Antitumour Activity of Antioxidants: An Overview

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ABSTRACT

Oral cancer holds the eighth position in the cancer incidence ranking worldwide, with squamous cell carcinoma encompassing at least 90% of all oral malignancies. The World Health Organization expects prognosis for many of these patients to be grave and even in cases of successful treatment the degree of dysfunction and disfigurement post-operatively is well-appreciated by all of us. Hence, understanding of the disease process is of paramount importance for early diagnosis and successful treatment. Dietary substitutes such as beta-carotene, pro-vitamin A, vitamin A, vitamin C, vitamin E, lipoic acid, zinc, selenium and spirulina can prevent oral cancer at a very early stage i.e., in premalignant lesions, in premalignant conditions. The antitumor activity of micronutrients is by their capability of destroying cancer cells through three major mechanisms. (a) Tumor inhibition by immune cytokines, (b) Stimulation of cancer suppressor genes, such as “wild type p53,” and diminished expression or dysregulation of oncogenes such as mutant p53 and H-ras, (c) Inhibition of angiogenesis-stimulating factors such as TGFα. Retinoid action differs, in some respects, from other micronutrient anticancer mechanisms and appears to relate to its stimulation of cellular differentiation and resultant apoptosis of neoplastic cells. The ultimate goal of modern medicine is the prevention of disease. Nutrients will be utilized and will play an important role in preventive medicine, once their effectiveness is conclusively demonstrated by prospective clinical studies and when the mechanisms of their actions are more clearly understood.

Key words: Angiogenesis; Antioxidants; Free radical; Oncogenes

Introduction

Humans literally swim in a sea of environmental carcinogens. Oral cancer holds the eighth position in the cancer incidence ranking worldwide, with epidemiologic variations between different geographic regions. Squamous cell carcinoma encompasses at least 90% of all oral malignancies. The World Health Organization expects a worldwide rising oral squamous cell carcinoma incidence in the next decades. The prognosis for many of these patients is grave and even in cases of successful treatment the degree of dysfunction and disfigurement post-operatively is well-appreciated by all of us. Hence, understanding of the disease process is of paramount importance for early diagnosis and successful treatment. Dietary substitutes can prevent oral cancer at a very early stage i.e., in premalignant lesions, in premalignant conditions and also in carcinoma in situ. These dietary substitutes are beta carotene, pro-vitamin A, vitamin A, vitamin C, vitamin E, lipoic acid, zinc, selenium and spirulina. The function of antioxidants is to remove free oxygen radicals from the body and, as a result, prevent the cells from cell damage or undergoing any carcinomatous change.

Antioxidants are a group of chemical compounds that can deactivate the free radicals and prevent their formation. Free radicals are oxidants in the body. Oxidants have single unpaired electron that search for another electron to make the molecular structure stable. They become loose cannons that bombard and destroy cells and other molecules in their search for another electron. Major interest is now focused on the possible anticancer activity of the relatively non-toxic antioxidant nutrients beta carotene, alpha tocopherol and glutathione, as well as various retinoids. The carotenoids and tocopherols have been shown to be capable of cancer regression, as well as their inhibition and prevention of carcinogenesis. Their action has also been shown to be synergistic. Recent studies have suggested several probable pathways through which these antioxidant nutrients act to inhibit the development of cancer cells and to destroy them through apoptosis (programmed cell death), by their stimulation of cytotoxic cytokines, by their action on gene expression, by preventing the development of tumor’s necessary blood supply or by cellular differentiation.

Discussion

The complex mechanism of the antitumor activity of micronutrients is now becoming established. They appear to have the capability of destroying cancer cells through the following major mechanisms:

- Immune mechanisms
- Molecular genetics pathway
- Depression of tumor angiogenesis activity
- Stimulation of cell differentiation.

Immune mechanisms: Human immune system can recognize foreign cells and invades (bacteria, viruses etc.), because they have proteins and other structures that are different from the body’s ‘self’ markers. Cancer cells may have mutated ‘self-markers’ and are often destroyed by the immune system. The basic concept of immune enhancement is that the development of cancer cells in the organism stimulates a potent immune response that locates the cancer cells and destroys them. This process would involve signals, sent out by the developing cancer that can be interpreted by the host’s immune system, which then produces cells to destroy the cancer, sends them to the cancer site or sites. These immune cells are capable of elaborating cytotoxic chemicals that can infiltrate and destroy cancer cells. Examples of these agents are tumor necrosis factor alpha carried by macrophages and mast cells, and tumor necrosis factor beta, carried by lymphocytes. The cytotoxic macrophages, mast cells and lymphocytes have the capability of recognizing the tumor site and “homing in” on it.
The antioxidant micronutrients, such as alpha tocopherol and beta carotene, have been shown to enhance the production and activity of cytotoxic immune cells, carrying cytokines that can destroy cancer cells. In the hamster buccal pouch cancer model, it has been shown that beta-carotene and alpha tocopherol stimulated the migration of cytokine laden macrophages and lymphocytes to the sites of developing squamous cell carcinoma (Figure 1). The macrophages were engorged with TNFα and the lymphocytes engorged with TNFβ, and then cytokines were deposited at the tumor sites to destroy the tumor cells of the developing and proliferating cancers. Mast cells were also found to migrate to developing cancer sites in the hamster model and release their cytokine granules.

Antioxidant nutrients were also found to stimulate the activity of Langerhans cells in the hamster carcinogenesis model. This is another indication of immunostimulation, since Langerhans cells are macrophages equivalents with Fc receptors and la cell surface antigen.

**Molecular genetic mechanisms:** Tumor suppressor genes (oncosepressors or anti- oncogenes) are present in epithelial and other cells that normally appear to act as regulators of cell proliferation. Several oncosepressor genes have now been described: p53 gene is one of the better-known genes that have antiproliferative effects. The p53 gene plays a role in maintaining the integrity of the genome. Activation of normal p53 by DNA-damaging agents leads to cell cycle arrest in G1 and induction of DNA repair, by activation of p21. Successful repair of DNA allows cells to proceed with cell cycle; if DNA repair fails, p53 induced activation of the BAX gene promotes apoptosis. In cells with loss or mutation of p53, DNA damage does not induce cell cycle arrest or DNA repair, hence genetically damaged cells proliferate, giving rise eventually to malignant neoplasms (Figure 2). Antioxidant nutrients, such as beta-carotene, can inhibit, prevent or regress experimental cancer through control of the p53 mechanism. Antioxidant nutrients have been found to enhance the expression of "wild type" p53, a well-known cancer suppressor gene product, and to diminish the expression of mutant p53, the oncogenes expressed in a large number of malignant tumors, including Squamous cell carcinoma of the mouth. The cancer cells are then destroyed in the process referred to as apoptosis or programmed cell death (Figure 3).

**Depression of tumor angiogenesis activity:** Tumors stimulate the growth of host blood vessels, a process called angiogene-
sis, which is essential for supplying nutrients to the tumor. Tumors cannot enlarge beyond 1 to 2 mm in diameter or thickness unless they are vascularized. Proliferating cancer cells produce cytokines or chemical mediators that stimulate the proliferation of endothelial cells to form an extensive vascular supply to nourish the developing tumor. If the blood supply to the tumor did not develop, the tumor growth would be significantly inhibited. One of these potent angiogenic agents is TGFα, a cytokine, found in significantly increased amounts in experimental oral cancer. In the experimental animals receiving vitamin E, β carotene, or glutathione in addition to applications of carcinogens, the developing tumors were expectedly smaller, fewer in number, and the notable angiogenesis seen in the control animals was not observed in the animals receiving the nutrients.24-25 (Figure 4).

Epithelial cell differentiation: The role of vitamin A in epithelial differentiation was first demonstrated in 1925 when squamous metaplasia was reported in vitamin A deficient rats. The theories proposed to explain the possible protective role of vitamin A include the following: (a) a deficiency of vitamin A disturbs normal epithelial growth; (b) tumor surveillance is dependent on adequate levels of vitamin A; and (c) vitamin A directly influences gene expression. A major function of retinoids has been shown to be their action in stimulating epithelial cell differentiation.26-30 This action would serve to prevent the proliferation of dedifferentiated or undifferentiated carcinoma cells and would suppress the developing malignant tumor.31,32

Summary and Conclusions

The increasing public awareness of antioxidants may prompt a patient’s request to be treated without surgery if a premalignant lesion is discovered. Clinical trials have also shown clinical improvement in oral leukoplakia, a characteristic oral pre-cancerous lesion.33,34 This suggests that anti-oxidants nutrients can play a significant role in the prevention of oral cancer.35 The ultimate goal of modern medicine is the prevention of disease. Nutrients will be widely utilized and will play an important role in preventive medicine once their effectiveness is conclusively demonstrated by prospective clinical studies, and when the mechanisms of their actions are more clearly understood.

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