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Possibilities of Ascorbic acid for the prevention of cancer

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Abstract
Vitamin C (Ascorbic acid, abbreviated as AsA) is functional in different processes in the human body. In this paper, we discuss some of them with a focus on functions related to anticancer activity. We demonstrate that AsA can play a role in cancer prevention by looking at previous clinical trials and other theoretical implications.

Keywords: antioxidant, Ascorbic acid, cancer, cytotoxicity, reactive oxygen species

1-Introduction

Ascorbic acid (AsA, vitamin C) is a water-soluble vitamin isolated by a Hungarian biochemist in 1923. Humans cannot synthesize AsA because they lack the enzyme gluconolactone oxidase, which plays a role in the final stage of the synthesis of AsA. Thus, humans must obtain this vitamin from external sources such as fruits and vegetables to meet the body's need for it[1].

The ascorbate monoanion, AscH−, is the dominant form at physiological pH[1]. Ascorbate is an excellent reducing agent and readily undergoes two consecutive, one-electron oxidations to form ascorbate radical (Asc•−) and dehydroascorbate (DHA). The ascorbate radical is relatively unreactive. Ascorbate is an effective donor antioxidant and oxidizes easily. Ascorbate and ascorbyl radical offer low one-electron potentials. This characteristic enables them to reduce relevant radicals and oxidants such as hydroxyl, superoxide anion, hypochlorous acid, or singlet oxygen.

Ascorbate is renewable through the dismutation of Ascorbyl radical to dehydroascorbate. Ascorbate can be regenerated from both DHA and the ascorbyl radical. This process can be done either enzymatically (e.g. thioredoxin reductase, glutaredoxin) or non-enzymatically (e.g. glutathione, lipoic acid) [2]

Pauling and Cameron in 1970 investigated the therapeutic effect of mega doses of AsA in cancer prevention and treatment. They observed extended survival in patients with advanced cancer treated with intravenous infusions of 10g ascorbate daily over months[3].

Research suggests that intravenous administrations yield a high dose of vitamin C which is crucial for cytotoxic activity. While it doesn't happen with oral administration. When this vitamin is given orally, concentrations in the plasma are less than 100 μM,[4]

2-characteristic related to anticancer activity

2-1-Pro oxidant effect

These mechanisms highlight the diverse ways vitamin C can exert anti-tumor effects. The pro-oxidant properties of pharmacological concentrations of vitamin C, particularly when administered intravenously, can induce the formation of hydrogen peroxide and the subsequent generation of reactive oxygen species (ROS) that directly target cancer cells. This oxidative stress leads to cell cycle arrest, upregulation of p53, decreased ATP levels, compromised mitochondrial function, suppression of antioxidant gene expression, and ultimately cell death through apoptosis.[5]

Furthermore, vitamin C's impact on 2-oxoglutarate-dependent dioxygenases, including histone and DNA demethylases, can induce significant epigenetic changes that affect gene expression in cancer cells. Preclinical studies have also demonstrated synergistic effects between vitamin C and certain chemotherapy or immunotherapy agents, enhancing their efficacy against cancer cells.[3]

Interestingly, even at lower concentrations well below 1 mM, vitamin C has been shown to sensitize cancer cells to conventional chemotherapeutic drugs like etoposide, cisplatin, or doxorubicin. Additionally, vitamin C's ability to act as a pro-oxidant by reducing transition metal ions such as iron and copper can further contribute to its anti-tumor effects. The reduction of these metal ions by ascorbate can lead to reactions with hydrogen peroxide or lipid hydroperoxides, generating highly reactive hydroxyl radicals or lipid alkoxyl radicals that contribute to the cytotoxicity observed in cancer cells.

In vivo generation of hydrogen peroxide by ascorbate is likely to occur in extracellular fluids, and not in blood due to the efficient removal of hydrogen peroxide by red blood cells, suggesting that vitamin C could act as a prodrug to deliver hydrogen peroxide into tissues. This concept highlights the importance of the site of hydrogen peroxide production as a critical parameter for the activity of ascorbate.

The preference of cancer cells for ascorbate uptake due to their overexpression of facilitative glucose transporters, which can transport dehydroascorbate, leading to the

accumulation of vitamin C in tumors, provides a potential explanation for the greater sensitivity of cancer cells to AsA. Additionally, the higher basal status of intracellular ROS in cancer cells, induced by oncogenic transformation (e.g. by cMyc or Bcr-Abl), may also contribute to their greater sensitivity towards oxidative stress. This heightened sensitivity suggests that cancer cells, with their high endogenous levels of ROS, are more susceptible to being killed by agents that promote ROS, such as vitamin C.

These insights into the preferential targeting of cancer cells by ascorbate-induced oxidative stress and the potential role of vitamin C as a prodrug for delivering hydrogen peroxide further support its potential as an effective anti-tumor agent.[2]

Ascorbate exerts its anti-tumor effects, particularly through its ability to generate hydrogen peroxide and promote oxidative stress in cancer cells. The susceptibility of cancer cells to H2O2 and oxidative stress compared to primary cell lines is attributed to differences in their metabolism of H2O2 and antioxidant capacity.

The chelating and reducing properties of ascorbate towards transition metal ions, such as Fe3+ and Cu2+, play a crucial role in its ability to promote iron uptake and generate reactive oxygen species through the Fenton reaction. This leads to the production of superoxide, hydrogen peroxide, and highly reactive oxidants like the hydroxyl radical, contributing to oxidative stress in cancer cells.

Studies have shown that the presence of high concentrations of ascorbate (1 mM or above) in cell culture medium can induce oxidative stress, leading to cell cycle arrest, upregulation of p53, decreased ATP levels, compromised mitochondrial function, and suppression of antioxidant gene expression. Even lower levels of ascorbate (as low as 100 μM or 1 mM) have been shown to enhance the susceptibility of cancer cells to chemotherapeutic agents like etoposide, cisplatin, or doxorubicin, ultimately leading to cell death by apoptosis.

The structural similarity of dehydroascorbate (DHA) to glucose enables its uptake into cells via glucose transporters (GLUTs), contributing to the intracellular pool of ascorbate. Once inside the cell, DHA is reduced by enzymes dependent on molecules like glutathione (GSH), NADH, and NADPH, potentially depleting these essential molecules in the cell.

The upregulated expression of GLUT1 in cancer cell lines allows for rapid uptake of DHA, but the exact causal relationship between this uptake and the observed cytotoxicity is still not fully understood. Overall, these findings provide valuable insights into the mechanisms underlying the anti-tumor effects of ascorbate and its potential as a therapeutic agent for cancer treatment.

The cytotoxic activity of millimolar concentrations of ascorbate on cancer cell lines in vitro is indeed intriguing and suggests a dual role for vitamin C, beyond its traditional

antioxidant properties. The ability of ascorbate to generate reactive oxygen species (ROS) at high concentrations is crucial for its anti-tumor effects, highlighting its pro-oxidant nature in certain contexts.

As mentioned earlier, the pro-oxidant effects of ascorbate are primarily mediated by its interactions with transition metal ions, such as iron and copper. In the presence of these metals, ascorbate can undergo redox reactions that lead to the production of ROS, including hydrogen peroxide and hydroxyl radicals. These ROS can induce oxidative stress in cancer cells, disrupting cellular processes and ultimately triggering cell death pathways.

The paradoxical nature of ascorbate's pro-oxidant effects in cancer cells stems from its ability to switch between antioxidant and pro-oxidant roles depending on the cellular context. While ascorbate can act as an antioxidant by scavenging free radicals and protecting cells from oxidative damage under normal conditions, its pro-oxidant activity becomes prominent in environments rich in transition metals or under specific physiological conditions.

The mutagenic potential of ascorbate in the presence of transition metals further underscores the complexity of its interactions with cellular components. The generation of ROS by ascorbate-metal interactions can lead to DNA damage and mutations, potentially contributing to the cytotoxic effects observed in cancer cells.

Overall, the dual nature of ascorbate as both an antioxidant and a pro-oxidant highlights its versatility as a therapeutic agent in cancer treatment. By exploiting its ability to induce oxidative stress and trigger cell death pathways in cancer cells, high concentrations of ascorbate hold promise as a novel approach for targeting tumors and overcoming chemoresistance.[3]

2-2-Impact on the immune system:

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The observation of low vitamin C plasma concentrations in patients undergoing intensive chemotherapy and stem cell transplantations for hematological malignancies is intriguing and suggests a potential link between vitamin C status and cancer treatment outcomes. The decreased vitamin C levels in these patients could be due to various factors, including reduced dietary intake, increased metabolic demand, or altered distribution and utilization of vitamin C in the body during cancer therapy.

The increased need for vitamin C in tumor cells and immune cells during cancer treatment is particularly noteworthy. Tumor cells are known to exhibit altered metabolic activities and increased oxidative stress, which may contribute to their heightened demand for vitamin C. Additionally, the activation and proliferation of immune cells, such as T-lymphocytes and natural killer cells, during the body's response to cancer can also lead to an increased requirement for vitamin C to support their functions.

The potential impact of low vitamin C levels on immune cell function and anti-tumor immune responses is an area of growing interest. As mentioned, vitamin C has been shown to stimulate the production and activation of immune cells, including T-lymphocytes and natural killer cells, which play critical roles in combating cancer cells and pathogens. Therefore, maintaining adequate vitamin C levels in patients undergoing cancer treatment, especially those receiving intensive chemotherapy and stem cell transplantations, may be important for supporting immune function and optimizing treatment outcomes.

Given the multifaceted roles of vitamin C in cancer therapy, including its pro-oxidant effects on tumor cells and its potential immunomodulatory properties, further investigation into the interplay between vitamin C status, immune function, and cancer treatment is warranted. This research could provide valuable insights into the therapeutic potential of optimizing vitamin C levels as an adjunctive approach to conventional cancer therapies.[5]

2-3- Role in Hypoxia

The role of hypoxia-inducible factor 1 (HIF-1) in cancer progression and adaptation to hypoxic conditions is crucial for the survival and growth of cancer cells. Under hypoxic conditions, the stabilization and activation of HIF-1 lead to the transcriptional activation of genes encoding factors that promote angiogenesis, glycolysis, cell survival, and invasion, all of which are essential for tumor progression.

The inhibition of HIF-1 activity has been identified as a promising target for cancer therapy due to its central role in solid tumor progression. Interestingly, research has shown that the activity of prolyl hydroxylases, enzymes responsible for regulating HIF-1 stability, can be enhanced in the presence of ascorbate (vitamin C). Ascorbate acts as a cofactor for prolyl hydroxylases by maintaining the iron center of these enzymes in a reduced state, thereby optimizing their activity[2].

2-4-Epigenetic changes

Global DNA hypomethylation can lead to genomic instability and increased chromosomal fragility, as well as activate the transcription of transposable elements and oncogenes, contributing to oncogenesis. On the other hand, hypermethylation of tumor suppressor gene promoters can lead to the silencing of these genes, further promoting cancer development.

Ascorbate's potential impact on epigenetic regulation could have implications for developing novel cancer therapies, given the reversible nature of epigenetic changes compared to genetic mutations.[3]

Ascorbate supplementation may enhance the function of epigenetic modifiers during the reprogramming of induced pluripotent stem cells (iPSCs). This is because many of

these modifiers are dependent on ascorbate dioxygenases. Thus, ascorbate and other nutritional supplements could potentially prevent cancer by modulating the components of the systems that establish the epigenetic code.

This concept implies that by influencing the epigenetic regulation of gene expression through supplementation with substances like ascorbate, it may be possible to prevent or inhibit the development of cancer. This approach targets the reversible epigenetic changes that play a significant role in cancer progression, offering a potential avenue for novel cancer prevention strategies.[4]

2-5-Cofactor of hydroxylases

Ascorbate plays a role in maintaining the activity of Fe2+–2-oxoglutarate-dependent dioxygenases, which are enzymes involved in various cellular processes. It also highlights the importance of collagens in the extracellular matrix (ECM) as physical barriers against invasion and metastasis of cancer cells.

Furthermore, it suggests that ascorbate stimulates the production of certain types of collagens, particularly types I and III, which are important for the structural integrity of the ECM. Additionally, it references a proposal by Cameron and Pauling that mega doses of ascorbate could inhibit cancer growth by preventing cancer cell invasion.

Moreover, the passage mentions that a type IV collagen domain inhibits the proliferation of capillary endothelial cells and blood vessel formation, ultimately suppressing tumor growth. This indicates that certain components of the ECM, such as type IV collagen, may play a role in inhibiting tumor growth.[4]

2-7-Synergism with anticancer drugs

in classical anticancer treatments, such as radiotherapy and certain chemotherapies induce oxidative stress. Radiotherapy generates reactive oxygen species in irradiated tissues, while some chemotherapeutic drugs, like paclitaxel, may induce oxidative stress as part of their mechanism of action.

The use of antioxidants or prooxidants in combination with chemotherapies should be carefully considered based on preclinical studies. Vitamin C has been reported to enhance the efficacy of some chemotherapeutic drugs and radiotherapy in both in vitro and in vivo studies. However, there are instances where the activity of certain agents may decrease when used with AsA, possibly due to the direct inactivation of the drug by vitamin C.

It should be noted that oral supplementation of vitamin C and other antioxidants does not seem to influence the outcomes of patients undergoing chemotherapeutic regimens, suggesting that it may not protect cancer cells from oxidant damage induced by chemotherapy.[2]

3- role in cancer prevention

As mentioned earlier, AsA is functional in balancing intracellular redox through its antioxidant activity. Therefore, it can reduce the oxidative damage caused by free radicals and thus, reduce the risk of cancer. Also, there is some evidence that AsA enhances immune response. leukocytes are a kind of lymphocytes and are functional in destroying cancer cells. These cells usually show a high concentration of AsA. Thus, AsA concentration may play a role in immunological surveillance[6]. The same was observed with Natural killer cells that function in killing tumor cells. The role of ascorbic acid in promoting their proliferation has been demonstrated[7].

4-clinical data

Kim et al. investigated mice lacking the enzyme involved in the biosynthesis of AsA, The results suggest cytotoxic activity of AsA on NK cells. [8]

Jacobs et al. demonstrated that AsA induces apoptosis in osteosarcoma cells via the downregulation of the MAPK pathway. This pathway is crucial for extracellular signal transduction to begin cellular responses.[9]

Another study suggests that pharmacological concentrations of AsA show selective cytotoxic activity against colorectal cancer.[10]

5-conclusion

Administration of high doses of AsA through intravenous infusions can result in plasma concentrations much higher than those achieved through oral dosing. These high concentrations of vitamin C have been shown to potentially improve the efficacy of chemotherapy and reduce the side effects of this treatment. Indeed, they are considered relatively safe for long-term use.[11] [2]

However, it is important to note that even though AsA is generally perceived as non-toxic, high doses administered intravenously can lead to adverse effects. For example, in patients with glucose-6-phosphate dehydrogenase deficiency, high concentrations of vitamin C can trigger hemolysis. Additionally, the oxidation of AsA produces oxalic acid, leading to hyperoxaluria. This condition can promote the precipitation of stones or drugs in the urinary tract, such as urate, cystine, or oxalate stones.

Overall, while intravenous injections of AsA may have potential benefits in enhancing chemotherapy efficacy, they should be treated with caution due to the possibility of side effects. It is essential to consider the individual patient's health status and potential risks before administering high doses of vitamin C intravenously.[2]

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