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REPAIR OF RADIATION DAMAGE IN MAMMALIAN CELLS

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INTRODUCTION FIRST LINE OF TEXT (FIRST PAGE)

The responses, such as survival, mutation, and carcinogenesis, of mammalian cells and tissues to radiation are dependent not only on the magnitude of the damage to macromolecular structures--DNA, RNA, protein, and membranes--but on the rates of macromolecular syntheses of cells relative to the half-lives of the damages. Cells possess a number of mechanisms for repairing damage to DNA. If the repair systems are rapid and error free, cells can tolerate much larger doses than if repair is slow or error prone. ~~The general subject of repair of DNA damage has been reviewed extensively (1-4).~~

It is important to understand the effects of radiation and the repair of radiation damage because there exist reasonable amounts of epidemiological data that permits the construction of dose-response curves for humans. The shapes of such curves or the magnitude of the response will depend on repair. ~~We emphasize in this chapter~~ radiation damage, because (a) radiation dosimetry, with all its uncertainties for populations, is excellent compared to chemical dosimetry; (b) a number of cancer-prone diseases are known in which there are defects in DNA repair and radiation results in more chromosomal damage in cells from such individuals ~~(5-7)~~ than in cells from normal individuals; (c) in some cases, specific radiation products in DNA have been correlated with biological effects ~~(1)~~ and, (d) many chemical effects seem to mimic radiation effects ~~(1,2)~~. A further reason for emphasizing damage to DNA is the wealth of experimental evidence indicating that damages to DNA can be initiating events in carcinogenesis ~~(8)~~.

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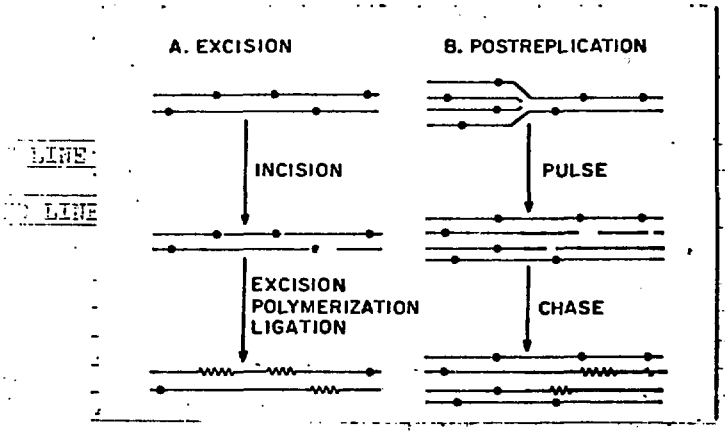

Fig. 1. Schematic diagrams of repair in mammalian cells. (a) Nucleotide excision. (b) Postreplication repair. The solid circles represent damages to DNA, the dark lines, DNA synthesized during a pulse; and the jagged lines repair replication for excision, or gap filling for postreplication repair. The average size of the former is about 100 nucleotides and 200 nucleotides for the latter.

ULTRAVIOLET DAMAGE

In prokaryotic systems, ultraviolet (UV) induced pyrimidine dimers are known to be one of the most important lesions. In higher eukaryotic systems the effects cell killing mutagenesis and neoplastic transformation of wavelengths less than 313nm, all follow action spectra--sensitivity versus wavelength--similar to that for making pyrimidine dimers in DNA (9-11). Moreover, when it has been possible to test it, photoreactivation (see Repair of Ultra-Violet Light Induced Damage in Human Skin) indicates that the important damages are pyrimidine dimers. There are a number of easy experimental ways to measure dimers and their repair (12).

Excision Repair

Fig. 1a shows a schematic diagram of the process of nucleotide excision repair. Such repair takes place in cells of all tissues of normal individuals that have been examined (fibroblasts, epithelial cells and lymphocytes). The rate-limiting step in such repair seems to be the initial endonucleolytic incision and it is this step that is very slow, although not zero, (see below) in excision defective xeroderma pigmentosum cells. The details of action of the

Table 1. Excision Repair in Mouse and Human Cell Lines[a] (Sato and Setlow, 15)

Cell line	Dimers[b] removed in 24 hr (%)
mouse, L5178y	18
Q31	3
human, Raji	39

[a] See Fig. 2 for survival curves

[b] Measured as endonuclease sensitive sites after 10J/m^2, 254nm

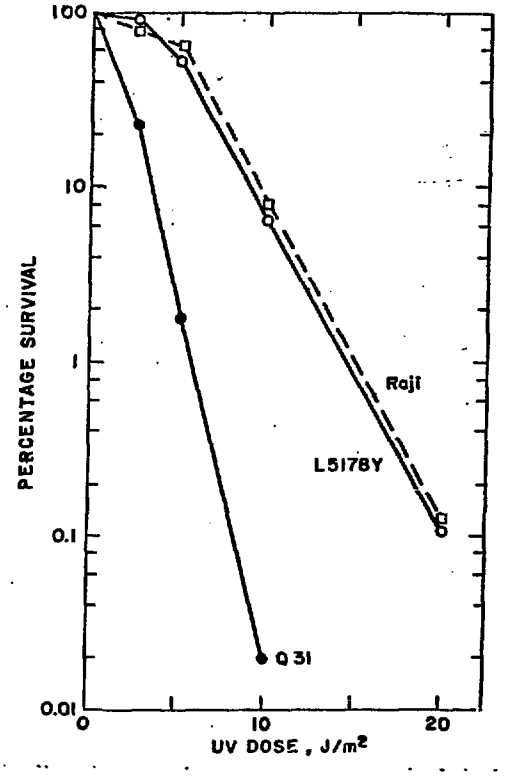

Fig. 2. Survival curves as a function of UV dose for two mouse lymphoma cell lines and a human cell line (adapted from Sato and Setlow, 15). These survival data should be compared with the excision data in Table 1.

endonucleolytic step have not been elucidated for mammalian cells. Thus, it is not clear whether an initial obligatory glycosylase action is needed before incision as is the case for purified prokaryotic enzymes (13,14). Xeroderma pigmentosum cells are killed and mutated more readily than are normal cells and there is a rough correlation between the extent of the defect in excision repair, or the defect in the ability to do host cell reactivation of UV irradiated viruses, and the enhancement of the cytotoxicity of UV and the sensitivity of skin to sunlight induced skin cancer. However, such a correlation, although good within one species does not seem to extend across species lines as indicated by the data in Table 1, and the survival curves in Fig. 2 comparing two mouse cell lines and a human cell line.

The extrapolation from cellular repair data to humans is complicated because the cellular data are obtained with acute UV doses and the development of non-melanoma skin cancer in humans follows from long chronic exposures. At low chronic dose rates, the

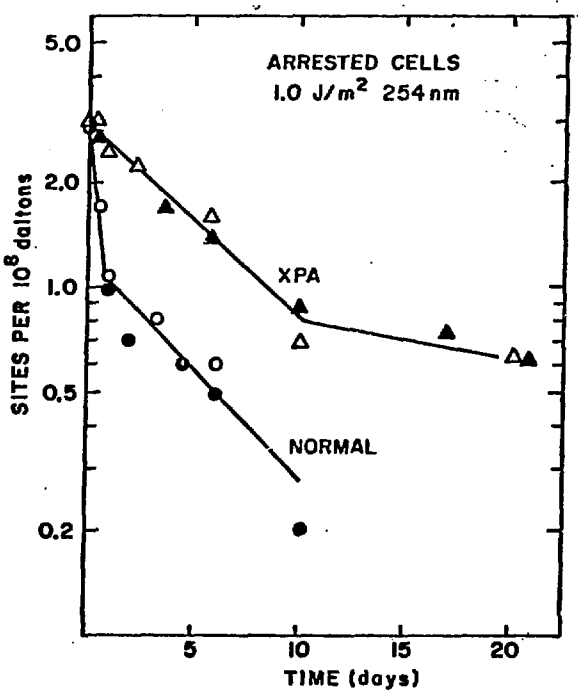

Fig. 3. The excision of pyrimidine dimers, measured as endonuclease sensitive sites, from non-dividing normal or xeroderma pigmentosum cells as a function of time (from Kantor and Setlow, 16).

difference in the magnitude of repair between proficient and deficient cells may not be as marked as shown in Table 1. For example, xeroderma pigmentosum cells are able to do some repair although, for acute doses, with different kinetics than for normal cells (see Fig. 3). However, even, in midday sunlight the low acute doses indicated in Fig. 3 might take times greater than 1 h to deliver to human skin. Thus, there is an urgent need for DNA repair studies at the chronic dose rates found in the environment.

Post Replication Repair

DNA synthesis is inhibited by UV irradiation of cells but the blockage of replication is not complete even in excision repair defective strains. Synthesis returns to normal levels in times compatible with the excision of dimers except for cells from individuals with the light sensitive disease Cockayne's Syndrome. DNA synthesis in these cells remains depressed for much longer times, and the cells are killed more readily by UV than are normal ones (17). Replication takes place on the damaged template in almost all cells before excision repair is complete, and if this replication is faulty, the cell may die, be mutated or transformed.* Replication on a damaged template is often detected experimentally by the changes in molecular weight of newly synthesized, pulse labeled DNA. Hence, the process is called postreplication repair. At short times after irradiation, pulse labeled DNA is small and this small DNA is chased into larger pieces. As Fig. 1b shows, replication seems to leave gaps in the newly synthesized DNA, and the gaps are filled in during a subsequent chase. XP variant cells are proficient in excision but are deficient in postreplication repair (19), and are mutagenized more readily than normal cells at equal levels of survival (20). Such observations indicate that the postreplication repair process may have an error prone component to it as do prokaryotic systems. Split UV doses, separated by a number of hours, to normal and especially XP variant cells enhance the rate of post-replication repair following the second dose (21). Moreover, the rate of fork motion in Chinese hamster cells is enhanced as is the rate of resumption of bulk DNA synthesis in normal cells (22,23). The enhancing effects of small ultraviolet doses to cells are also found for the survival and mutagenesis of UV irradiated viruses plated on such cells (24), although the kinetics of such an enhanced process seem quite different from the kinetics for DNA synthesis.

*In non-dividing cells, replication is not relevant, but the data indicate that transcription on the damaged template may lead to cell death (18).

Inter-Individual Variation

Most skin cancers arise from sunlight exposure and the response seems to be an exponential function of the annual dose (25). The ultraviolet dose rate changes drastically during the day and during the year. Since habits of sun exposure vary markedly among people the variation in received dose among individuals can be tremendous and this large variation might account in part for the exponential shape of the dose response curve. The tremendous ($10^3 - 10^4$ fold) difference in skin cancer prevalence between normal and XP individuals is explicable in terms of the repair deficiencies of XP cells. On the assumption that defective DNA repair is the explanation for the skin cancer prevalence of XP individuals, one can estimate that proficient DNA repair--photoreactivation, excision and postreplication repair--is able to reduce the effective UV dose to normal individuals by seven to twenty fold compared to XP individuals (26). If such numbers are close to the truth, small changes in repair of UV damage might change the skin cancer susceptibility of individuals by significant factors, although nowhere near the orders of magnitude encountered for XP individuals. What sort of variation is observed among the presumptive non-repair deficient population? Two types of experiments have been done to measure such variations: one used the bromodeoxyuridine photolysis technique to measure excision repair in

Table 2. Variations in Excision Repair among Cells Exposed to 254nm UV

A. Normal cells type	no.	method	dose(J/m^2)	Std. deviation	Ref.
fibroblasts	30	BrUra photolysis	20	17	27
leukocytes	40	UDS	20	26	28
leukocytes	90	UDS	20	44	29
		UDS	max	66	29

B. Abnormal cells type	no.	method	repair rel. to normal	Std deviation	Ref.
XP fibroblasts	10	BrUra photolysis	0.1	50	27
leukocytes from heroin addicts	38	UDS	0.3	100	29

fibroblast strains from a number of presumptive normal individuals, the other measured unscheduled DNA synthesis (UDS) in terms of cpm/μg of DNA in unstimulated leukocytes from a number of individuals with different lifestyles and ages. The results of such studies are shown in Table 2. Two points of great interest are apparent: lifestyle--heroin addiction--seems to affect the level of DNA repair and, there is a tremendous variation among individuals. The large variation is made up of variances in technique, and real variations from day-to-day for the same individual and variations among individuals. The breakdown of these variations indicates that there is a significant difference among individuals--a difference beyond the experimental or day-to-day variation. The causes for the variations, whether they be genetic or lifestyle related, are not known; nor is there any information on the prognostic value of such findings. However, the lymphocytes of individuals with actinic keratoses, have on the average, less repair than those of normal individuals (30). The keratoses are felt to be precursor lesions to non-melanoma skin cancer, and the may indicate that individuals with less repair are more prone to develop actinic keratoses. Skin cancer data are confounded not only by unknown dosimetry but by the fact that individuals have different skin types--types that show relatively large variations in pigmentation and presumably UV transmission. It might be possible by making measurements on the repair capabilities and the skin transmission properties of individuals who have had skin cancer to disentangle these two variables and obtain an estimate of the role of DNA repair capability in skin cancer prevalance among presumably normal individuals.

IONIZING RADIATION

Definitive studies on the molecular mechanisms for the repair of ionizing radiation damage are hampered by our ignorance of which radiation products are responsible for killing, mutation, and

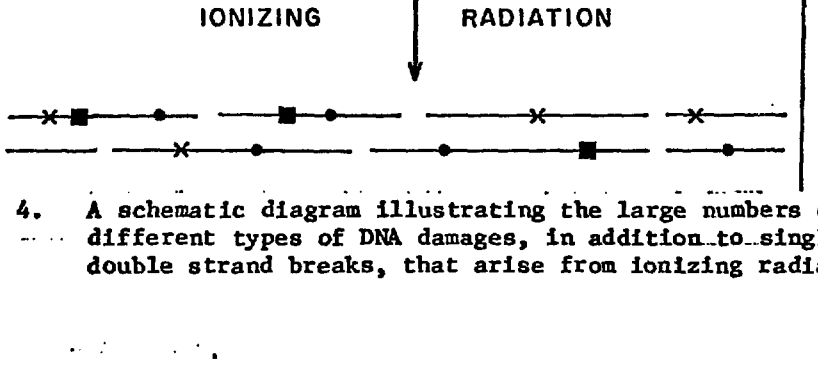

Fig. 4. A schematic diagram illustrating the large numbers of different types of DNA damages, in addition to single and double strand breaks, that arise from ionizing radiation.

transformation (Fig. 4). The easiest damage to measure--single strand breaks in DNA--is repaired at high speed and seems relatively innocuous. No mammalian cell strains have been found that are reproducibly deficient in this type of repair. Cells from individuals with ataxia telangiectasia (AT) are more sensitive to the cytotoxic effects of ionizing radiation than are those from normal individuals (Fig. 5) (6,31). However, such cells are very efficient at single strand break repair. Some of the AT fibroblast strains are deficient in repair replication and in the ability to remove endonuclease sensitive sites from their DNA.* Other AT strains although sensitive to ionizing radiation seem to be as repair proficient as are normal cells. Hence, except for the greater number of chromosome aberrations per unit dose in irradiated AT cells, there seems to be no direct connection between DNA repair defects and cellular sensitivity to ionizing radiation. Moreover, AT cells are hypomutable by ionizing radiation and there is no indication that this type of radiation is the etiologic agent responsible for the increase in cancer risk of AT individuals.

There is some epidemiological evidence indicating that AT heterozygotes may be more cancer prone than the average (33), and hence, it would be useful to be able to identify such individuals since they apparently make up close to 1 percent of the population. Five out of seven heterozygote fibroblast strains are more sensitive to the cytotoxic effect of anoxic radiation (34) and eight out of eight heterozygote lymphoblastoid lines do not proliferate after eighty rads, whereas normal transformed cells proliferate after 100 rads (35).

DNA Synthesis

Low doses to normal human cells result in a rapid decrease in the incorporation of exogenous ^{3}H thymidine and in the appearance of the incorporated label in the high molecular weight component of the DNA sedimented in alkali. These data indicate that ionizing radiation inhibits the initiation of new replicons (36). Since the effect is observed at low doses--doses that make an initial number of 1000 single strand breaks per 3×10^{12} daltons (5) most of which are repaired in the 30 minutes before DNA synthesis is measured--there must be a big target, i.e., a cluster of replicons is affected. One could infer that there must have been a big change in

*Extracts of M. luteus or E. coli have activities able to nick DNA irradiated by ionizing radiation (32) but the nature of the damage(s) recognized by these enzymes is not known. The numbers of such base damages approximate the number of single strand breaks for anoxic irradiation but is only about half the number of breaks observed for irradiation in air.

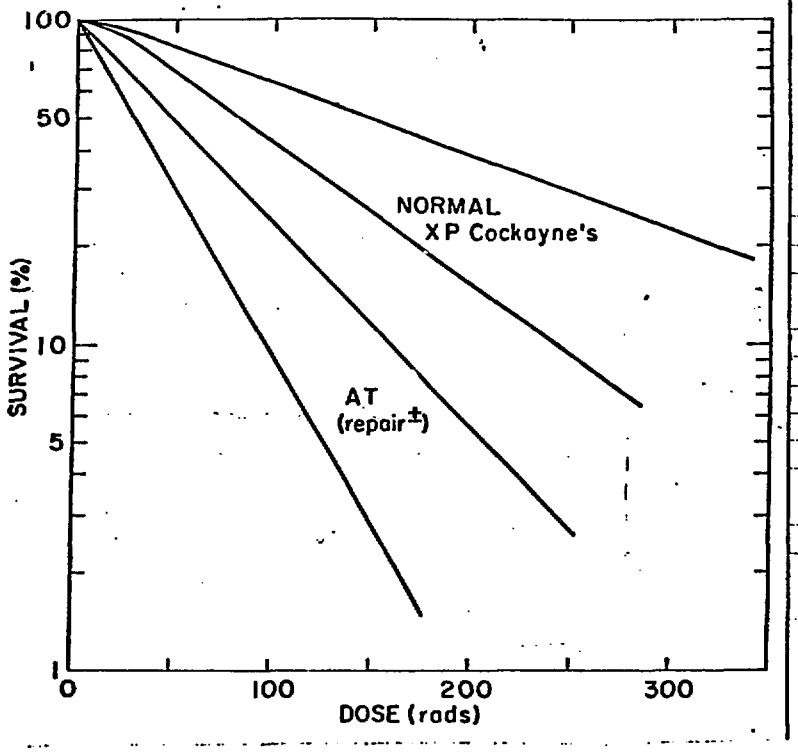

Fig. 5. Survival curves as a function of ionizing radiation dose illustrating the ranges of sensitivities observed (adapted from Arlett and Harcourt, 31). The range of sensitivities for AT cell strains seems to be independent of the abilities to remove endonuclease sensitive sites or to do repair replication.

the large scale conformation of DNA, a change that does not go to zero for an appreciable time. AT cells, however, show no such inhibition of DNA synthesis (Fig. 6), although one group of investigators (37) observes inhibition in repair proficient AT cells and another does not (38). Thus, there is the intriguing possibility that AT cells have the capability of winding up the DNA quickly to its preirradiation conformation and so permitting clusters of replicons to initiate synthesis. In any event, the continuation of DNA synthesis in AT cells implies that the growing points will traverse more base damage in DNA than will the growing points in normal cells because base damage is repaired slowly (32). Hence, the yield of lethal events in AT cells would be expected to be larger than in normal cells. This explanation is consistent with the observation of no defect in AT cells for host-

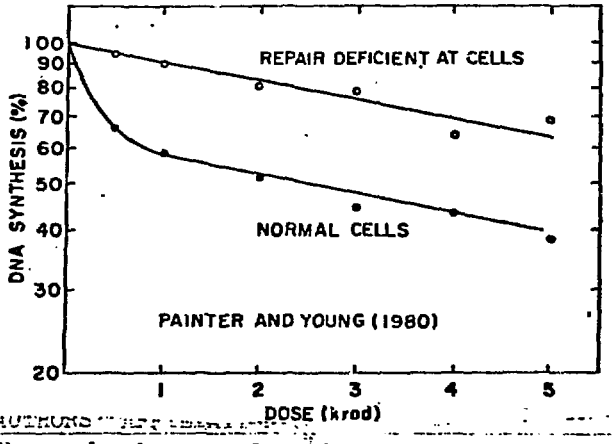

Fig. 6. DNA synthesis as a function of ionizing radiation dose for normal and AT cell strains (adapted from Painter and Young, 37).

cell reactivation of x-ray irradiated herpes simplex virus (39). Note, incidentally, that DNA synthesis in Cockayne's syndrome cells was suppressed for a long time by UV irradiation and the suppression was interpreted as giving rise to lethal events. These two different conclusions from the inhibition of DNA synthesis simply indicate that the damage from UV and from ionizing radiations are very different and that the mechanisms of repair of the two types of damage are very different. In the excision repair of UV damage there are long patches; whereas in the repair of ionizing radiation damage there are, on the average, short patches. After long repair times, times comparable to those usually used for UV, some long patch repair is observed (40).

DNA repair activity, repair replication or loss of endonuclease sensitive sites, can only be measured at very high doses--doses near 50 krads, and no distributions of repair activities among normal cells have been obtained as they have for UV.

313 NM RADIATION

The absorption coefficient of DNA decreases rapidly at wavelengths greater than 300 nm and at such wavelengths is much more characteristic of GC residues (41). Hence one might expect that photoproducts, other than thymine-containing dimers, would be of increasing importance biologically at these longer wavelengths. Such additional photoproducts might be ring saturated thymines (42) or single strand breaks (43). For 313 nm irradiation, these other products do not seem to be of importance for cytotoxic effects on

normal or XP fibroblasts since the relative sensitivity per dimer formed seems to be the same at 313 nm as at shorter wavelengths (9).

Two out of four AT fibroblast strains show enhanced cytotoxic sensitivity to 313 nm (but not to 254 nm) and four out of seven Bloom's syndrome (BS) fibroblasts also show enhanced cytotoxic sensitivity at the long wavelength (44,45). There is a rough, but not a complete, correlation between the higher sensitivity of BS cells and the induction of single strand breaks in cells exposed to 313 nm at 37° (46). However, for irradiation at 0° there is no big increase in single strand breaks (46). Since gamma irradiation of BS cells makes the same numbers of single strand breaks as in normal fibroblasts, and the repair of such breaks is about the same, it was concluded that the breaks observed after ionizing radiation are different from those observed after 313 nm irradiation (44). Moreover, such observations lend force to the argument that the breaks observed as a result of 313 nm irradiation in some of the BS cells result from some alteration in repair capacity—an alteration that is a step beyond the initial endonucleolytic one.

A clastogenic factor in the medium of BS cells could be reduced substantially by superoxide dismutase (47). This result indicates that reactions at the longer UV wavelength may take place by an active oxygen species and not by a direct action on DNA. As a matter of fact, other than the approximate correlation between the cytotoxicity and single strand break enhancement in irradiated BS cells, there is no good evidence that the enhanced cytotoxicity to 313 nm arises from damage to DNA. Irradiations at this wavelength require large fluxes of light and it is conceivable that other cellular components could be the ultimate targets.

ACKNOWLEDGMENT

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