Essay

Advantages of Vitamin C Anticancer Therapy over Other Pharmacological Interventions

Alexander V. Peskin *

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Advantages of Vitamin C Anticancer Therapy over Other Pharmacological Interventions

Alexander V. Peskin *

Mātai Hāora - Centre for Redox Biology and Medicine, Department of Pathology and Biomedical Science, University of Otago Christchurch, Christchurch, New Zealand; alexander.peskin@otago.ac.nz

Abstract

This article reviews pharmacological strategies targeting key metabolic pathways in cancer cells and highlights their inherent limitations, including metabolic plasticity and lack of selectivity. It is proposed that these vulnerabilities can be addressed through a global redox-based approach using high-dose vitamin C. Evidence suggests that the anticancer activity of vitamin C is mediated by its oxidation to dehydroascorbic acid (DHA). Although DHA cannot be administered directly due to its instability, it can be generated in situ in the circulation. Once taken up by cancer cells, DHA perturbs multiple redox-sensitive processes, leading to depletion of NADPH and collapse of cellular redox homeostasis. We present a mechanistic framework outlining how controlled generation of DHA may enable a more robust and clinically effective anticancer strategy.

Keywords: cancer; vitamin C; dehydroascorbic acid; hydrogen peroxide; thiols; NADPH

"What is now proved was once only imagined"
William Blake (*The Marriage of Heaven and Hell*)

1. Introduction

Despite substantial advances in cancer therapy, malignancy remains a leading cause of mortality worldwide. A central strategy in oncology has been to exploit metabolic differences between cancer and normal cells in order to achieve selective cytotoxicity while minimising collateral damage.

Although numerous metabolic targets have been identified, clinical translation has often been disappointing. Many therapies that effectively inhibit individual pathways in vitro fail in vivo due to metabolic plasticity, limited selectivity, or systemic toxicity. These limitations suggest that targeting single metabolic nodes may be insufficient [1–3].

This review analysed some metabolic strategies explored to date and proposes an alternative concept: use controlled oxidation of vitamin C to dehydroascorbic acid (DHA) to target many metabolic pathways which would lead to global disruption of tumour redox homeostasis through depletion of intracellular reducing capacity.

2. Glucose Metabolism

The first identified metabolic difference in cancer cells was their dependence on glucose, even in the presence of oxygen, as the main energy source, coupled with lactate production [4,5]. This phenomenon, known as the Warburg effect, has been consistently observed in cancer cells of various tissue origins [6].

Inhibition of increased glycolysis in tumours has been considered and targeted for anticancer treatment. Extensive reviews on research on inhibitors of pathways related to glucose metabolism and using the knowledge for patient treatment are available [7–12]. Here we discuss some of the most promising treatments as examples to estimate how progress in this field could lead to health benefits.

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2.1. 2-Deoxyglucose

2-Deoxyglucose (2-DG) is a competitive inhibitor of glucose metabolism [13]. After uptake by cells, 2-DG is phosphorylated by hexokinase and inhibits glycolysis because unlike phosphorylated glucose it cannot be processed by phosphoglucose isomerase. Therefore, no conversion of phosphorylated glucose to phosphorylated fructose occurs and ATP production downstream of this pathway is blocked. While 2-DG shows high efficacy in cell-based studies [14], clinical studies have not demonstrated comparable benefits. Although patient tolerance is generally good, anticancer efficacy is limited, even in combination therapies [15–17[. This discrepancy is largely attributed to metabolic plasticity, which enables tumour cells to bypass inhibited pathways [18,19].

2.2. Lonidamine

Lonidamine is a derivative of indazole-3-carboxylic acid and an inhibitor of hexokinase 2 [20] highly overexpressed in cancer cells [21].

It exhibits cytotoxicity to cultured cancer cells in combination with other drugs [22]. In addition to its metabolic role, hexokinase 2 may protect cells from apoptosis through interactions with other proteins and may contribute to metastasis [23]. However, clinical trials have not demonstrated improved patient survival [24]. Modified derivatives show increased cytotoxicity, possibly due to effects beyond hexokinase 2 inhibition [25].

2.3. 3-Bromopyruvate

3-Bromopyruvate (3-BP) is a pyruvate mimetic with promising anticancer activity [26]. In animal models, it can completely inhibit hexokinase 2 and significantly inhibit tumour growth [27].

However, its mechanism likely involves non-specific alkylation of thiol groups in glycolytic enzymes and other proteins [28,29]. As a highly reactive electrophile, 3-BP may also affect thiol-containing proteins in normal cells, limiting its clinical applicability.

3. Thiols

Thiol metabolism is widely considered a target for anticancer therapy due to the reliance of cancer cells on elevated antioxidant defences [30]. This vulnerability has historically been exploited by traditional medicine long time ago by using arsenic for treatment [31]. Arsenic (As^{3+}) binds strongly to the sulfhydryl (-SH) groups. Although toxic and carcinogenic, it has shown therapeutic benefit at controlled doses.

Here we review some topics of thiol metabolism considered as the most promising for anticancer treatment.

3.1. GAPDH

GAPDH is an oxidant-sensitive thiol protein [32]. Although primarily involved in glycolysis, it also performs other functions [33]. A selective inhibitor koningic acid (KA) has been identified; it is a sesquiterpene lactone isolated from fungi and it directly binds to the active site of human GAPDH [34]. So far, no information on using KA in clinical trials is available. Interestingly thiol oxidation of GAPDH may act as redox switch to stimulate the oxidative pentose phosphate pathway by rerouting glucose [35]. This study highlighted that aiming at a single target even if it looks very promising may not be a winning strategy in anticancer action.

3.2. Thioredoxin-Thioredoxin Reductase System

Thioredoxin-thioredoxin reductase system is recognized as a central for controlling cellular redox state via thiol-disulfide exchange and considered as a target for anticancer treatment [36,37]. Thioredoxin (Trx) is a small thiol protein, it can reduce disulfides by a mechanism of thiol exchange oxidising Trx to internal disulfide. Oxidised Trx is recycled to its reduced form by thioredoxin

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reductase (TrxR) which uses NAPDH as a source of reducing equivalents. While Trx and TrxR participate in various processes like transcription, proliferation, apoptosis, we would like to specifically highlight that synthesis of deoxyribonucleotides depends on Trx, which makes the system vital for DNA synthesis [38]. Trx and TrxR inhibitors are cytotoxic for cancer cells in culture or in mouse models and the search for inhibitors that disable Trx and/or TrxR specifically in cancer cells with limited toxicity for patients is ongoing [39–41].

3.3. Peroxiredoxin

Peroxiredoxins (Prdxs) are thiol-containing proteins that cycle between oxidised and reduced forms [42]. They react with hydrogen peroxide exceptionally rapidly [43] and play critical roles in cell signalling [44,45]. Reduction of oxidised Prdxs depends mostly on Trx and in some cases on Grx [42,46]. There is a growing body of evidence that Prdxs promote tumour survival, progression, and metastasis, and are upregulated in cancers [47–51]. It has been reported that adenanthin, a diterpenoid isolated from plants that directly targets the conserved resolving cysteines of Prdxs, promotes differentiation of leukemic cells in culture [52]. Subsequent studies showed that the reaction of adenanthin with Prdxs lacks specificity, as it also reacts with other thiols, while selenoproteins appear to be even more favourable targets [53]. Thus, the remarkable biological effects of adenanthin may be attributed to a broader disruption of thiol metabolism in leukemic cells rather than to specific inhibition of Prdxs.

3.4. Glutathione

The importance of glutathione, GSH for cancer cells progression, metastases, and resistance to treatment is widely appreciated [54–57]. The problem is that GSH is pivotal for normal cells [58] and selective targeting remains difficult.

4. Methionine

Methionine depletion has been shown to induce cell cycle arrest and apoptosis in cancer cells [59]. This phenomenon, known as methionine auxotrophy—where cancer cells are unable to proliferate in the absence of methionine while normal cells remain relatively unaffected—has been observed in many, although not all, human cancer cell lines [60,61].

Methionine dependence has also been explored therapeutically in vivo. Methionine-restricted diets have been investigated, and to further reduce plasma methionine levels recombinant methionine-γ-lyase (MGL) has been employed [62–65]. MGL catalyses the oxidative deamination of L-methionine to α-ketobutyrate, ammonia, and methanethiol. Although MGL demonstrated promising anticancer activity, clinical studies revealed significant adverse effects, including immunogenic reactions, gastrointestinal disturbances, hyperammoniemia, which is harmful to the kidneys and liver [66,67].

One of the major biological functions of methionine is its involvement in DNA methylation. Although global hypomethylation is common in cancer cells, methionine depletion, particularly in combination with other anticancer agents, may produce undesirable epigenetic alterations that reprogram gene expression toward a more aggressive phenotype [68].

5. DNA Synthesis

Cell proliferation is a hallmark of tumours, and targeting processes related to DNA metabolism has been widely explored in cancer research. In attempts to eliminate cancer cells, several strategies have been pursued: i) inhibition of DNA replication by targeting various stages and components of the replication machinery; ii) suppression of DNA repair pathways, which are essential for maintaining genome stability and supporting survival of genetically unstable cancer cells, as well as resistance to DNA-damaging therapies; and iii) interference with the supply of precursors required for DNA synthesis [69–76].

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Many of these approaches have led to clinically effective anticancer drugs. Nevertheless, important limitations remain. Due to the genetic heterogeneity of tumours, some drugs are effective only in cancers carrying specific mutations. In addition, metabolic plasticity enables cancer cells to bypass biochemical blocks induced by therapy. Selectivity also remains a major challenge and is often associated with toxic side effects. Furthermore, some highly effective anticancer agents may increase the risk of secondary malignancies.

6. Vitamin C

Interest in using vitamin C for cancer patients' treatment was inspired by Linus Pauling's work [77]. Since then there has been great progress in understanding vitamin C's role in cell metabolism, deciphering pathways it is involved in and how it affects human health. Ultimately, data obtained resulted in understanding of the necessity to consume significant amount of vitamin C daily [78]. The current Recommended Dietary Allowance for vitamin C, which reaches up to 100 mg/day, appears increasingly at odds with the classical definition of a vitamin. Regarding the effect of vitamin C on cancer cells, numerous reports clearly showed toxicity [79–81]. Nevertheless, effective treatment of cancer patients with vitamin C failed to materialize as no clinical trials came with a positive recommendation [82–84].

6.1. What Is the Mechanism of Vitamin C Toxicity for Cancer Cells?

To display toxicity vitamin C needs to be at high concentration. Vitamin C, ascorbic acid is a strong reducing agent. At neutral pH ascorbic acid, AH_2 presents mostly as the ascorbate monoanion (AH^-) as the first dissociation constant is 4.1. In the presence of oxygen AH^- donates an electron to produce ascorbate radical, $A^{\cdot-}$ and superoxide, $O_2^{\cdot-}$. Ascorbate radicals disproportionate to form oxidised vitamin C, dehydroascorbic acid (DHA) and superoxides disproportionate to form hydrogen peroxide, H_2O_2. The presence of metals of transition group like ferric, Fe^{3+} or copper, Cu^{2+} ions greatly facilitates the reaction. These ions are reduced by vitamin C very fast and then pass the electron onto oxygen. So, it is not surprising to see significant formation of hydrogen peroxide in cell culture medium in the presence of high concentrations of vitamin C [85–88]. Ultimately, the experiments showing that removal of H_2O_2 with catalase abolished toxicity led to the widely accepted conclusion that toxicity of high doses of vitamin C was due to H_2O_2 [89–92]. This may explain the striking discrepancy between the strong cytotoxic effects observed in cultured cancer cells and the poor outcomes reported in clinical trials. In cell culture media, the loss of H_2O_2 in the absence of added peroxide-removing enzymes is relatively slow, whereas in blood, H_2O_2 generated from vitamin C is rapidly eliminated. Erythrocytes constitute almost half of the circulating blood volume and are densely packed with peroxide-removing enzymes [93], enabling efficient removal of H_2O_2 from the circulation [94]. Furthermore, high-dose vitamin C is rapidly cleared from the blood [95], while transferrin limits the availability of free iron ions and thereby suppresses metal-dependent oxidation of vitamin C [88]. Under these conditions, it appears highly unlikely that vitamin C-derived H_2O_2 could reach tumours at cytotoxic concentrations.

Thus, the use of high-dose vitamin C in cancer therapy appeared to present a catch-22 situation: generation of H_2O_2 was considered necessary for cancer cell killing, yet tumours could not realistically be exposed to sufficient levels of H_2O_2 in vivo. It is therefore unsurprising that research into vitamin C-based anticancer therapy hit a glass ceiling, and even the Linus Pauling Institute shifted its focus away from this field. Nevertheless, occasional positive outcomes reported in clinical trials [82] suggest that an important aspect of the treatment mechanism may have been overlooked.

6.2. Is Vitamin C-Derived Hydrogen Peroxide Ultimately Responsible for Its Anticancer Effect?

Well-founded doubts have been raised as to whether H_2O_2 generated by high doses of vitamin C can fully account for its anticancer effects [96,97]. Thorough and carefully conducted study addressing this question have not been published in peer-reviewed journal, likely because no

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alternative mechanism capable of explaining the observed toxicity had been proposed at the time [96]. However, another mechanism that warrants consideration is the involvement of dehydroascorbic acid (DHA), the product of two electron oxidation of vitamin C or dismutation of ascorbic radicals. DHA has been shown to be toxic to cancer cells [97–103]. Within cells, DHA can be reduced back to ascorbic acid by a variety of reducing agents [104–108]. In solution, however, DHA is highly unstable and, in the absence of reductants, undergoes rapid decomposition [109–111]. Consequently, the direct clinical administration of DHA would present substantial technical challenges, as even freshly prepared DHA solutions intended for intravenous infusion would be expected to undergo significant hydrolysis.

DHA degradation generates reactive carbonyl compounds, including 3-deoxythreosone, which can induce extensive protein modification through mechanisms such as lysine crosslinking and adduct formation [112,113]. Nevertheless, as discussed below, consideration of the mechanisms and selectivity of DHA toxicity, together with the potential for DHA generation in the bloodstream, suggests that these limitations do not necessarily preclude the therapeutic exploitation of DHA-mediated toxicity in cancer treatment.

6.3. Mechanism of DHA Toxicity for Cancer Cells

DHA uptake occurs via Glucose Transporter (GLUT) family of membrane transporters, it shares this pathway with glucose and other hexoses. These transporters are overexpressed in tumours [112]. Within a cell DHA can react with GSH, thioredoxin, glutaredoxin, and other thiols leading to their oxidation, recycling of oxidised vitamin C also can be performed by reductases of thioredoxin or cytochrome b_5 [104–108,115,116[. These are all ultimately dependent on a supply reducing equivalents from NADPH. DHA can oxidise and inactivate thiol proteins to disulfide form unable to react with H_2O_2, as observed for GAPDH and Prdx2 [117].

We can propose a complex picture of how a high concentration of DHA could exert toxicity for cancer cells (Figure 1). During the uptake by a cell high doses of DHA would compete with glucose and therefore diminish ATP production by glycolysis and NADPH when glycolysis switched to pentose phosphate pathway. Reactions with thiols resulted in oxidation of thioredoxin, GSH, glutaredoxin, Prdx would put a pressure on the corresponding enzymes involved in their regeneration. These enzymes need NADPH to perform the reduction. Formation of deoxyribonucleotides needs thioredoxin and NADPH. Therefore, deficit of precursors inflicted by DHA treatment will inevitably inhibit DNA synthesis.

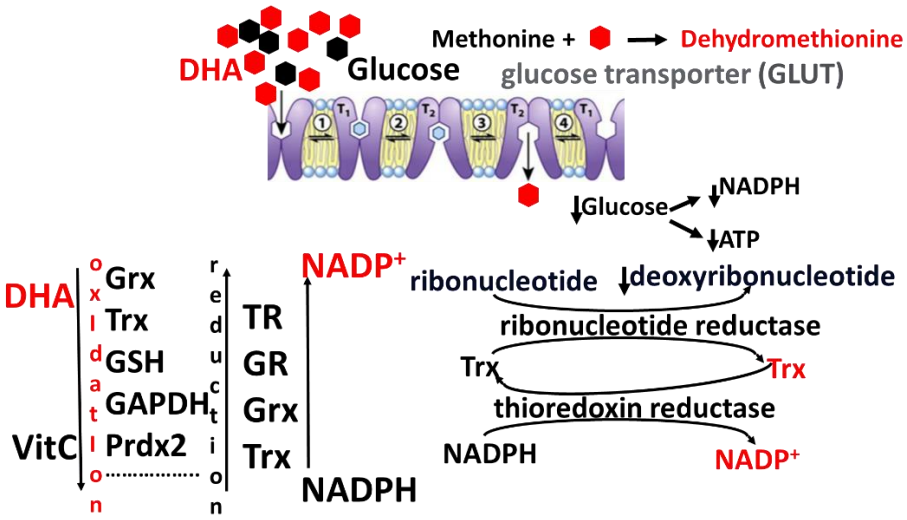

Figure 1. Interaction of dehydroascorbic acid (DHA) with cellular metabolism. DHA can oxidise methionine, potentially disrupting intracellular pathways dependent on methionine uptake. DHA enters cells via glucose transporters (GLUTs) in competition with glucose. Reduced glucose uptake diminishes ATP production through

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glycolysis and decreases NADPH generation via the pentose phosphate pathway. Inside the cell, DHA can oxidise multiple thiol groups, resulting in inhibition of thiol-dependent enzymes and increased consumption of NADPH by systems involved in the reduction of oxidised thiols. Depletion of reduced thioredoxin and NADPH impairs deoxyribonucleotide synthesis, thereby limiting DNA synthesis.

With prolonged DHA uptake and decreasing rate of DHA reduction in cells there is increased possibility for oxidation of thiol proteins and formation of protein adducts with DHA [106,118,119], DHA could also interfere with S-thiolation of proteins [129]. In neuroblastoma cells, an adduct formed between DHA and homocysteine has been detected [121]. Notably, homocysteine levels are elevated in cancer patients and have been associated with tumour progression and metastasis [122].

Hydrolysis of the DHA would also result in the formation of reactive secondary products [112,113].

Additional pressure on cancer cells which are dependent on methionine [60] can be done by methionine deficit resulting from oxidation of methionine into dehydromethionine by DHA [117].

6.4. Selectivity of Anticancer Effect of DHA

Could DHA bring about oxidative stress into a normal cell? Cancer cells uptake DHA preferentially whereas normal cells in culture do not show selectivity between DHA and ascorbic acid [123,124]. Therefore, in a normal cell oxidation by DHA would be balanced by reductive power of ascorbic acid.

Reactivity of thiols with an oxidant depends on a thiol pKa as well as microenvironment [125,126]. While DHA effectively reacted with Prdx2 and GAPDH it did not oxidise thiol in p16 ^{INK4A} [117]. Protein $p16^{INK4a}$ is a negative regulator of cell division, inhibiting the cyclin dependent kinases 4 and 6 and preventing progression of the cell cycle. Thiol oxidation of $p16^{INK4a}$ leads to the formation of disulfide-bridged dimers that subsequently form amyloid fibrils. The loss of $p16^{INK4a}$ activity is widely believed to be a common and important event in the development of cancer [127]. It is tempting to suggest that DHA may lack pro-carcinogenic action which is quite often observed for anti-cancer agents.

DHA effect on DNA synthesis would be reversible and restricted to proliferating cells and those where NADPH mainly provided by glucose metabolism. Notably, even with dividing cells in culture DHA was dramatically more toxic for cancer cells than for normal ones [124].

6.5. Does High Dose Vitamin C Treatment Have a Future for Anti-Cancer Treatment?

High dose vitamin C can serve as a vehicle for delivering DHA to tumours. It is known that ascorbic acid reacts effectively with myeloperoxidase (MPO) [128], an enzyme residing in white blood cells (WBC) and activated during immune response [129]. During the activation MPO reacts fast with H_2O_2 generated by another enzyme of activated WBC and then Compound I formed upon reaction of MPO with H_2O_2 can react with ascorbic acid with the second order rate constant 10^6 $M^{-1}s^{-1}$ [128].

The main product of activated MPO is a strong oxidant HOCl formed by oxidation of chloride anions by H_2O_2. HOCl oxidises ascorbic acid very fast, k = $6x10^6M^{-1}s^{-1}$ [130]. Interestingly, ascorbic acid can compete with chloride anions for reaction with Compound I, and at high doses undergoes oxidation by MPO effectively stopping HOCl generation [117].

6.6. Why Were Numerous Vitamin C Clinical Trials Unsuccessful?

Based on the discussion above one may summarise that successful anti-cancer treatment would require:

1. high concentration of vitamin C in blood ;
2. fast oxidation of vitamin C in blood to expose tumour with blood supply to high influx of DHA;
3. maintenance of high DHA long enough to kill cancer cells.

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High doses of vitamin C were used in clinical trials, and patient tolerance was generally good [83,84]. However, no attempts were made to induce oxidation of vitamin C in the circulation during treatment in order to ensure tumour exposure to DHA. It is possible that successful outcomes observed in some patients [84] occurred in the presence of inflammatory conditions associated with activated WBCs, resulting in MPO-mediated oxidation of vitamin C. Retrospective analysis of clinical trial data in this context may therefore be of interest.

Another limitation of vitamin C therapy was the methodology used for intravenous administration. Vitamin C is cleared from the circulation relatively rapidly, with plasma concentrations declining from millimolar to micromolar levels within a few hours after intravenous infusion [95]. Maintenance intravenous administration may therefore be required to sustain prolonged DHA generation at levels sufficient to exhaust the reducing capacity of cancer cells and achieve tumour elimination. In this regard, an analogy may be drawn with prolonged antibiotic treatment protocols.

7. Conclusions

High dose vitamin C treatment has a potential for patients with tumours having blood supply. For successful anticancer action to occur vitamin C would need efficient oxidation in blood. As it was discussed above DHA can affect many targets considered attractive for anti-cancer treatment. Intracellular influx of DHA occurs in cancer cells preferentially and competes with glucose. In blood DHA can oxidise methionine and prevent cancer cells from obtaining methionine which for them is the essential amino acid. Inside cells DHA can oxidise thiol groups resulting in overspending NADPH and over a certain period of time may result in drop of NADPH to unsustainable level. It has been suggested that maintenance of NADPH levels is often more limiting for tumour growth than are energy levels or biosynthetic precursors [131].

Disulfidptosis was recently identified as a form of programmed cell death induced by disulfide stress during glucose deprivation [132,133]. It would be interesting to see whether the cancer cell death inflicted by DHA occurs by the disulfidptosis mechanism.

As there are many targets for DHA one may suggest that metabolic plasticity of cancer cells would not be able to cover all of them. Notably, some modes of action such as competition with glucose for cellular uptake could not be lethal on their own. Glucose concentration in blood is approximately 5mM and therefore it would not be possible for DHA totally outcompete glucose. But maintenance of IV vitamin C to ensure millimolar DHA along with fasting regime for patients during treatment which could bring glucose down by 20% would contribute to the overall DHA effect by decreasing glucose influx. The therapeutic potential of methionine depletion, particularly for brain tumours where drug delivery is hindered by the blood–brain barrier, has been limited by significant adverse effects of methods used (66–68). In this context, oxidation of methionine by DHA appears to be an especially attractive therapeutic strategy. The strength of high dose vitamin C/DHA treatment is that it is not metabolic-selective but rather a global inhibitor killing cancer cells by a thousand cuts without collateral damage. Apart from efficiency of anti-cancer treatment itself one needs to keep in mind that patients tend to report poorer functioning and quality of life in the long term. Survivors of childhood cancer frequently develop cognitive and functional deficits that impair their ability to complete education successfully and obtain employment, ultimately reducing psychological well-being, financial security, and overall quality of life [134,135]. Currently, we are investigating how high dose vitamin C which are well tolerated can be effectively oxidised in human blood without side effects.

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