

The Paradoxical Role of Lipid Peroxidation on Carcinogenesis and Tumor Growth: A Commentary

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Abstract — Lipid peroxidation has been shown to both enhance carcinogenesis and to have an anticarcinogenic effect. This paradox is of great relevance to the fields of free radical biology, biochemistry, pathology, nutrition and oncology among others and needs to be addressed. A proper understanding of this issue can be a key to more effective treatment of malignant tumors in the near future.

Introduction

Cancer can be considered a multistep, multievent, polygenic process. This complex pathological process is divided into phases, in order to facilitate its study. The induction phase is composed of two major steps, initiation and promotion. At the initiation step, a genetic change occurs that deregulates the normal division pathways of the cell. Most of these transformed cells acquire the capacity to proliferate without control – in this way, cells are ‘initiated’ into malignancy. This occurs after a mutation, amplification or translocation of a cellular oncogene and/or loss of a repressor gene, also initiation appears to be irreversible. Chemical or physical initiators (carcinogens) can produce potent free radicals (1). Active oxygen species such as superoxide radicals and hydrogen peroxide have been associated with the induction of cancer (2). It has also been documented that patients with known genetic defects in their deoxyribonucleic acid (DNA)

repair system (e.g. Xeroderma pigmentosum, Franconi’s syndrome and Bloom’s syndrome) are highly predisposed to the development of cancer (3). We should mention that most of the damage in the DNA suffered by these patients is due to free radicals. This can suggest indirect evidence that protection against cancer initiation can be provided by antioxidant supplementation. In addition, more direct evidence of antioxidant inhibition of carcinogenesis is available in studies by Wattenberg (4), Shamberger (5) and Shklar (6).

Discussion

Oxygen radicals and related species may also be involved in the following step of carcinogenesis: promotion. Promotion involves the selection and clonal amplification of initiated cells. This process seems reversible and accounts for a large proportion of the

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latent period of carcinogenesis. Probably the best-studied cancer promoters are the phorbol esters. Phorbol esters' carcinogenic mechanism is related to the reduction of cellular levels of catalase and superoxide dismutase (7). In addition, phorbol esters can also stimulate inflammatory leukocytes to release superoxide (8). This is a paradoxical view since, despite the role of inflammatory white blood cells in combating tumor development, it could be argued that they can also contribute to tumor promotion by providing oxygen species capable of damaging cells, therefore liable to produce mutations.

In general, reduced levels of intercellular antioxidant enzymes can lead to a cellular pro-oxidant state capable of inducing mutations of proto-oncogenes giving rise to oncogenes. These oncogenes, in turn can give rise to altered growth regulatory proteins or deviated nuclear transcription factors, in this manner facilitating cellular growth (cell division).

The last stage of tumor growth is progression in which a loss of growth control with little or no immune response against the tumor is evident. This last stage can involve further mutational events in which free radical formation may arise. Interestingly, low concentrations of superoxide and hydrogen peroxide have been shown to be effective stimulators of growth of oncogene transformed hamster and rat fibroblast (2). In contrast, high concentrations of either superoxide and/or hydrogen peroxide have proved to be highly cytotoxic to cell lines *in vitro* (2) providing yet another paradox to this discussion.

Conclusions

In summary, a normal tissue once exposed to free radicals the probability of suffering genetic damage capable of transforming the cell into a malignant one seems very logical.

Adding to the complexity, once the cell is transformed, further damage can most likely cause one of these two outcomes:

1. *Increase in cancer progression* – by creating a more invasive or malignant tumor.
2. *Cell death* – due to unsurvivable genetic damage.

In this sense we can 'safely' consider lipid peroxidation or any uncontrolled oxidative reaction as a double-edged sword.

There is a definite influence of certain free-radical species on tumor development (9,10). These free radicals can be formed in considerable quantities and be further converted to more toxic derivatives de-

pending on the originating source and the environment where it arises. The many different oxidative species that emerge in a system may influence the different phases of carcinogenesis in various ways, some enhancing, some inhibiting. These complex but relevant interactions will depend on controlling variables such as: the fatty acid composition of the lipids present in the tissue in question, the environment in which these reactions are taking place (quantity and quality of antioxidants, quantity of divalent cations or metal ions, efficiency of oxidation inhibitory enzymes, presence of reducing agents in tissue membranes), the particular sensitivity of the tissue in question to the oxidative species formed and the number and concentration of growth-inhibitory or growth-enhancing oxidative species. We should guide our future efforts towards identifying which dietary fats produce which type of oxidative species and identifying the role or action of each oxidative species formed in relevant quantities in the studied tissue or model of interest.

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