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POSSIBILITIES AND PROBLEMS IN UV RADIATION CARCINOGENESIS EXPERIMENTS

R. J. M. Fry, R. D. Ley and D. Grube*

Biology Division, Oak Ridge National Laboratory,** Oak Ridge, Tennessee, and the Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois.

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Dose response relationships are required for a number of aspects of studies on ultraviolet radiation (UVR) carcinogenesis. However, quantitative studies have been difficult because of the problem of dosimetry. First, it is difficult to determine the precise dose to the cells at risk in the basal layer of the epithelium and secondly, almost all UVR carcinogenesis experiments invo a number of exposures. Early exposures in a fractionation regime may result in an altered thickness of the epidermis and therefore a different absorbed dose with the later exposures.

We have approached these problems in a series of experiments designed to investigate the role of psoralen-DNA crosslinks in skin cancer induced by exposure to 8-methoxypsoralen (8-MOP) and UVR.

We determined the dose response relationship for psoralen-DNA crosslinks by assaying these lesions after exposure to graded fluences of UVR. It was found that the number of psoralen-DNA crosslinks/cell increased in an apparently linear fashion between 0.33×10^3 J/m^2 per fraction 320-400 nm UVR (Westinghouse F40BLB lamp) up to 1.31×10^3 J/m^2 but declined by 1.65×10^3 J/m^2/fractions. The determinations were made after 6 weeks of exposure to 3 fractions per week. The decrease in crosslinks/cell at the highest fluence could have resulted from a decreased penetration of 8-MOP or UVR to the basal layer as a result of hyperplasia. The hyperplasia in the epidermis is a response to damage to the basal cell layer. We have found that hyperplasia appears to occur with doses which result in a degree of cell killing that cannot be

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compensated for by increased proliferation rate brought about by shortening of the cell cycle.

In the carcinogenesis experiments with 8-MOP and UVR we used two different stocks of hairless mice namely SKH:hairless-1 and HRS/J/Anl and three sources of UVR which had (1) 300-400 nm, (2) 320-400 nm and (3) 365 nm wavelength emissions. We found that the induction of psoralen-DNA crosslinks was wavelength dependent but independent of the stock of mouse that we used. The fluences were adjusted to induce similar numbers of psoralen-DNA crosslinks in the mice exposed to the different UVR sources and yet it was found that the incidence and time of appearance was dependent on both the UVR sources and the stock of mice. These results suggested no obvious relationship between the induction of psoralen-DNA crosslinks and squamous cell carcinomas. In order to investigate the strain-dependency in susceptibility for cancer induction mice from both stocks were exposed to a relatively small number of fractions of 8-MOP plus UVR but followed with application of 12-O-tetradecanoylphorbol-13-acetate (TPA) for 24 weeks. With this protocol most of the strain-dependent differences disappeared suggesting that the difference was not due to differences in initiation events but in the expression of these events. In the initial tumor studies mice had been exposed to 8-MOP plus UVR 5 times a week. In subsequent experiments the same dose per fraction (1.31×10^3 J/m^2), but 3 exposures per week were used, and although the total dose was less the tumors appeared earlier. Further experiments were done to examine these time-dose relationships. Equal total doses 1 and 3 fractions/week were equivalently effective and more so than 5 times/week. However, when the same total dose was given but with a reduced fluence per fraction and a greater total number of fractions we found a higher incidence of tumors.

It is clear that time-dose relationships for UVR carcinogenesis are complex and more work is needed before we can understand the factors involved.

Our results have shown a clearcut wavelength dependence for tumorigenesis. As a photosensitizer was used in these experiments this was not unexpected in the sense that the induction of the initial lesions were presumably dependent on the photoproducts. It was also clear that many of the exposures used in the fractionation regimes were contributing to expression of the lesions. In order to investigate the wavelength dependence for the expression or promotion of the initial events we exposed mice to topical 8-MOP (250 μg) plus 1.31×10^3 J/m^2 (320-400 nm) 3 times a week for 12 weeks. This regime produces about a 25% incidence of carcinomas in 70 weeks. At the end of the 12 week exposure regime the mice were divided into 5 groups which received one of the following 3 times a week for 24 weeks: (1) 1.5×10^3 J/m^2 320-400 nm, (2) 5.5×10^3 J/m^2 365 nm, (3) 500 J/m^2 280-400 nm, (4) 5 μg TPA, and (5) no further treatment. The exposure to the UVA sources increased slightly the incidence of tumors but much less than the TPA treatment. It was of interest to find that the source containing UVB had as great an effect as the TPA. The fluence of UVB was about 20% of a D_{37} dose for mouse cells.

These results underline the importance of the UVR spectrum not only in initiation but in the expression of tumors. In the case of exposure to photosensitizers for therapy the nature of subsequent exposures is also of importance.

While the design of UVR carcinogenesis experiments still poses a number of problems the ability to assay UVR induced photolesions opens up the possibility of doing experiments which will indicate the dose-response relationship for both the initial events and the expression of those initial events.

*D. Grube, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois.

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