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Final Report
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Title: Molecular Mechanisms in Radiation Damage to DNA

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Abstract:

The objectives of this work were to elucidate the molecular mechanisms that are responsible for radiation-induced DNA damage. The overall goal was to understand the relationship between the chemical and structural changes produced by ionizing radiation in DNA and the resulting impairment of biological function expressed as carcinogenesis or cell death. The studies were based on theoretical explorations of possible mechanisms that link initial radiation damage in the form of base and sugar damage to conformational changes in DNA. These mechanistic explorations should eventually lead to the formulation of testable hypotheses regarding the processes of impairment of regulation of gene expression, alteration in DNA repair, and damage to DNA structure involved in cell death or cancer.

Accomplishments:

In the following we refer to the numbers of the publications listed below.

We have shown (#1) that H-abstraction and β-cleavage are processes that are closely linked to the participation of water in the possible damage. We have investigated the effects of radicals adding to the base on the distortion from planarity of the base (#2). Such effects have an important consequence on the distortions induced in DNA by the damage. These initial results have been summarized in a review (#3) which received an award from IBM for supercomputer usage.

We have investigated in great detail the molecular factors contributing to the kinetics and thermodynamics of H-abstraction from methanol and ethanol in gas phase (#4). These are fundamental studies which demonstrate that the computational methods used by us are an excellent tool to predict bond strengths, stabilities and the barriers for chemical reactions. We have subsequently presented an overview of our work in progress and its implications to radiation damage to DNA (#5).

We have performed for the first time a molecular dynamics simulation of a dodecamer of DNA (#6) which established the conceptual basis for the dynamic approach to the understanding of radiation damage to DNA. In preparation for the simulations of damaged DNA we have calculated the properties of thymine glycol and dihydrothymine (#7) and showed the molecular basis for the possible disruption of polymerase action by thymine glycol but not by thymine dimer.

Computational methods are an excellent tool for predicting spectra especially of short lived species such as radicals. Using a sophisticated approach we have computed the spectra of hydroxyl radical adduct to uracil (#8) and showed that the 5-hydroxy-6-uracilyl radical has only absorption in the visible whereas the 6-hydroxy-5-uracilyl radical absorbs in the visible. This provided an explanation of the observed spectroscopy of base radicals. We have investigated with quantum mechanical methods the relative stabilities and conformational properties of deoxyribose radicals (#9) and showed that they undergo significant distortion upon H-abstraction. Further studies on spectroscopy of radicals were performed on peroxyl radicals (#16) and on model systems in which addition of hydroxyl radicals to conjugated systems was the basis for understanding the various spectroscopic consequences (#17).

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We have performed molecular dynamic simulations and showed the nature of the distortion introduced in DNA upon addition of a radical to a base (#10, #18). The molecular basis of such distortions and their implication to biological effect was reviewed in a invited presentation (#12) and published in a scientific journal (#13). The basis for such distortions was evaluated with quantum mechanical methods (#11).

The mechanisms of radiation damage and their simulations with computational techniques were reviewed in an invited lecture (#14). These include Brownian dynamics simulations, quantum mechanical approaches to the study of radicals and conformational changes in damaged DNA.

The last period of the grant was marked by a new development of the recognition elements of damaged DNA by repair enzymes. We have shown that these are: the structural changes in the DNA (I.e., bending), the changes in ion distribution and the changes in the binding energy of water to the DNA (#15).

Published Articles and Conferences:

1. L. Pardo, R. Osman, J. Banfelder, A. P. Mazurek and H. Weinstein, Molecular Mechanisms of Radiation Induced DNA Damage: H-Abstraction and β-Cleavage. *Free Radical Res. Comms.*, **12-13**, 461-463, 1991.
2. R. Osman, L. Pardo, J. Banfelder, A. P. Mazurek, L. Shvartzman, R. Strauss and H. Weinstein, Molecular Mechanisms of Radiation Induced DNA Damage: H-Addition to Bases, Direct Ionization and Double Strand Breaks. *Free Radical Res. Comms.,* **12-13**, 465-467,1991.
3. Weinstein, H., Osman, R., Mercier, G.A., Mazurek, P.A., Pardo, L., Rubenstein, L.A. Theory and computation of molecular mechanisms in biological processes. In *Computer Assisted Analysis And Modeling on the IBM 3090.* H. U. Brown, III, ed., 1989 IBM 3090 Supercomputing Competition, MIT Press, 1990, pp. 629-673.
4. L. Pardo, J. Banfelder and R. Osman. Theoretical Studies of the Kinetics, Thermochemistry, and Mechanism of H-Abstraction from Methanol and Ethanol, *J. Am. Chem. Soc.*, **114**:2382-2390,1992.
5. Osman, R., Miaskiewicz, K., Weinstein, H. Structure-function relations in radiation damaged DNA. In: *Physical and Chemical Mechanisms in Molecular Radiation Biology*. Editors: W. A. Glass and M. N. Varma, Plenum Press, NY, 1991, pp.423-452.
6. Miaskiewicz, K., Osman, R. and Weinstein, H. Molecular dynamics simulation of the hydrated d(CGCGAATTCGCG)$_2$ dodecamer. *J. Am. Chem. Soc.,* **115**, 1526-1537, 1993.
7. Miaskiewicz, K. Miller, J. and Osman, R. Ab Initio theoretical study of the structures of thymine glycol and dihydrothymine. *Int. J. Radiat. Biol.,* **63**, 677-686, 1993.
8. Krauss, M. and Osman, R. The electronic spectra of the neutral radical and H and OH adducts of uracil. *J. Phys. Chem.,* **97**, 13515-13518,1993.
9. Miaskiewicz, K. and Osman, R. Theoretical study of deoxyribose radicals formed by hydrogen abstraction. *J. Am. Chem. Soc.,* **116**, 232-238, 1994.
10. Miaskiewicz, K. and Osman, R. Molecular dynamics simulation of DNA with a primary radiation damage. *Rad Protect. Dosim.*, **52**, 149-153, 1994.
11. Miaskiewicz, K. Miller, J. and Osman, R. Energetic basis for structural preferences in 5/6-hydroxy-5,6-dihydropyrimidines: Products of ionizing and UV radiation action on DNA bases.