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DNA DAMAGE IN MAMMALIAN CELLS

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The major justification for studying the radiation chemistry of DNA is the central role this molecule plays in the biological radiation response. Information can be gained from model systems which is unlikely to be obtained from studies of the molecule irradiated in the cell. From the biological point of view there are several areas in which useful information can be gained from model systems. Two of these are:

a. Accurate descriptions of the mechanisms by which significant damage is produced. This information would permit development of rational protocols for the modulation of product yields and of product types.

b. Accurate definitions of the structures of the types of damage which would be produced. This will permit definitive studies of repair of specified damage to be undertaken.

It is unlikely that an *a priori* description of damage types can be achieved using irradiated cells — it can be calculated that to cause 1% alteration of DNA moieties by irradiation in cells would require a dose of 10^4 Gray.

To be able to extrapolate from the wealth of model system information, a pertinent description of the DNA's intracellular environment is essential. However this information, in sufficient detail to be of use to radiation chemists is only available for DNA nucleosome moieties which have been isolated from cells.

It is clear from model studies that a plethora of radiation products is possible. Are all these products equally biologically significant? A consideration of the effectiveness of other DNA damages in cell killing is informative: Damage induced by many other agents is easily tolerated in cellular DNA (for summary see 1). The mammalian cell can overcome tens of thousands of mono-adducts in its DNA. Such damage can be easily repaired by conventional enzymatic mechanisms, e.g. using the complementary undamaged DNA strand as template. Singly damaged sites produced by radiation induced OH radicals will have the same identities as those produced by the reaction of chemically induced oxidizing species. The cell would be expected to have evolved protective strategies against such damage. By the same argument, DNA double strand breaks, lethal at 40 per cell, would be expected to be more toxic; at current background radiation levels the mammalian cell sees a radiation induced DNA double strand break only once every 25 years (on average).

Thus it is argued that the DNA DSB, as a biologically significant lesion, should be studied. Two mechanisms by which DSBs can be produced have been postulated:

1. By the interaction of a high radical density region (spur, blob etc.) with the DNA.[1]

2. Initiated by a single radical and involving radical transfer from one strand to the other.[2]

An argument against the latter mechanisms occuring in cells has been that no DSBs are detected following treatment of cells at O°C with hydrogen peroxide — this

treatment efficiently causes single strand breaks. However, the possibility exists that the mechanisms of SSB induction by H_2O_2 does not involve $OH^{\cdot}$ or organic free radicals. Johnson *et al.*[3] have shown that the $Cu^+ + H_2O_2$ oxidation of methanol occurs by a two electron transfer and that the $^{\cdot}CH_2OH$ radical is not formed as an intermediate. If a similar reaction is involved in producing SSBs by H_2O_2 then no radical intermediate would be formed.

The resolution of the mechanism by which DSBs are produced in cells is crucial and represents an example of the type of information which is only attainable by model studies. There are different implications from the two mechanisms:

1. The conditions they postulate to be necessary for the modification of damage yields: The radical transfer mechanism implies the occurrence of relatively long lived intermediate radicals which would be scavengeable by lower concentrations of chemical repairers than that predicted for the two radical mechanism of DSB production.

2. The spacings of the SSBs on opposite strands: The spacing would be expected to be more constricted by the radical transfer process than for the random spacings expected for multiple radical attack.

3. The significance of single *vs.* multiple radical damage which would occur by high LET radiation.

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