

Chapter 2

Anticancer Mechanisms of Vitamin C

Cancer Preventative Mechanisms of Vitamin C

Antioxidant Properties of Vitamin C

Vitamin C is considered a very strong reductant and radical scavenger. Vitamin C reduces unstable oxygen, nitrogen, and sulfur radicals. In addition, it acts as primary defense against aqueous radicals in blood [1, 2]. In studies with human plasma, vitamin C protected plasma lipids against peroxidative damage induced by aqueous peroxy radicals [3]. Thus, by efficiently trapping peroxy radicals in the aqueous phase before they can reach the lipid-rich membranes and initiate lipid peroxidation, vitamin C can protect bio-membranes against primary peroxidative damage. Vitamin C may also protect membranes against lipid peroxidation due to its synergistic antioxidant function with vitamin E. Vitamin C may enhance or reinstate the activity of tocopherol (vitamin E), the principal lipid soluble antioxidant [1]. Vitamin C reacts with the tocopheroxyl (chromanoxyl) radical that arises in cell membranes as a result of vitamin E antioxidant activity; and simultaneously regenerates tocopherol and transfers the oxidative challenge to the aqueous phase [3]. At this point, the less reactive ascorbate radical can be enzymatically reduced back to ascorbic acid by an NADH-dependent system [4–6]. This probably explains how ascorbate reduces nitrates and prevents the formation of carcinogenic nitrosamines [7]. Vitamin C is found naturally in the following foods: broccoli, cabbage, potatoes, peas, red peppers, brussel sprouts, kale, cauliflower, cantaloupe, strawberries, mangoes, tangerines, orange, grapefruit, lemons, and limes.

Primary Anticancer Mechanisms of Vitamin C

Oxidative, Oxidant, and Pro-oxidant Properties of Vitamin C

Vitamin C not only possesses antioxidant activity, but also can generate cytotoxic activity at higher concentrations [8–10]. It has also been suggested that vitamin C may promote oxidative metabolism by inhibiting the utilization of pyruvate for anaerobic glycolysis [11]. Vitamin C in high concentrations inhibits prostaglandins of the 2-series (arachidonic acid derived), which have been correlated with inflammation and increased cell proliferation [12]. A growth inhibitory action has been reported for vitamin C or its derivatives in at least seven types of tumor cells [13–19]. This inhibitory activity was not observed in normal fibroblasts [13–18], while other researchers have reported a fibroblast inhibition [19–23]. Nevertheless, all reports concur that this cytotoxic effect produced by vitamin C in an array of cell lines (mostly malignant) has been associated with its pro-oxidant activity [8, 24–30]. Vitamin C and its radical potentiate the activation of transcription factor NF-kappa B, which has been associated with inhibition of cell growth [31].

Hydrogen Peroxide and Vitamin C

Vitamin C can generate hydrogen peroxide (a reactive oxygen species) upon oxidation (with oxygen) in biological systems [32–34]. This action can be enhanced by divalent cations such as iron and copper [10, 24, 35]. Hydrogen peroxide may further generate additional reactive species, such as the hydroxyl radical and secondary products of oxidation, such as aldehydes. These reactive species can compromise cell viability mainly by damaging the cell membranes and mitochondria. Malignant cells are relatively deficient in catalase activity [27, 35–40]. However, these oxidative reactions may only form in minute quantities in healthy organisms. This is mainly because most transition metal ions are bound to proteins in serum, which makes them unavailable to participate in biochemical reactions [41]. Nevertheless, these oxidation reactions may take place in pathological states such as malignancy, in which cohesive forces that inhibit the liberation of the metal ion from the proteins as well as the control of the cell's replication mechanisms are drastically reduced [41]. These reactive species are capable of inducing multiple negative cellular effects such as DNA strand breaks, disruption of membrane function via lipid peroxidation, and depletion of cellular ATP [39]. The failure to maintain high ATP production (cell energy level) may be a consequence of oxidative inactivation of key enzymes, especially those related to the Krebs cycle and the electron transport system. A distorted mitochondrial function (transmembrane potential) may result. This aspect could be suggestive of an important mitochondrial involvement in the carcinogenic process [42]. In this respect, vitamin C may serve yet another metabolic and physiological function by providing reductive energy, i.

e., the electrons necessary to direct energy pathways in the mitochondria [43–47]. Interestingly, vitamin C has been detected within the mitochondria where it is also regenerated [48].

In general, the cytotoxicity induced by vitamin C seems to be primarily mediated by hydrogen peroxide [13–16, 21, 36, 49–51]. Of interest, is the observation that in proliferating cells very low levels of hydrogen peroxide (3–15 μM) stimulate cell division, whereas greater concentrations induce cell growth arrest, apoptosis and/or necrosis [50]. It has also been shown that the amount of hydrogen peroxide generated by the cells was proportionally dependent on the vitamin C concentration and inhibited by serum [20, 51–53]. Human serum, as part of its normal contents, has certain proteins such as albumin and glutathione with antioxidant capacity that may stabilize vitamin C (directly or indirectly by chelating available transition metals). In addition, serum contains antioxidant enzymes such as catalase, which decomposes hydrogen peroxide. Other antioxidant enzymes including glutathione peroxidase and superoxide dismutase complement the catalase enzymatic function.

Hydrogen peroxide is most likely generated during ascorbate's metabolic oxidation to dehydroascorbate. Hydrogen peroxide reduces cellular levels of thiols and can initiate membrane lipid peroxidation [13–19, 35–37, 49, 54–56]. As previously mentioned, the antiproliferative action of vitamin C in malignant cultured cells, animal, and human tumor xenografts has been augmented by the addition of the cupric ion, a catalyst for the oxidation of vitamin C [19, 24–26, 57–59]. In addition, the combination of vitamin C and copper has been shown to inactivate lactate dehydrogenase [60], the enzyme responsible for the reduction of pyruvate to lactate (a metabolic dead end product prevalent in anaerobic environments such as in cancer). Copper in the form of copper sulfate may also inhibit tyrosinase activity [61, 62]. It has also been suggested that the selective toxicity of vitamin C in malignant cells may be due to reduced levels of antioxidant enzymes, catalase, superoxide dismutase, and glutathione peroxidase [63] in these cells, leading to cellular damage through the accumulation of hydrogen peroxide [29, 57, 64–68]. There is a 10- to 100-fold greater content of catalase in normal cells than in tumor cells [29, 64].

Furthermore, the addition of vitamin K3 (menadione) to vitamin C produces a synergistic antitumor activity [69–73]. Since menadione is reduced intracellularly via one or two electron transfer action (probably by vitamin C), this may lead to formation of hydrogen peroxide and other reactive oxygen species, concomitant with the depletion of glutathione. Decreases of glutathione have also been associated with vitamin C metabolism [74]. Interestingly, a new form of cell death (autschizis) has been described for this synergistic vitamin (vitamins C and K) phenomenon in which tumor cells undergo profound perturbations of cytoskeleton and membranes that ultimately kill the cells by a form of cell death that is distinct from apoptosis, oncosis, or necrosis [71–75]. For this reason, the combination of megadoses of IV ascorbate together with oxygen, vitamin K, lipoic acid, carnitine, magnesium, Coenzyme Q10, and small doses of copper may seem logical as part of a non-toxic treatment protocol for cancer. Intravenous administration of vitamin C

can yield very high plasma levels that seem to be necessary for vitamin C's toxic effect on malignant cells [76–79].

Other Vitamin C Oxidation Products with Anti-cancer Potential

Furthermore, vitamin C oxidation products such as dehydroascorbic acid, 2,3-diketogulonic acid, and 5-methyl 1-3,4-dehydroxytetrone, all degradation products of ascorbic acid, have demonstrated antitumor activity [19, 24–27]. In addition, other compounds arising from the oxidation or degradation of ascorbate can inhibit tumor growth. The most effective ones are: gamma-cronolactone and 3-hydroxy-2-pyrone. The available evidence suggests that these vitamin C oxidation products and/or metabolic by-products have a function in controlling mitotic activity. All active compounds consist of an unsaturated lactose ring with a double bond conjugated with a carbonyl group, suggesting that this particular structural feature of the lactose ring may be relevant in the antitumor activity [19]. The antitumor activity shown by these compounds could be due to their ability to produce active molecular species that inhibit tumor growth such as hydrogen peroxide and certain aldehydes. Most of these compounds are very unstable and their growth inhibitory activities could be attributed to their chemical instability which favors the formation of reactive species. These antiproliferative mechanisms of vitamin C and/or its oxidation products on tumor cells are probably of a very complex nature, since they seem to involve a series of pleiotropic chain reactions.

Large amounts of vitamin C intake can change the levels of certain amino acids in body fluids [80–83] and may deplete the bioavailability of lysine, glutamine and cysteine, two amino acids which are required for rapidly growing tumors [84]. Experiments using tissue homogenate show that the interactions between vitamin C, metal ions, and oxygen are capable of inducing structural changes in protein [82–84]. These electron transfer reactions need a conductor in order to proceed; and proteins can serve as electron conductors for these reactions. Metal ions, such as copper, are good electron conductors because their valence bonds are partially filled. The resulting molecules contain one or more uncoupled electrons and are very reactive-free radicals.

Dehydroascorbic acid (the oxidized, nonionic, and more lipid soluble form of ascorbate) and the semi-dehydroascorbic acid radical have been shown to promote lipid peroxidation [19]. One of us (MJG) has demonstrated that secondary products of lipid peroxidation have an inhibitory action on human malignant cell proliferation [38, 40, 49, 54]. There is evidence to suggest that dehydroascorbic acid may work as a mitotic inhibitor in vivo [76]. Dehydroascorbic acid may prevent cell division by inhibiting protein synthesis at the ribosomal level [76]. Interestingly, prolonged exposure to high concentrations of dehydroascorbic acid may cause irreparable damage resulting ultimately in complete lysis of the cells [76].

In summary, there are various oxidative species related to vitamin C biophysiology that may produce a cytostatic or cytotoxic action. Moreover, a synergistic interaction seems very likely involving these cell growth inhibitory mechanisms.

Secondary Anticancer Mechanisms of Vitamin C: Host Resistance to Cancer

Vitamin C and Intracellular Matrix

Vitamin C metabolism is associated with other mechanisms known to be involved in host resistance to malignant disease. Cancer patients are significantly depleted of vitamin C. This could indicate an increase requirement and utilization of this substance to potentiate these various resistance mechanisms. Scurvy results from the severe dietary lack of vitamin C. It is a syndrome of generalized tissue disintegration at all levels, involving the dissolution of intercellular ground substance, the disruption of collagen bundles, and the lysis of the inter-epithelial and inter-endothelial cement. This disintegration leads to ulceration with secondary bacterial colonization, to vascular disorganization with edema and interstitial hemorrhage, and to generalized undifferentiated cellular proliferation throughout the tissue reverting to a primitive form [85]. The generalized stromal changes of scurvy are identical to the local stromal changes observed in the immediate vicinity of invading neoplastic cells [86]. Thus, stromal resistance may be a physical line of defense against cancer by encapsulating neoplastic cells with a dense fibrous tissue. This feature can be enhanced by high doses of vitamin C. Vitamin C also enhances the resistance of the intercellular ground substance to local infiltration.

A brisk lymphocytic response is a systemic factor indicative of enhanced host resistance and is associated with a more favorable prognosis of the disease. In order to proliferate, cells must escape the restraint imposed by highly viscous intercellular glycosaminoglycans and can do this by the release of the enzyme hyaluronidase [87]. There is evidence that a physiological hyaluronidase inhibitor is an oligoglycosaminoglycan that requires ascorbic acid for its synthesis [88]. Decreases in hyaluronic acid have been shown to be conducive to cell proliferation [89]. In addition, ascorbate is involved in the synthesis of collagen. Collagen rich extracellular matrix including the basement membrane is a major barrier to the metastatic and invasive spread of cancer cells [85]. The intercellular matrix is reinforced by a tri-dimensional network of interlacing collagen fibers. The amount of collagen present determines the strength of the tissue and also its resistance to malignant infiltration. Lack of ascorbate sharply reduces hydroxylation of prolyl and lysyl residues into hydroxyproline and hydroxylysine, leading to instability of the triple helix of collagen [90], which is a common feature in scurvy and also present in cancer. This is also of importance in vitamin C's role on wound healing including decubital ulcers, surgery recovery, and other traumatic injuries [91].

Vitamin C and Immuno-competence

Ascorbate is essential to ensure the efficient working of the immune system. The immuno-competence mechanisms are a combination of humoral and cell-mediated defensive reactions with ascorbate involved in a number of ways. In terms of humoral immuno-competence, ascorbate is essential for immunoglobulin synthesis [92]. In cell-mediated immunity, immuno-competence is exercised overwhelmingly by lymphocytes which contain high concentrations of ascorbate relative to other cells. In addition, ascorbate is required for active phagocytosis [93]. Ascorbate has also been shown to enhance interferon production [93–95].

Ascorbic acid has other identified functions related to cancer prevention. Ascorbate is required by the mixed function oxidases for the hydroxylation of amino acids [85]. The mixed function oxidases are a group of closely related microsomal enzymes that metabolize many classes of compounds and are particularly important in the inactivation of chemical carcinogens. Microsomal metabolism of carcinogens yields products generally more water soluble which greatly increases their rate of excretion. In addition, ascorbate has been shown to protect against nitrate-induced carcinogenesis [96]. Another important anticancer function of vitamin C when provided in large quantities is that it enhances the removal of sodium via the urine thereby reducing the level of sodium ions in the serum. In cancer, there is a disturbed sodium/potassium ratio. It has been suggested that vitamin C may also have a role inhibiting prostaglandins of the two series in carcinoma cells [97, 98]. In the process of prostaglandin biosynthesis, the release of arachidonic acid from cell membrane phospholipids is implicated as one of the synergistic signals leading to cell proliferation. Also, vitamin C has been shown to stabilize p53, a protein involved in cell proliferation control [99, 100].

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