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COMMENT

ANTIOXIDANTS AND PRO-OXIDANTS: A COMMENTARY ABOUT THEIR APPARENT DISCREPANT ROLE IN CARCINOGENESIS

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The Role of Antioxidants

The specific role of dietary antioxidants in carcinogenesis and tumorigenesis has not been unequivocally elucidated. Earlier studies suggested a protective role of dietary antioxidants against carcinogen-induced malignancies (1-4). The main mechanism proposed for this protective action against carcinogenesis exhibited by antioxidants is related to their free radical scavenging power.

It is known that once normal cells are exposed to a free radical rich environment, the probability of these cells suffering relevant genetic damage is highly increased. This, in turn, increases the chances of mutations, amplifications and translocation of cellular oncogenes or the loss of repressor genes. This detrimental free radical-induced genetic damage can transform a normal cell into a malignant one in this phase; this is where dietary antioxidants may have a protective role against carcinogenesis. Once this transformation stage has been achieved, inducing further damage to the cell can only lead to either of two terminal paths: 1) to further enhance cancer progression (malignancy, aggressiveness); in other words, the cancer cell can become more invasive. This can probably occur by increasing production of cell proteases, favoring malignant dissemination throughout the organism, or 2) the cell will suffer unsurvivable genetic damage that will lead to cell death. Having all this in mind, we encounter a paradoxical role of free radical pathology or oxidative damage pertaining to the cancerous process.

Of interest is the number and concentration of different oxidative species that originate during lipid peroxidation or any other oxidative process. This aspect requires special attention since it has been demonstrated that low concentrations of superoxide and hydrogen peroxide (two oxidative species) are effective stimulators of transformed cell growth (5). In contrast, high concentrations of these same oxidative species have exhibited cytotoxic activity against cell lines *in vitro* (6).

In general, the type and quantity of oxidative species that arise in metabolism depend on many variables. Probably the main one is the type and quantity of dietary fat consumed. This variable itself brings yet another variable within, the issue of fatty acid composition. In addition the formation of oxidative by-products will also depend on the environment where these reactions are taking place and the particular sensitivity of the cells that will be exposed to the resulting oxidative species.

In relation to the effect of diets high in fish oil on tumors *in vivo*, we believe that the high concentration of secondary products of oxidation (e.g. aldehydes) of cytotoxic nature impedes cell proliferation, thereby inhibiting tumorigenesis (7). The production of growth-inhibiting oxidative species can be favored *in vitro* by the presence of divalent cations (such as iron or copper) and *in vivo* by the presence of various forms of these minerals (free or bound). The lower pH environment in the tumor (which can increase cation dissociation from bound protein sources) can significantly enhance this action leading to a higher cell death.

Antioxidants, by preventing or delaying further oxidation of highly polyunsaturated fatty acids, can potentially negate the formation of these secondary products of oxidation, hence protecting the proliferative capacity of tumor cells.

Nevertheless, we should also have in mind that certain antioxidants may have a role increasing certain parameters of the immune system and in this way affect tumor growth negatively in an indirect manner. Antioxidants in very high doses have the potential of creating oxidative species, although this particular aspect, to our knowledge, has not been observed *in vivo*.

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