

Metabolic Activation of Naturally Occurring Compounds and Cancer

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SUMMARY: It has been reported that the majority of all cancer deaths are caused by chemicals in the environment. It is certainly evident that human beings are exposed via air, water, food and medical treatment to a great many chemical substances such as drugs, pesticides, herbicides, food additives, antioxidants, cosmetic products, alcohol, tobacco, etc. Most of these substances are transformed into as many as one hundred molecular species (metabolites). Depending on their chemical structures, these metabolites may be rapidly excreted, mostly through the urine and the bile. The effects of metabolites of administered drugs may be quite different from the effects of the parent compound.

With the exception of a few direct-acting agents, the chemical carcinogens usually require the so-called "metabolic activation" in order to exert their cancer-inducing properties. The following sequence can be given:

- All chemical carcinogens that are not themselves chemically reactive must be converted metabolically into a chemically reactive form (called "ultimate carcinogen").

- The activated metabolite is an electrophilic agent.

- This activated metabolite reacts with nucleophilic groups in cellular macromolecules (DNA and possibly RNA, proteins) to "initiate" the process of carcinogenesis.

The active metabolites bind covalently to macromolecules in organelles, involving proteins, nucleic acids and lipids. If the covalent binding to nucleic acids takes place, then cancer is initiated. The parent compounds are harmless but after oxidation many of them become potent carcinogens. The activation system involves a monooxygenase system that utilizes molecular oxygen, NADPH and cytochrome P-450. Cytochrome P-450 is a well known enzyme which detoxifies and activates a wide variety of exogenous as well as endogenous compounds. Recent studies have established that there are multiple forms of cytochrome P-450 in liver microsomes, which are major organelles that metabolize drugs and toxicants.

It is therefore evident that any factor affecting the enzymes involved in the metabolism of chemical carcinogens should be investigated in order to elucidate the mechanisms of action. It should be borne in mind that these factors can be endogenous such as modification of hormone equilibrium or can be exogenous compounds that are not cancerogenic in themselves such as drugs used in medical treatment but which are known to be potent inducers or inhibitors of liver enzymatic systems. Furthermore, other factors such as the state of health, nutritional habits etc. must be considered. It is well known, for example, that our food contains chemical carcinogens. These are not food additives, but

compounds that are naturally present in the food we eat or are produced by the way we prepare it. Among these are the naturally occurring compounds such as N-Nitroso compounds, aflatoxins, ascaridole, etc.

These mechanisms are more complex than was initially believed and it is hoped that a better understanding of them will lead to a way of reducing the incidence of cancer as well as improving the treatment.



Use of Viruses as Probes in the Study of DNA Repair Processes in Mammalian Cells

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S U M M A R Y: We live in an environment which continuously threatens our genetic material. Radiation from the sun and chemical agents cause alterations in the DNA which could soon have destroyed our

planet, if there was not a constant cellular monitoring and repair of most of these defects. Cellular DNA is also subject to spontaneous damage that includes chemical alteration of bases, changes in base sequence due to replicative and recombinational infidelity and loss of bases. The repair of DNA must be regarded together with replication and recombination as an essential transaction of the genetic material in all life form.

The study of the DNA damage and repair has undergone massive expansion during the past 30 years. Most of the interest in this field is due to the evidence which shows the relevance of DNA repair to human health. Damage to DNA has been clearly implicated in cancer and there are suggestions that it may be a component in the Biology of aging.

The DNA repair systems of the living organisms could be studied using a large number of modern techniques of the Molecular Biology. In the present review an analysis of the advantages of using viruses as probes for the study of DNA repair in mammalian cells is been attempted.