuries, whether mechanical, chemical or radiation, is characteristic of all living things and favored by natural selection. Therefore, it is not surprising to find genetic systems which enable bacteria and their viruses to recover from the potentially lethal effects of ultraviolet light, nor is it surprising to find this repair system tightly regulated and subject to loss by mutation. Most of the premutational lesions in bacterial and viral DNA can be eliminated by essentially "error-proof" repair pathways. The inducible "SOS"-repair system, which is coordinately expressed with a number of other phenomena, is efficient, but error-prone. The induction of a DNA polymerase that allows postreplicative repair past noncoding lesions in the template DNA increases cell survival and mutations and thereby adds to the variability and survival of the species.

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