Abstract | Over the past century, the notion that vitamin C can be used to treat cancer has generated much controversy. However, new knowledge regarding the pharmacokinetic properties of vitamin C and recent high-profile preclinical studies have revived interest in the utilization of high-dose vitamin C for cancer treatment. Studies have shown that pharmacological vitamin C targets many of the mechanisms that cancer cells utilize for their survival and growth. In this Opinion article, we discuss how vitamin C can target three vulnerabilities many cancer cells share: redox imbalance, epigenetic reprogramming and oxygen-sensing regulation. Although the mechanisms and predictive biomarkers that we discuss need to be validated in well-controlled clinical trials, these new discoveries regarding the anticancer properties of vitamin C are promising to help identify patient populations that may benefit the most from high-dose vitamin C therapy, developing effective combination strategies and improving the overall design of future vitamin C clinical trials for various types of cancer.

The ‘magic bullet’ theory serves as a paradigm for modern cancer research and has inspired numerous ground-breaking targeted therapies such as imatinib and vemurafenib. However, despite remarkable initial responses, the eventual acquisition of resistance and therapy-associated toxic effects continues to impede progress towards achieving meaningful patient survival. Thus, a new strategy for treating and managing cancer is needed. In this Opinion article, we propose that vitamin C, a natural compound with an unusually high safety profile, can be used to target multiple critical pathways in cancer.

The utilization of high-dose vitamin C as a cancer therapy has a controversial history. Much of this controversy stems from conflicting results in early clinical trials, as well as the lack of biomarkers and a clear understanding of vitamin C’s mechanism of action. Despite this, publications over the past 40 years suggest that these contradictory results can be explained, at least in part, by differences in the administration route of vitamin C; the millimolar concentration of vitamin C cytotoxic to cancer cells is achievable only by intravenous injection, not by oral administration. As a result, there are approximately a dozen ongoing clinical trials exploring the safety and efficacy of intravenous high-dose vitamin C for treating various types of cancer as a monotherapy or combination therapy (TABLE 1). Given the revived clinical interest in vitamin C as a cancer therapy, this Opinion article examines the evidence supporting the therapeutic potential of vitamin C and highlights advances in the current understanding of its mechanisms of action. First, we summarize the biological functions and chemical properties of vitamin C. Second, we examine three different mechanisms by which high-dose vitamin C can selectively kill cancer cells. Understanding the multiple targets and mechanisms by which vitamin C exerts anticancer effects will be essential for identifying predictive biomarkers for patient stratification and developing potent combination strategies that lead to durable remission. Finally, we close our Review by sharing our perspective on the future of vitamin C research as a treatment for cancer.

Biology of vitamin C

Synthesis of vitamin C

Vitamin C is a six-carbon ketolactone synthesized from glucose by most animals in the kidney or liver. However, humans – as well as other primates, guinea pigs and fruit bats – are unable to synthesize vitamin C because they harbour inactivating mutations in the gene encoding L-gulonolactone oxidase (GULO), the enzyme responsible for catalysing the last step of vitamin C synthesis. Owing to this ‘inborn metabolic error’, humans must acquire vitamin C from dietary sources. The current recommended daily allowance of vitamin C (75–90 mg per day) can easily be achieved by consuming a balanced diet consisting of fruits and vegetables, yielding a plasma ascorbate concentration of 30–80 μM (REF.). By contrast, sustained malnutrition or low dietary vitamin C intake will lead to plasma levels below 10 μM and result in scurvy, a vitamin C deficiency disease characterized by bleeding gums, impaired wound healing, anaemia, fatigue, depression and, in severe cases, death.

Redox forms of vitamin C

Vitamin C exists in different redox forms depending on the biological conditions (FIG. 1a). Fully reduced vitamin C (ascorbate or ascorbic acid) can be oxidized both intracellularly and extracellularly. Extracellular ascorbate is oxidized by free radicals or reactive oxygen species (ROS) producing a weak radical intermediate, ascorbate radical (Asc•−), which is then oxidized fully into dehydroascorbic acid (DHA). DHA, having a short half-life (less than 1 minute), accounts for only approximately 1–5% of vitamin C in the human body and is either transported inside the cell (BOX 1) or becomes irreversibly hydrolysed into 2,3-L-diketogluconate (2,3-DKG). 2,3-DKG is then degraded into oxalic acid and threonic acid, resulting in a net loss of vitamin C. Inside the cell, DHA is rapidly reduced back to ascorbate by reacting with a reduced glutathione (GSH). Oxidized glutathione (glutathione disulfide (GSSG)) is then recycled back to GSH by NADPH.
**PERSPECTIVES**

Table 1 | List of active intravenous vitamin C clinical trials as an anticancer therapy

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial name</th>
<th>Institution</th>
<th>Trial design</th>
<th>Cancer type</th>
<th>Drugs</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>Gemcitabine, ascorbate, radiation therapy for pancreatic cancer</td>
<td>Holden Comprehensive Cancer Center at the University of Iowa (USA)</td>
<td>Single arm</td>
<td>Pancreatic neoplasms</td>
<td>Gemcitabine; radiation + IV ascorbate</td>
<td>142</td>
</tr>
<tr>
<td>Phase I</td>
<td>High-dose ascorbate in glioblastoma multiforme</td>
<td>Holden Comprehensive Cancer Center at the University of Iowa (USA)</td>
<td>Single arm</td>
<td>Glioblastoma</td>
<td>Radiation + temozolomide + IV ascorbate</td>
<td>143</td>
</tr>
<tr>
<td>Phase I/II</td>
<td>High-dose ascorbate + nanoparticle paclitaxel protein bound + cisplatin + gemcitabine in patients who have had no prior therapy for their metastatic pancreatic cancer</td>
<td>Piedmont Cancer Institute (USA)</td>
<td>Single arm</td>
<td>Metastatic pancreatic cancer</td>
<td>Paclitaxel, cisplatin, gemcitabine + IV ascorbate</td>
<td>144</td>
</tr>
<tr>
<td>Phase I/II</td>
<td>High-dose ascorbate + nanoparticle paclitaxel protein bound + cisplatin + gemcitabine in patients who have no prior therapy for their metastatic pancreatic cancer</td>
<td>HonorHealth Research Institute, University of California–San Diego Moores Cancer Center and Piedmont Cancer Institute (USA)</td>
<td>Single arm</td>
<td>Pancreatic cancer</td>
<td>Paclitaxel protein-bound, cisplatin + IV ascorbate</td>
<td>145</td>
</tr>
<tr>
<td>Phase II</td>
<td>High-dose ascorbate in stage IV non-small-cell lung cancer</td>
<td>Holden Comprehensive Cancer Center at the University of Iowa (USA)</td>
<td>Single arm</td>
<td>Non-small-cell lung cancer</td>
<td>Paclitaxel; carboplatin + IV ascorbate</td>
<td>146</td>
</tr>
<tr>
<td>Phase II</td>
<td>Therapeutic use of IV vitamin C in allogeneic stem cell transplant recipients</td>
<td>Virginia Commonwealth University–Massey Cancer Center (USA)</td>
<td>Single arm</td>
<td>Hodgkin lymphoma, lymphoid leukaemia and multiple myeloma</td>
<td>IV and oral vitamin C</td>
<td>147</td>
</tr>
<tr>
<td>Phase II</td>
<td>Pharmacological ascorbate combined with radiation and temozolomide in glioblastoma multiforme: a phase II trial</td>
<td>Holden Comprehensive Cancer Center at the University of Iowa (USA)</td>
<td>Single arm</td>
<td>Glioblastoma multiforme</td>
<td>Radiation + temozolomide + IV ascorbate</td>
<td>148</td>
</tr>
<tr>
<td>Phase II</td>
<td>High-dose vitamin C IV infusion in patients with resectable or metastatic solid tumor malignancies</td>
<td>Weill Cornell Medicine (USA)</td>
<td>Single arm</td>
<td>Colorectal, pancreatic and lung cancer with KRAS or BRAF mutation</td>
<td>IV ascorbate</td>
<td>149</td>
</tr>
<tr>
<td>Phase II</td>
<td>Pharmacological ascorbate with concurrent chemotherapy and radiation therapy for non-small-cell lung cancer</td>
<td>Holden Comprehensive Cancer Center at the University of Iowa (USA)</td>
<td>Single arm</td>
<td>Non-small-cell lung cancer</td>
<td>Radiation, paclitaxel, carboplatin + IV ascorbate</td>
<td>150</td>
</tr>
<tr>
<td>Phase II</td>
<td>Pharmacological ascorbate, gemcitabine, nab-paclitaxel for metastatic pancreatic cancer</td>
<td>Holden Comprehensive Cancer Center at the University of Iowa (USA)</td>
<td>Randomized two-arm</td>
<td>Pancreatic neoplasms</td>
<td>Paclitaxel, gemcitabine + IV ascorbate</td>
<td>151</td>
</tr>
<tr>
<td>Phase II</td>
<td>Ascorbic acid in combination with docetaxel in men with metastatic prostate cancer</td>
<td>Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (USA)</td>
<td>Randomized two-arm</td>
<td>Hormone-resistant prostate cancer, metastatic prostate carcinoma and stage IV prostate cancer</td>
<td>IV ascorbate + docetaxel</td>
<td>152</td>
</tr>
<tr>
<td>Phase II</td>
<td>IV ascorbic acid as an adjunct to pazopanib in the first-line setting for metastatic or unresectable clear cell renal cell carcinoma (ccRCC)</td>
<td>Mayo Clinic in Florida and Minnesota, Illinois CancerCare-Peoria, Iowa–Wide Oncology Research Coalition NCORP and Sanford Medical Center Fargo (USA)</td>
<td>Randomized two-arm</td>
<td>Clear cell renal cell carcinoma</td>
<td>Pazopanib hydrochloride + IV ascorbate</td>
<td>153</td>
</tr>
<tr>
<td>Phase II</td>
<td>Ascorbic acid and combination chemotherapy in treating patients with relapsed or refractory lymphoma</td>
<td>Mayo Clinic in Arizona, Minnesota and Florida and Holden Comprehensive Cancer Center at the University of Iowa (USA)</td>
<td>Randomized two-arm</td>
<td>B cell lymphoma with MYC and BCL2/BCL6 rearrangement, and recurrent Hodgkin lymphoma</td>
<td>Carboplatin, cisplatin + IV ascorbate</td>
<td>154</td>
</tr>
<tr>
<td>Phase III</td>
<td>IV ascorbic acid in advanced gastric cancer</td>
<td>Sun Yat-Sen University Cancer Center (China)</td>
<td>Randomized two-arm</td>
<td>Gastric cancer</td>
<td>mFOLFOX6 + IV ascorbate</td>
<td>155</td>
</tr>
<tr>
<td>Phase III</td>
<td>IV ascorbic acid in combination with FOLFOX−bevacizumab versus treatment with FOLFOX−bevacizumab alone as first-line therapy for advanced colorectal cancer</td>
<td>Sun Yat-Sen University Cancer Center (China)</td>
<td>Randomized two-arm</td>
<td>Colorectal neoplasms</td>
<td>mFOLFOX6, bevacizumab + IV ascorbate</td>
<td>156</td>
</tr>
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</table>

IV, intravenous.
**Biological functions of vitamin C**

The biological functions of vitamin C can be attributed to its biochemical property as an electron donor. Acting as an antioxidant, physiological ascorbate at micromolar concentrations can reduce harmful ROS. Paradoxically, it can also function as a pro-oxidant at millimolar plasma concentrations, which can be achieved by intravenous administration of pharmacological ascorbate. In addition to its redox functions, vitamin C affects iron metabolism by increasing ferritin.

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**Fig. 1** Integrated pro-oxidant mechanism of vitamin C and cancer cell cytotoxicity. **a** Ascorbate can be oxidized in the extracellular space by reactive oxygen species (ROS), producing ascorbate radical, which can be oxidized to dehydroascorbic acid (DHA). DHA can be taken up by cells or irreversibly converted to 2,3-diketoglutonate (2,3-DKG), which is degraded into oxalic acid and threonic acid. **b** Pharmacological ascorbate can kill cancer cells by increasing oxidative stress via two possible mechanisms that complement each other. First, extracellular H₂O₂ may directly kill cancer cells by generating "OH via the Fenton reaction. Increased levels of labile ferric iron, Fe³⁺, in the tumour microenvironment can facilitate the oxidation of ascorbate, resulting in ascorbate radical, DHA and ferrous iron, Fe²⁺. Once Fe²⁺ is formed, Fe²⁺ may be oxidized by oxygen, producing superoxide anions, O₂⁻. Superoxide dismutase (SOD) catalyses the conversion of O₂⁻ to H₂O₂ and O₂. Fe²⁺ can enter the cell when bound to transferrin (Tf), which binds to the Tf receptor (TfR) and is processed and oxidized in the endosome to then contribute to the intracellular Fe²⁺ pool. H₂O₂ can enter the cell through diffusion facilitated by aquaporins. H₂O₂ reacts with either extracellular or intracellular labile Fe²⁺ to generate highly reactive hydroxyl radicals ("OH) that are harmful to cells. These reactions are further perpetuated by the recycling of Fe²⁺ to Fe³⁺ by ascorbate and ascorbate radical, generating fully oxidized vitamin C, DHA. Second, H₂O₂ may contribute to the increased levels of extracellular DHA by creating a more oxidative tumour microenvironment. DHA can then efficiently enter cells through glucose transporter 1 (GLUT1) and consume the intracellular reducing potential of reduced glutathione (GSH) and NADPH, resulting in increased levels of intracellular ROS. This leads to poly(ADP-ribose) polymerase (PARP) activation, a DNA repair enzyme, thereby depleting cellular NAD⁺ levels, a cofactor of PARP. NAD⁺ is required by glyceraldehyde 3-phosphate dehydrogenase (GAPDH) as a cofactor. Consequent inhibition of GAPDH activity inhibits glycolysis in cancer cells, leading to inhibition of ATP production and cell death. In addition, cellular ROS can also be released from cells, resulting in a positive feedback loop. Because high levels of labile Fe²⁺, GLUT1 overexpression and addiction to glycolysis frequently occur in many types of cancer cells, certain cancer cells may present all three of these characteristics and those populations might be more sensitive to ascorbate treatment. 1,3BPG, 1,3-bisphosphoglyceric acid; GAPDH, glyceraldehyde 3-phosphate; G6PD, glucose-6-phosphate dehydrogenase; GSSG, glutathione disulfide; PPP, pentose phosphate pathway; SVCT, sodium-dependent vitamin C transporters.
Box 1 | Transport of vitamin C

The highest tissue concentrations of vitamin C are found in the brain, the adrenal gland and white blood cells, with concentrations ranging from 1 to 15 mM. These concentrations are 15–200 times higher than those in the plasma owing to active transport mechanisms, mainly via sodium-dependent vitamin C transporters (SVCT1 and SVCT2). SVCT1 is mainly expressed in intestinal and renal epithelial cells, where it mediates absorption and re-absorption of vitamin C, respectively. SVCT2 is expressed throughout the entire body and is considered to be the primary vitamin C transporter. Interestingly, 50% of SVCT1-knockout mice do not survive until weaning, and the deletion of SVCT2 in mice leads to neonatal death. Unlike ascorbate, dehydroascorbic acid (DHA) is transported by a class of facilitative glucose transporters (GLUTs). Among more than 12 different GLUTs, GLUT1 and GLUT3 have a higher affinity for DHA than for glucose. However, under physiological conditions, GLUT transporters are unlikely the dominant path for ascorbate accumulation in most tissues, because glucose levels in the plasma (2–5 mM) are significantly higher than DHA levels (5–10 μM). Red blood cells, and certain cancer cells, do not express SVCTs but transport vitamin C mainly as DHA via GLUT1 (REF. [1]). The rate of DHA uptake via GLUT1 or GLUT3 is at least 10–20 times faster than ascorbate uptake via SVCTs. This difference is because the highly favourable reduction in intracellular DHA to ascorbate drives DHA uptake by cells. Furthermore, local DHA concentrations in body fluids can be higher under pathological conditions, such as cancer, where ROS released from cancer cells can facilitate the oxidation of extracellular ascorbate to DHA. For example, intestinal tumours harbouring KRAS mutations exhibited an increase in intracellular ascorbate level from 100 μM (basal level) to more than 10 mM within 1 hour following intraperitoneal injection of high-dose ascorbate to a mouse model of intestinal tumours (Apc−/−;KrasG12D/+). This drastic increase in intracellular ascorbate level in KRAS mutant tumours can be explained by the selective uptake of DHA via GLUT1 and its subsequent reduction to ascorbate. Tumours from Apc−/−;KrasG12D/− mice highly express GLUT1 compared with Apc−/− mice, whereas both tumours express low levels of SVCTs.

Increased labile iron level. In the presence of redox-active transition metals, such as iron, vitamin C exerts pro-oxidant effects. Iron is an essential prosthetic metal ion for a number of proteins. Most organisms require iron owing to its unique ability to efficiently switch between two oxidation states — ferrous iron (Fe2+, reduced) and ferric iron (Fe3+, oxidized) — in response to changes of ligands in the environment. Because of iron's highly reactive biochemical property, most labile iron must be sequestered by transferrin (TF) in plasma, stored in ferritin inside the cell or embedded as cofactors, such as haem, in proteins. However, cells also keep small pools (~3–5% or ~1 μM in humans) of loosely coordinated Fe2+, called labile iron pools, in the cytosol and the mitochondrial matrix for easy access. When labile Fe2+ in these pools reacts with H2O2, it can generate the damaging hydroxyl radical (OH·) via the Fenton reaction. To perpetuate this reaction, ascorbate effectively donates electrons to Fe2+ to regenerate redox-active Fe3+, thereby generating ROS continuously and contributing to cell death. Thus, although iron is essential for a variety of biological processes, it can be a dangerous liability at the same time.

Numerous in vitro cell culture studies have shown that pharmacological ascorbate produces extracellular H2O2, which can directly kill cancer cells. However, the exact mechanisms for this observation are currently unclear. Some studies showed that extracellular H2O2 can be generated via spontaneous autoxidation even in the absence of iron by reacting with oxygen when supraphysiological, millimolar concentrations of ascorbate are added to the medium in both cell-free and cell culture systems. Other studies demonstrated synthesis, inhibiting ferritin degradation, suppressing iron efflux and enhancing intestinal absorption of iron. Interestingly, vitamin C also functions as a critical cofactor for numerous enzymes by readily donating its electrons to prosthetic metal ions to achieve full enzymatic activity. In general, these enzymes are categorized into two families: copper-containing monooxygenases and Fe2+-dependent and α-ketoglutarate (αKG; also known as 2-oxoglutarate (2OG))-dependent dioxygenases (αKGDAs). αKGDAs are iron-containing enzymes that consume oxygen and αKG as co-substrates while producing CO2 and succinate. αKGDAs catalyse a wide range of hydroxylation reactions involved in collagen synthesis, hypoxia-inducible factor 1α (HIF1α) stability, carnitine synthesis, the catabolism of tyrosine and the demethylation of protein, DNA and RNA. Thus, vitamin C is responsible for regulating a variety of important biological processes.

Anticancer mechanism of vitamin C

Over the past decade, a growing number of studies have demonstrated that millimolar concentrations of pharmacological vitamin C can kill cancer cells in vitro and slow tumour growth in vivo. However, the mechanism by which some cancer cells are sensitive to vitamin C, while normal cells remain resistant, is poorly understood. Given the diversity of processes affected by vitamin C, the mechanistic basis for vitamin C's action could depend on a variety of different factors, including the type of cancer being treated, and the tumour's dependency on particular pathways. Here, we discuss three distinct vulnerabilities in cancer that can be exploited by pharmacological ascorbate.

Targeting redox imbalance

It is generally accepted that cancer cells experience more oxidative stress compared with normal cells owing to an elevated metabolic rate and defective mitochondria. Although ROS can facilitate tumour development by stimulating cell proliferation and promoting genetic instability, excessive ROS can also be detrimental to cancer cells. To compensate, cancer cells often enhance pathways that help mitigate the toxic effects of ROS. On the basis of the premise that ROS promotes cancer development, antioxidant treatment has been investigated as an anticancer strategy. However, recent results from both human and animal studies have found no clear evidence of the benefit of antioxidant treatment in preventing or suppressing cancer development. In some cases, antioxidant treatment even appeared to accelerate cancer progression and metastasis in mouse models of lung adenocarcinoma and melanoma and increase the risk of prostate and lung cancers in patients. Together, these results indicate that certain cancer types may rely on antioxidants for survival and may thus be vulnerable to pro-oxidant therapies. Indeed, pro-oxidant anticancer therapies, such as radiation, have been employed in the clinic. However, current pro-oxidant strategies often cause serious collateral damage, resulting in a narrow therapeutic window. Here, we propose that pharmacological ascorbate can potentially circumvent this problem by exploring two common features of cancer cells: their increased levels of labile transition metals, especially iron, and their increased reliance on glucose uptake and glycolysis. Although we discuss these two mechanisms individually in this section, they are not mutually exclusive and can occur simultaneously, synergizing the selective toxicity of ascorbate in cancer cells (FIG. 1b).
that labile metals, especially Fe\(^{2+}\), in the medium, catalyse ascorbate autoxidation, thereby generating extracellular H\(_2\)O\(_2\) in both cell-free and cell culture systems\(^{1,2}\). Because most labile Fe\(^{2+}\) is known to be sequestered by Tf in vivo\(^{3}\), these studies argue that ascorbate’s ability to produce H\(_2\)O\(_2\) is an in vitro artefact\(^{3,4}\). Disputing against this hypothesis, it was shown that Asc\(^-\) and H\(_2\)O\(_2\) were generated in vivo following intravenous ascorbate injections in rats (0.5 g kg\(^{-1}\)), and the production was ascorbate-dose-dependent\(^5\). In another study, daily intraperitoneal injection with high-dose ascorbate (4 g kg\(^{-1}\)) inhibited neuroblastoma growth in a xenograft model, and tumours had the increased activity of checkpoint kinase 2 (CHK2) and histone 2AX (H2AX). This observation suggests that pharmacological ascorbate can cause DNA damage in in vivo tumours, although an in vivo link between ascorbate and the generation of H\(_2\)O\(_2\) has not been demonstrated in this study\(^6\).

The important question then is how extracellular H\(_2\)O\(_2\) generated from pharmacological ascorbate can contribute to the selective toxicity to cancer cells compared with normal cells. If ascorbate generates extracellular H\(_2\)O\(_2\) equally in both cancer cells and normal cells regardless of the exact mechanism (for example, autoxidation and/or labile iron reactions in the medium or the serum in vivo), pharmacological ascorbate would not provide any additional advantage over other pro-oxidant therapies in terms of therapeutic window. Here, we propose three potential mechanisms by which ascorbate-induced H\(_2\)O\(_2\) selectively kills certain types of cancer cells compared with normal cells. First, if the tumour microenvironment is enriched for labile iron, its reaction with ascorbate will generate H\(_2\)O\(_2\) and ‘OH, which can be lethal to cancer cells. Second, if tumour cells have increased levels of intracellular labile iron compared with normal cells, extracellular H\(_2\)O\(_2\) from ascorbate autoxidation can diffuse into tumour cells and react with the intracellular pools of labile iron and generate ‘OH within tumour cells. Third, extracellular H\(_2\)O\(_2\) can contribute to the increased level of extracellular DHA by generating an oxidative microenvironment. As a result, DHA is transported into tumours that express high levels of glucose transporter 1 (GLUT1), generating oxidative stress in those cells, which is discussed in the following section. In this section, we discuss the first and second possibilities.

Numerous iron-containing and haem-containing enzymes are involved in many important cellular processes such as cellular respiration, DNA synthesis, cell cycle and epigenetics\(^7,8,9\). For this reason, cancer cells have a high demand for easily accessible labile Fe\(^{2+}\) for their survival and growth. It has been shown that reprogramming of iron metabolism can occur via a variety of mechanisms, including the upregulation of several iron-iron pathways or downregulation of iron export and storage pathways in various types of cancer such as breast, prostate and lymphoma\(^10,11\). For example, the pool of intracellular labile Fe\(^{2+}\) in breast cancer cells is approximately twice as high as in normal breast epithelial cells\(^12\). In addition, tumour-associated macrophages may promote iron release in the tumour microenvironments\(^13,14\). Patients with advanced breast cancer have significantly higher levels of Fe\(^{2+}\) in plasma than healthy human control groups\(^15\). Thus, tumour cells with the high levels of extracellular and/or intracellular labile iron may be more vulnerable to high-dose ascorbate than normal cells as they can generate more H\(_2\)O\(_2\) and ‘OH than normal cells\(^{16}\). Supporting this hypothesis, a recent study showed that an increased level of mitochondrial ROS in lung and glioblastoma cancer cells led to increased levels of intracellular labile iron through the upregulation of the Tf receptor (TfR), thus increasing the sensitivity of these cancer cells to ascorbate\(^17\). Another study indicated that multiple myeloma cells have an elevated labile iron pool owing to the low expression of the iron exporter, ferroportin 1, which led to their selective sensitivity to pharmacological doses of ascorbate\(^18\).

Despite these promising preclinical studies, researchers still need to determine whether there is any correlation between ascorbate sensitivity, ascorbic radical or H\(_2\)O\(_2\) production and intracellular labile Fe\(^{2+}\) levels in a large set of cancer cell lines or patient samples. Moreover, identifying potential biomarkers or gene expression signatures to predict ascorbate sensitivity related to the increased labile iron level would be useful in the clinic.

**Increased DHA uptake via GLUT1.** Tumour cells exhibit a high rate of glycolysis, even in conditions with ample oxygen — a phenomenon that was first described by Otto Warburg, nearly a century ago\(^19\). This metabolic reprogramming, also known as the Warburg effect, is essential for tumour survival and proliferation\(^20\). Oncogenic KRAS or BRAF mutations contribute to the Warburg effect, in part by upregulating GLUT1 (REF.\(^{21}\)). These results suggest that exploiting the selective expression of GLUT1 and the metabolic liability associated with increased reliance on glycolysis may be a viable therapeutic strategy to target cancer. Indeed, we recently showed that high-dose ascorbate can target these vulnerabilities in KRAS or BRAF mutant colorectal cancer (CRC) cells\(^22\). When ascorbate is administered, it is oxidized to DHA. Owing to its structural similarity to glucose, DHA is efficiently taken up via GLUT1 in KRAS or BRAF mutant cells\(^23,24\) (BOX 1). Inside the cell, DHA is rapidly reduced back to ascorbate at the expense of GSH and NADPH\(^25,26\). This reduction depletes intracellular antioxidants and increases endogenous levels of ROS\(^27,28\). The elevated ROS, in turn, inactivates a glycolytic enzyme, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), by oxidizing a cysteine residue in the active site. In addition, ROS leads to activation of poly(ADP-ribose) polymerase (PARP), which in turn leads to depletion of NAD\(^+\) (a key cofactor of GAPDH), thereby further inhibiting GAPDH\(^29\) (FIG. 1B). Inhibiting GAPDH in highly glycolytic KRAS or BRAF mutant cells ultimately leads to an ‘energy crisis’ and cell death not seen in their wild-type counterparts\(^30\). Consistent with in vitro results, daily intraperitoneal injection of ascorbate (4 g kg\(^{-1}\)) inhibited tumour growth in Apc\(^−/−\)Kras\(^G12D/G12D\) mutant mice whereas it did not affect tumour growth in Apc\(^−/−\) mice\(^31\). Our findings also suggest that ascorbate therapy may be extended to other cancers as long as they present high GLUT1 expression and high glycolytic activity. For example, recent studies showed that gastric cancers and von Hippel-Lindau (VHL)-null renal cancers, which have high GLUT1 expression and addiction to glycolysis, were selectively killed by high-dose ascorbate, supporting our proposed mechanism\(^32,33\).

Owing to the unstable nature of DHA and the chemical and biological equilibrium between ascorbate and DHA, it is difficult to quantify the exact amount of DHA generated from ascorbate. Despite this challenge, many studies have shown that cancer cells with high GLUT1 but not sodium-dependent vitamin C transporters exclusively take up ascorbate in the form of DHA both in vitro or in vivo\(^34,35,36\). Although our study indicated that DHA is the pharmacologically active agent, it is important to note that ascorbate (not DHA) needs to be used for both preclinical and clinical anticancer therapies. Bolus treatment of high-dose DHA has only transient effects on cancer cells in vitro and in vivo owing to its extreme instability in neutral pH\(^37\). Moreover, degradation of DHA generates...
many undesirable chemicals such as 2,3-DKG and oxalate\textsuperscript{52}, which may confound the efficacy of ascorbate therapy. By contrast, ascorbate has a significantly longer half-life in cell culture medium and plasma. Because the tumour microenvironment is known to be oxidative\textsuperscript{53,54}, adding high concentrations of ascorbate would efficiently and continuously generate DHA from ascorbate. Moreover, when the oxidation of millimolar levels of ascorbate generates extracellular 

\begin{align*}
\text{H}_2\text{O}_2
\end{align*}

as we discussed before, this will result in high amounts of extracellular DHA as DHA is the main oxidized form of ascorbate.

The effect of oxidative stress in cancer cells due to high-dose ascorbate via the mechanism discussed above is also supported by evidence in humans. Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency showed haemolytic anaemia following high-dose intravenous ascorbate therapy\textsuperscript{56–59}. Although erythrocytes anaemia following high-dose intravenous ascorbate therapy are pre-screened for G6PD deficiency to avoid this complication. The fact that the most obvious and immediate oxidative stress, effects of high-dose ascorbate in this genetic disorder occur in erythrocytes indicates the importance of increased GLUT1 levels and dependency on glycolysis in ascorbate-induced oxidative stress.

**Targeting epigenetic regulators**

Epigenetic reprogramming in cancer includes DNA hypermethylation, which frequently occurs on CpG island promoter regions and is known to silence tumour suppressors such as the retinoblastoma and VHL tumour suppressors\textsuperscript{50}. Most of the aberrant DNA hypermethylation patterns observed in cancer can be explained by mutations or altered expression of two protein families: gain of function of DNA methyltransferases (DNMTs; which methylate cytosine to generate 5-methylcytosine (5mC)) and loss of function of ten-eleven translocation (TET) proteins.

TET proteins (TET1, TET2 and TET3) demethylate DNA and belong to the αKGDD enzyme family. Using oxygen and αKG, they catalyse multiple oxidation reactions, first converting 5mC to 5-hydroxymethylcytosine (5hmC), which ultimately results in an unmodified cytosine (5C). TET2 is frequently mutated or lost, and is critical for myeloid cell differentiation\textsuperscript{66}. TET2 loss is mutually exclusive with gain-of-function mutations in isocitrate dehydrogenase 1 (IDH1) and IDH2 (REF\textsuperscript{67}). IDH1 and IDH2 convert isocitrate to αKG in the cytosol and mitochondria, respectively. However, a neomorphic mutation in IDH1 and/or IDH2 causes a change in enzymatic activity and the accumulation of 2-hydroxylglutarate (2-HG), which inhibits the function of αKG-dependent enzymes such as TET2, resulting in the loss of 5hmC, an increase in DNA methylation and ultimately altered gene expression programmes that drive cancer development\textsuperscript{68}.

Vitamin C can activate TETs as a cofactor and is required for optimal activity. Ascorbate can donate an electron to Fe\textsuperscript{2+} to generate Fe\textsuperscript{3+}, which is required for TET activity (FIG. 2). The majority of TET2 mutations in AML are heterozygous, and each TET isoform has some functional redundancy. Therefore, ascorbate treatment may enhance the activity of residual TET proteins and thus rescue the abnormal DNA methylation pattern. Indeed, the growing number of recent studies supports this hypothesis. For example, daily intraperitoneal injection of high-dose ascorbate (4 g kg\textsuperscript{-1}) treatment in an inducible TET2 deletion mouse model of leukaemia recapitulated the TET2 restoration phenotypes by promoting DNA demethylation and the expression of genes critical for myeloid cell differentiation\textsuperscript{58}.

Similarly, ascorbate treatment in vitro increased DNA demethylation at enhancers and promoters of genes associated with myeloid differentiation and increased the expression of several key haematopoietic genes in murine bone marrow cells expressing mutant IDH1 (REF\textsuperscript{59}). In certain types of lymphomas where TETs are frequently mutated, ascorbate treatment
Patients with cancer often have lower plasma concentrations of ascorbate than healthy adults\textsuperscript{121,122}, and vitamin C deficiency is associated with an increased risk of cancer mortality\textsuperscript{123,124}. In Western countries, plasma ascorbate levels can vary among individuals, but the lowest quartile of men have a significantly higher risk of mortality from cancer\textsuperscript{125}. In a meta-analysis of 21 studies, including ~9,000 lung cancer cases\textsuperscript{126}, a correlation was shown between an individual’s risk of lung cancer and their vitamin C intake, where male adults in the USA who took 100 mg per day of dietary vitamin C had a 7% reduced lung cancer risk. This dose is also associated with a reduced overall mortality and breast-cancer-specific mortality in women\textsuperscript{127,128}. That vitamin C may prevent or delay cancer development was further supported by preclinical studies. In ascorbate-deficient Gulo\textsuperscript{−/−} mice, ten-eleven translocation 2 (TET2) deletion drives development of acute myelogenous leukaemia (AML)\textsuperscript{72}, which is suppressed by administration of oral ascorbate. Similarly, administration of oral ascorbate 7 days before inoculation of cancer cells decreased tumour development in a lymphoma xenograft model\textsuperscript{129}. Taken together, oral doses of vitamin C may be an effective agent to prevent the development of certain types of malignancy, especially for individuals who may have mutations such as TETs predisposing them to cancer.

Genetic variation in ascorbate transporters has also been found to associate with cancer risk\textsuperscript{73,130}. Although the correlation with cancer remains weak and plasma ascorbate was often not measured, single-nucleotide polymorphisms (SNPs) in the sodium-dependent vitamin C transporters SLC23A1 (SVCT1) and SLC23A2 (SVCT2) have been linked to the risk of certain cancers\textsuperscript{131,132}. Some of these SNPs are associated with reduced levels of ascorbate systemically, which may have adverse consequences for ascorbate-dependent biochemical processes that involve, for example, Fe\textsuperscript{2+}-dependent and α-ketoglutarate-dependent dioxygenases\textsuperscript{130}. However, it remains unclear whether reduced ascorbate levels associated with those SNPs can be directly attributed to compromised function of transporters. Together, these findings support the profound importance of the amount of oral ascorbate to humans’ optimized health and disease prevention. However, to address the definitive benefits of supplementary oral intake of ascorbate, potentially in combination with therapeutic intravenous ascorbate therapy, rigorous preclinical and randomized clinical trials will be required.


cell death

**Box 2** | Oral intake of high-dose vitamin C and cancer prevention

Patients with cancer often have lower plasma concentrations of ascorbate than healthy adults\textsuperscript{121,122}, and vitamin C deficiency is associated with an increased risk of cancer mortality\textsuperscript{123,124}. In Western countries, plasma ascorbate levels can vary among individuals, but the lowest quartile of men have a significantly higher risk of mortality from cancer\textsuperscript{125}. In a meta-analysis of 21 studies, including ~9,000 lung cancer cases\textsuperscript{126}, a correlation was shown between an individual’s risk of lung cancer and their vitamin C intake, where male adults in the USA who took 100 mg per day of dietary vitamin C had a 7% reduced lung cancer risk. This dose is also associated with a reduced overall mortality and breast-cancer-specific mortality in women\textsuperscript{127,128}. That vitamin C may prevent or delay cancer development was further supported by preclinical studies. In ascorbate-deficient Gulo\textsuperscript{−/−} mice, ten-eleven translocation 2 (TET2) deletion drives development of acute myelogenous leukaemia (AML)\textsuperscript{72}, which is suppressed by administration of oral ascorbate. Similarly, administration of oral ascorbate 7 days before inoculation of cancer cells decreased tumour development in a lymphoma xenograft model\textsuperscript{129}. Taken together, oral doses of vitamin C may be an effective agent to prevent the development of certain types of malignancy, especially for individuals who may have mutations such as TETs predisposing them to cancer.

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demonstrated that tumours that had the highest HIF1α activity were those deficient in ascorbate in tumours. It was also shown that patients with CRC who had high levels of ascorbate in their tumour had a better patient outcome and longer patient survival after surgery. Taken together, these data suggest that high-dose ascorbate treatment can slow tumour growth by moderating HIF1α. However, all studies thus far prove the association but not the causality. It would be interesting to see whether the deletion of PHDs or FIHs in tumour-bearing Gulo−/− mice abolishes the effects of high-dose ascorbate.

The stabilization of HIF1α even under normoxic conditions can occur, for example, in RCC, where deletion of the VHL tumour suppressor prevents HIF1α degradation in normoxia. VHL-deficient RCC cells undergo cell death when exposed to vitamin C in normoxia, in contrast to isogenic VHL-proficient cells. Mechanistically, the higher levels of GLUT1, a HIF1α downstream target, in normoxic VHL-deficient cells than in VHL-proficient cells facilitated increased uptake of ascorbate-derived DHA, leading to increased generation of ROS and cell death. In line with this, GLUT1 knockdown in VHL-deficient RCC cells conferred resistance to vitamin-C-induced toxicity. In addition to VHL mutations, HIF1α stability and activity can also be increased by mutations of two tumour suppressor enzymes in the tricarboxylic acid (TCA) cycle: succinate dehydrogenase (SDH) and fumarate dehydrogenase (FH). Loss-of-function mutations in SDH and FH cause a build-up of succinate and fumarate, respectively. Accordingly, increased levels of succinate and fumarate caused by mutations in these genes can compete with αKG and inhibit activity of HIF hydroxylases and thus induce normoxic HIF1α activity in vitro. Because inherited or somatic mutations in SDH and FH are tightly associated with the development of several tumours, such as paraganglioma, pheochromocytoma and RCC, it would be interesting to investigate whether ascorbate treatment of these mutant cells leads to inhibition of HIF1 activity and decreased malignancy in vivo.

Vitamin C as anticancer therapy
High-dose vitamin C should not be viewed as a ‘one-size-fits-all’ modality for cancer treatment. Understanding the critical differences between oral and intravenous ascorbate administration routes and knowing which patients to treat will be critical for clinical trial designs and the approval of new ascorbate therapies. Clinical trials in the 1970s involving patients with terminal cancer showed that intravenous high-dose ascorbate extended patient survival in response to ascorbate treatment, whereas large-scale randomized controlled trials (RCTs) in the 1980s failed to confirm these initial findings because ascorbate was given orally instead. As it turns out, the differences between oral and intravenous administration routes can affect the maximum achievable plasma concentration in patients. In the initial trials, ascorbate was administered both intravenously and orally and achieved a peak plasma concentration of 6 mM. However, in later trials, where the same dose of ascorbate was administered orally, a peak plasma concentration of less than 200 μM was achieved. It is now widely accepted that the millimolar concentration of ascorbate needed to induce cytotoxicity in cancer cells can be achieved only when administered intravenously. For example, a phase I clinical study revealed that ascorbate concentrations could safely reach 25–30 mM with intravenous infusion of 100 g of vitamin C. In this study, plasma concentrations around 10 mM were sustained for at least 4 hours, which, on the basis of preclinical studies, is sufficient to slow the growth of cancer cells. An increased understanding of the clinical pharmacokinetics of ascorbate has provided confidence in revisiting the clinical potential of ascorbate. Consequently, over the past decade, there have been an increased number of phase I/II clinical
trials and case reports testing the safety and efficacy of high-dose ascorbate as a treatment for various cancer types such as ovarian, brain, prostate and lung cancers as a monotherapy or in combination with radiation and other conventional chemotherapies\(^3,9,99,100\). In short, a significant number of clinical studies to date have indicated that intravenous high-dose ascorbate is well tolerated in patients with minimal toxicity, improves the quality of life for patients and has demonstrated synergistic therapeutic effects as well as reduced side effects when combined with radiation and standard chemotherapies. However, many of these studies were not designed as large-scale RCTs; thus, the efficacy of high-dose ascorbate therapy remains to be determined. Below, we discuss the future direction of clinical research into ascorbate as a cancer therapy.

**From bench to bedside**

In this Review, we propose that vitamin C serves as an excellent example of a natural compound that targets multiple vulnerable nodes to inhibit cancer growth. Although we identified three distinct mechanisms by which high-dose ascorbate can inhibit cancer growth, it is possible that each mechanism may not work independently. For example, subpopulations of KRAS or BRAF mutant CRC cells that were not completely killed via the pro-oxidant mechanism in vivo — potentially owing to their distance from blood vessels, poor perfusion\(^106\) or resistance to ROS — may still be affected by ascorbate therapy via inhibition of HIF1 signalling and/or activation of TET enzymes. In fact, reports show that many CRCs have low expression levels of TETs and relatively high expression levels of HIF1α, implying that pharmacological ascorbate may attack multiple nodes in tumours with minimum toxicity\(^106,107,108\), making it an ideal ‘magic bullet’ for cancer therapy.

Understanding the mechanisms of action gives us critical information about the patient populations who may receive the most benefit from ascorbate therapy. On the basis of current preclinical studies, ascorbate may be more effective in patients with cancer with mutations in KRAS, BRAF, TET2, IDH1 and/or IDH2, VHL, SH or FDH. Pending validation, these could be used as putative predictive biomarkers for ascorbate therapy in clinical trials. Multiple omics assays such as genomics, transcriptomics, proteomics and metabolomics can be performed using a patient's tumour biopsy samples not only to test existing hypotheses but also to generate hypotheses in an unbiased and comprehensive way. Furthermore, a patient's urine, blood and stool samples can also be analysed for biomarkers in these early trials, they will help to establish the future direction of clinical research into ascorbate as a cancer therapy.

### Glossary

- **2-Phosphate l-ascorbic acid**: A derivative of ascorbate that is not oxidized in culture or serum but releases ascorbate once it is inside the cells via hydrolysis mediated by alkaline phosphatase on the plasma membrane.
- **5-Aza-CdR (decitabine)**: A cytidine antimetabolite analogue that incorporates into DNA and inhibits DNA methyltransferase (DNMT) activity, which results in DNA demethylation (hypermethylation).
- **Biomarkers**: Any biological measurable indicators of the severity or presence of some disease state.
- **Fenton reaction**: A chemical reaction that converts hydrogen peroxide into a highly toxic hydroxyl radical in the presence of labile iron.
- **Ferritin**: A protein that contains iron and is the primary form of iron stored inside of cells.
- **Free radicals**: Molecules possessing unpaired electrons and thus are reactive and short-lived in a biological setting.
- **Haem**: An iron-containing group that gives myoglobin and haemoglobin the ability to bind oxygen.
- **Hydroxyl radical** (\(\cdot OH\)): A highly reactive and short-lived radical that attacks any molecule in its immediate vicinity, especially DNA, protein and lipids, eventually leading to cell death.
- **Imatinib**: A BCR-ABL-selective tyrosine kinase inhibitor, also known as Gleevec. Imatinib has been used to treat chronic myelogenous leukaemia and acute lymphocytic leukaemia.
- **Intraperitoneal (IP) injection**: Giving medicines or fluids into the peritoneum (body cavity), which is more often applied to animals than to humans.
- **Intravenous injection**: Giving medicines or fluids through a needle or tube inserted into a vein, allowing them to enter the bloodstream immediately.
- **Michaelis constant** \((K_m)\): The substrate concentration at the half of the maximum velocity \((V_{max})\). An enzyme with a high \(K_m\) has a low affinity for its substrate and requires a greater concentration of substrate to achieve \(V_{max}\).
- **Parenteral injection**: Giving medicine or fluids intravenously (into a vein), subcutaneously (under the skin) and intraperitoneally (into the peritoneum).
- **Pharmacodynamics**: The study of the biochemical and physiological effects of drugs. Generally refers to the dose–response relationship for a particular drug.
- **Pharmaceutical ascorbate**: Intravenous or intraperitoneal delivery of vitamin C, which allows for plasma concentrations to reach the millimolar scale.
- **Physiological ascorbate**: An oral dose of dietary vitamin C, usually resulting in a peak plasma concentration of 200 μM.
- **Predictive biomarkers**: A biomarker that gives information about the effect of a therapeutic intervention.
- **Prosthetic**: A group that is a tightly bound, specific non-polypeptide unit required for the biological function of some proteins. It may be organic or inorganic (such as a metal ion), but not amino acids.
- **Randomized controlled trials** (RCTs): A study design that randomly assigns participants into an experimental group or a control group (or placebo group).
- **Reactive oxygen species** (ROS): Derivatives of oxygen that are more reactive than molecular oxygen.
- **Single-nucleotide polymorphisms** (SNPs): A variation in a single nucleotide that occurs at a specific position in the genome, where each variation is present to some high degree within a population (for example, >1%).
- **Therapeutic window**: The range of doses of a drug that can treat disease effectively without having toxic effects.
- **Transferrin**: (Tf). The main protein in the blood that binds to iron and transports it throughout the body.
- **Vemurafenib**: A selective V600E mutant BRAF kinase inhibitor, also known as PLX4032. It has been used to treat BRAF V600E mutant melanoma.
of interferon-stimulated genes, leading to retroviruses and amplifying the expression of TET2 with myelodysplastic syndromes, where phagocytes and lymphocytes have ascorbate and lymphocytes. Although not much is known about neutrophils, macrophages combined use with other cancer therapies. Combination therapy has been shown to reduce the tumour growth in many different mouse models of cancer, the clinical potential of ascorbate as an anticancer therapy may also lie in its combined use with other cancer therapies. Numerous preclinical and clinical studies indicate that parenteral injection of pharmacological ascorbate does not interfere with chemotherapy or radiotherapy and may even act synergistically. Moreover, because the mechanisms of action of vitamin C are becoming better defined, we can propose vitamin C combinations in a more rational, hypothesis-driven manner. For example, on the basis of ascorbate’s known DNA demethylation effects via TET activation, a recent study found that vitamin C enhanced the effect of the DNMT inhibitor 5-aza-CdR (decitabine) by promoting the demethylation of human endogenous retroviruses and amplifying the expression of interferon-stimulated genes, leading to cancer cell death. Because decitabine is approved by the US Food and Drug Administration for the treatment of patients with myelodysplastic syndromes, where TET2 is also frequently deleted, it would be interesting to test these combinations in clinical trials.

Combining vitamin C with immune checkpoint inhibitors and immunomodulatory agents, such as cytotoxic T lymphocyte-associated protein 4 (CTLA4) receptor and programmed death 1 (PD-1)–programmed death ligand 1 (PD-L1) blockers, may also lead to durable therapeutic responses against a broad spectrum of cancers. A compelling hypothesis is offered by the utilization and combination of high-dose vitamin C, which is known to enhance the function of both innate and adaptive immune cells. Tumours exist in a complex immune milieu that includes neutrophils, macrophages and lymphocytes. Although not much is known about how ascorbate is utilized by the various cells that make up the tumour microenvironment, studies have shown that phagocytes and lymphocytes have ascorbate concentrations 10–100 times greater than plasma. Moreover, a wealth of knowledge is emerging that highlights the influence of ascorbate in inflammatory response and immune cell function, which suggests that ascorbate may have synergistic effects when combined with current immunotherapy.

**Concluding remarks**

Despite the unprecedented popularity of ascorbate among the public as an anecdotal ‘cure-all’ remedy, much of its biological functions and pharmacological activity have remained elusive. However, recent discoveries about the diverse biological functions of ascorbate, and its relevance to cancer therapy, generated exciting and promising hypotheses regarding the use of ascorbate in the treatment of cancer. We have discussed the critical role of ascorbate in the function of TETs, PHDs and FIHs, which are all aKGDDs. Given that more than forty aKGDDs exist, it is possible that other aKGDDs could contribute to the anticancer mechanisms of ascorbate. Discovering novel roles of ascorbate and the pathways it regulates will aid in the identification of molecules that can be targeted to sensitize tumours to ascorbate treatment and lead to the development of novel combination therapies.

To fully elucidate the biological functions of ascorbate and its relevance to cancer development, researchers will need to utilize better in vivo models that recapitulate the human condition. GEMMs are powerful tools for studying the pathogenesis of cancer and examining the systemic effects of vitamin C in vivo. Recent studies utilizing GEMMs have enhanced our understanding of anticancer properties of ascorbate and reinforced our understanding of its mechanism of action as it pertains to cancer. Also, *Gulo* mice are an ideal candidate for vitamin C research as they, similar to humans, cannot synthesize vitamin C de novo in the liver. A significant number of human studies consistently show that ascorbate treatment improved quality of life for patients with cancer, and in combination therapy, ascorbate protected normal tissues from toxicity caused by chemotherapeutic agents. The active role of vitamin C in mammalian iron metabolism much more than just enhanced iron absorption!

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**References**


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**Perspectives**


25. This study shows that pharmacological ascorbate selectively sensitizes non-small-cell lung cancer (NSCLC) and glioblastoma (GBM) DNA by generating redox-active labile iron and H2O2 in vitro cell lines and model mice. In addition, it shows the power of ascorbate therapy combined with other chemotherapies in patients with GBM and NSCLC.


30. This study demonstrates that uptake of DNA by GLUT1, and its subsequent reduction to ascorbate, depletes essential nutrients necessary to induce cell death in KRAS or BRAF mutant CRC cells.


39. H2O2 and the prevention of leukaemia in mice. In addition, this study reveals that vitamin C is necessary for normal haematopoietic cell development and the prevention of leukaemia in mice.


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95. This large-scale clinical trial showed that daily oral intake of high-dose vitamin C had no therapeutic benefit in patients with cancer.