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Short Review

Molecular Pathogenesis and Prevention of Prostate Cancer

GUSTAVO BOUNOUS and DIETER BEER

Research and Development Department, Immunotec Research Ltd., Vaudreuil-Dorion, Quebec, Canada

Abstract. *Studies in laboratory animals indicate inhibition of chemically-induced carcinoma by cystine-rich diets enhancing the cysteine-GSH antioxidant system. The progression of carcinoma of the prostate is also inhibited by these diets, which were later found to raise the level of GSH in the prostate epithelium of man. New data presented at the July 13, 2003 meeting of the American Association for Cancer Research indicates that higher levels of total cysteine in plasma may predict a reduced risk for breast cancer. This prospective investigation was conducted among 32,000 women in the Nurses Health study. The previously reported prostate cancer data appears then not to be strictly gender-related as the antioxidant role of the cysteine - GSH system may also apply to breast cancer prevention.*

Accumulation of intracellular oxygen species (ROS) is associated with the development of cancer as it is generally considered that oxygen radical generation is frequently a critical step in carcinogenesis (1). Accordingly, cancer patients show an accelerated shift to more oxidized conditions (2). On the other hand, glutathione (gamma-glutamyl cysteinyl glycine, GSH) functions as an antioxidant to limit oxidant-induced damage to lipids, proteins and genetic materials (3, 4). It is noteworthy that hydroxyl radical, the most reactive, hence dangerous, radical (• OH) can be neutralized only by GSH (Figure 1). GSH in its reduced form can donate its sulfhydryl proton to quench ROS. When sufficient intracellular quantities of glutamate, cysteine and glycine are present, GSH synthesis may occur in the cell, limited by the availability of cysteine (3, 4). Cystine is the disulfide form of cysteine and is reduced to 2 moles of cysteine for use in cellular GSH synthesis (3). Diets that are rich in cystine-containing proteins were found to sustain the GSH content of the lymphocytes in conditions which are typically associated with reduced GSH, as during the antigen driven immune response (5). Consumption of this diet can increase GSH concentration in the lymphocytes of healthy young adults (6) and is also effective in reducing the size and number of Dimethyl-hydrazine (DMH)-induced colon tumors in mice (7) and rats (8). The positive results of these studies were extended to other types of malignancies such as mammary tumors in female rats (9). The favorable effect of a cysteine pro-drug such as N-acetyl-cysteine (NAC) in cancer patients (10) strongly suggests that whey protein, in the diet, acts as a cysteine delivery system in inhibiting tumor growth. It does this *via* its effect on increasing GSH concentration in relevant tissues (8), probably by providing high levels of substrates for GSH synthesis that could detoxify free radicals in spontaneous carcinogenesis.

Prostate cancer is the most commonly diagnosed solid tumor in men and it is associated with aging. The importance of androgen in prostate carcinogenesis is suggested by the observation that it rarely occurs in eunuchs. Recently, scientists at the University of Wisconsin, investigated the pro-oxidant-antioxidant shift induced by androgen treatment of human androgen-responsive prostate carcinoma cells. The results (11) clearly indicate hydrogen peroxide and hydroxyl radical (Figure 1) formation following androgen treatment and a decrease in the level of GSH (an abundant antioxidant). These changes were associated with signs of lipid peroxidation. These and other epidemiological data may explain why the prostate is a frequent site of carcinogenesis in advanced age. The pro-oxidant effect of androgen exposure of the prostate cells may be opposed by the antioxidant effect of the cysteine-GSH system, which can inhibit the evolution of prostate cancer in man (12). These observations prompted scientists at Ohio State University to test the hypothesis that whey protein could elevate GSH in human prostate cells, thereby providing protection against oxidant-induced cell damage. The whey protein diet used in these studies was almost identical to the diet used in the previous clinical trial (12). These *in vitro* assays showed that, with whey protein treatment, prostate epithelial cells increased GSH by 64% compared with control casein which did not elevate GSH. Treatment with NAC significantly elevated intracellular GSH, supporting the concept that the cystine

Correspondence to: Gustavo Bounous, M.D., Immunotec Research Ltd., 292 Adrien-Patenaude, Vaudreuil-Dorion, Quebec, Canada, J7V 5V5. Tel: 450-424-9992, Fax: 450-424-9993, e-mail: jmolson@immunotec.com

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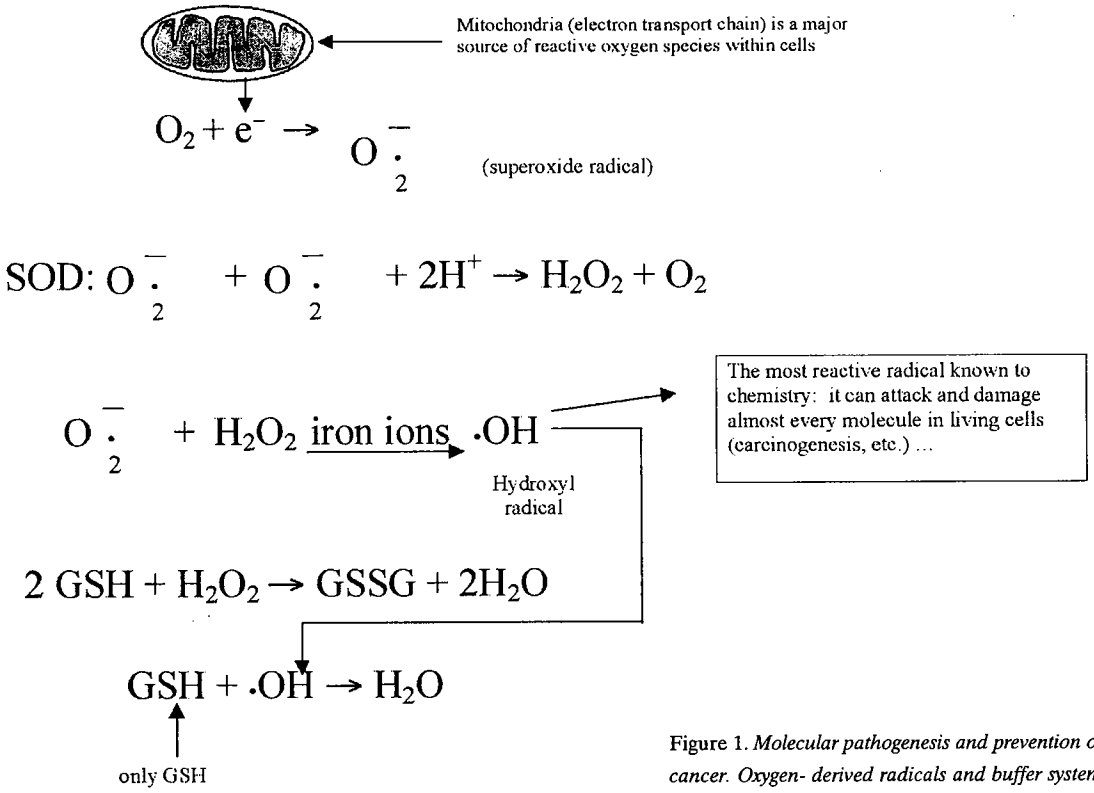

Figure 1. *Molecular pathogenesis and prevention of prostate cancer. Oxygen- derived radicals and buffer systems.*

content of the protein source is responsible for the observed increase in GSH within the prostate epithelium. The pro-oxidant-antioxidant status in the prostate epithelium appeared then to determine the fate of this organ (13). The negative effect of the prostate to androgen exposure may be minimized by the level of antioxidant action of GSH. Consumption of dietary whey proteins may provide a useful strategy to elevate intracellular GSH and protect the prostate against ROS-induced cell damage.

Recently, a prospective clinical trial conducted among 32,000 women of the Nurses Health Study showed that higher levels of total plasma cysteine may predict a reduced risk of breast cancer (14). The prostate cancer response to the whey protein appears then not to be strictly gender-dependent as the antioxidant effect of the cysteine-GSH system may apply to breast cancer prevention.

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