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# The potential role of vitamin C in empowering cancer immunotherapy

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ABSTRACT

Vitamin C also known as L-ascorbic acid is a nutrient naturally occurring in many fruits and vegetables and widely known for its potent antioxidant activity. Several studies have highlighted the importance of using high dose vitamin C as an adjuvant anti-cancer therapy. Interestingly, it has been shown that vitamin C is able to modulate the anti-cancer immune response and to help to overcome the resistance to immune checkpoints blockade (ICB) drugs such as cytotoxic T-lymphocyte antigen 4 (CLTA-4) and programmed cell death ligand 1 (PD-L1/PD-1) inhibitors. Indeed, it was reported that vitamin C regulates several mechanisms developed by cancer cells to escape T cells immune response and resist ICB. Understanding the role of vitamin C in the anti-tumor immune response will pave the way to the development of novel combination therapies that would enhance the response of cancer patients to ICB immunotherapy. In this review, we discuss the effect of vitamin C on the immune system and its potential role in empowering cancer immunotherapy through its pro-oxidant potential, its ability to modulate epigenetic factors and its capacity to regulate the expression of different cytokines involved in the immune response.

## 1. Introduction

Vitamin C is an important physiological antioxidant and an essential natural micronutrient that human and most animals are unable to synthesize [1]. It is known to play a role in preventing several types of diseases such as cardiovascular and neurodegenerative dysfunctions, especially those associated with oxidative stress [2–4]. Interestingly, it has been shown that vitamin C is also able to kill various types of cancer cells in vitro [5–7]. Additionally, several studies have demonstrated that combining high-dose vitamin C with conventional anti-cancer drugs resulted in promoting higher cytotoxicity in several models of cancer cell lines [6,8,9]. Indeed, vitamin C has been shown to enhance the chemo-sensitivity and to reduce the toxicity of chemotherapeutic drugs in many types of cancer cells [10,11]. Moreover, Kurbacher et al. reported that vitamin C potentiates the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro [12]. Interestingly, it has been shown that high-dose vitamin C has beneficial effects on the overall survival in patients with terminal cancer [13,14]. However, some studies showed that vitamin C therapy had no benefits in cancer patients [15,16]. Therefore, the anti-cancer effect of vitamin C is yet controversial and needs to be further investigated.

In clinical practice, high-dose intravenous vitamin C has been used since many decades as a complementary adjuvant therapy for cancer patients [17,18]. Indeed, it was speculated that only high concentrations of vitamin C could be considered as a drug and that the intravenous administration is more effective than the oral route [17]. Nevertheless, only a minority of cancer patients responded to intravenous and oral vitamin C therapy [15,16]. Thus, ongoing clinical trials are aimed at determining whether intravenous vitamin C may enhance the effectiveness of standard cancer treatment regimens such as chemotherapy and radiotherapy [19,20]. However, there are no clinical studies concerning the combination of vitamin C with immune checkpoint blockade (ICB) therapy. Immune checkpoint inhibitors represent a new class of immunotherapy drugs that block checkpoint protein expressed by T cells such as CTL-4 and PD-1, which are known to downregulate the

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**Nomenclature**

| | |
|---|---|
| **BRAF** | B-Raf murine sarcoma |
| **BRAF** | B-Raf murine sarcoma |
| **CDKN1** | Cyclin-Dependent Kinase inhibitor 1A |
| **CLTA-4** | cytotoxic T-lymphocyte antigen 4 |
| **CTA** | cancer-testis antigens |
| **DHA** | Dehydroascorbic acid |
| **GBM** | Glioblastoma |
| **GLUT1** | Glucose transporter 1 |
| **$H_2O_2$** | hydrogen peroxide |
| **HIF** | Hypoxia Inducible Factor |
| **HIF-1α** | Hypoxia inducible factor 1 alpha |
| **ICB** | Immune checkpoints blockade |
| **KRAS** | Kirsten rat sarcoma |
| **MMR-P** | including mismatch repair-proficient |
| **NSCLC** | non-small cell lung carcinoma |
| **ROS** | reactive oxygen species |
| **SMAD1** | small mother |
| **SVCT** | transporter expression |
| **TET** | ten eleven translocation |
| **GPRIN** | G protein-regulated inducer of neurite outgrowth 3 |
| **IL** | interleukin |
| **MAGEA4** | melanoma-associated antigen 4 |
| **5 hmC** | 5-hydroxymethylcytosine |
| **NRF2** | nuclear factor erythroid 2- related factor 2 |
| **miRNAs** | microRNAs |
| **ECM** | extracellular matrix |
| **TNF-α** | tumor necrosis factor alpha |
| **TIMP3** | TIMP Metallopeptidase Inhibitor 3 |
| **CRP** | C-reactive protein |
| **PDL-1** | programmed death ligand 1 |
| **TIMP3** | metallo-peptidase inhibitors |
| **MMR-D** | mismatch repair deficiency tumors |
| **HAT1** | histone acetyltransferase 1 |
| **PD-1** | programmed cell death protein 1 |
| **NF-kβ** | nuclear factor kappa- B |
| **PARPi** | poly ADP ribose polymerase inhibitors |
| **IFNγ** | interferon gamma |
| **FoxP3** | Forkhead box P3 |
| **Th1** | T helper1 |
| **IKKα/β** | IK Kinase α/β |
| GSH | glutathione |

activation of these immune cells leading to a reduced immune response. The use of these drugs has revolutionized cancer immunotherapy. However, not all patients respond to this therapeutic strategy and it is of utmost importance to develop more effective approaches to fight cancer.

Different molecular mechanisms have been suggested that underlie the anti-cancer activity of vitamin C, including the inhibition of cellular proliferation and growth through the generation of reactive oxygen species (ROS) and the alteration of expression of genes involved in glycolysis, angiogenesis and metastasis through down-regulation of the hypoxia transcriptional activity [21]. Interestingly, a recent study has reported an epigenetic regulatory role of vitamin C via DNA demethylation which may pertain to its anti-cancer effect [22]. Importantly, vitamin C can also be a modulator of the tumor microenvironment by enhancing T lymphocytes infiltration and cytokines generation [23]. Therefore, vitamin C could play an important role in the regulation of the anti-tumor immune response. Indeed, it has been shown that high-dose vitamin C synergized the anti-tumor effect of anti-PD-1 therapy in a syngeneic lymphoma mouse model [23]. Moreover, a recent study demonstrated that high-dose vitamin C can modulate immune cells infiltration into the tumor microenvironment, enhance the cytotoxic activity of adoptively transferred CD8 + T cells and cooperate with anti-PD-1 and anti–CTLA-4 checkpoint inhibitors in mice bearing syngeneic tumors [24]. Additionally, high-dose vitamin C potentiated the anti-PD-L1 effect by increasing CD8 + and CD3 + T cells tumor infiltration in vivo [25]. Despite growing evidence showing that vitamin C can potentially enhance response to immunotherapy, further pre-clinical and clinical studies are needed to investigate and validate such an effect.

In this review, we will briefly describe the pharmacological parameters involved in vitamin C activity then we will discuss the different mechanisms of anti-tumor activity that can be associated with a potential role of vitamin C in immunotherapy.

## 2. Physiological and pharmacological dose of vitamin C

The dose and the administration route of vitamin C have an important impact on its anti-tumor potential in humans. Previous studies have reported that plasma concentrations of vitamin C following high-dose intravenous injection in human can vary from 5 to 15 mM, while those achieved following oral administration are limited to a maximum of 0.2 mM [26–28]. Therefore, intravenous administration is required to achieve pharmacological or therapeutic plasmatic concentrations.

A phase I clinical trial was conducted to determine the safety, tolerability and pharmacokinetics of high-dose intravenous vitamin C as a monotherapy in patients with advanced solid tumors. This study showed that intravenous administration of vitamin C at 1 g/min for 4 consecutive days per week during 4 weeks resulted in a peak concentration of approximately 49 mM and was generally well tolerated [29]. Although high-dose intravenous vitamin C was well tolerated, it failed to demonstrate anti-cancer activity when administered to advanced cancer patients [30]. However, when high-dose vitamin C was combined with standard radio-chemotherapy, a prolonged survival was observed in mouse models with non-small-cell lung carcinoma (NSCLC) and glioblastoma (GBM) [31]. Interestingly, the same effect has also been observed in phase I and phase II clinical trials including patients with GBM and advanced NSCLC [31]. Moreover, in an observational retrospective study, 53 stages IIA–IIIB breast cancer patients who received 7.5 g intravenous vitamin C weekly (4 weeks) in parallel to standard therapies (surgery, chemotherapy, radiation, and hormonal treatment), have reported an enhancement of their appetite and regression of fatigue, depression, and sleep disorders during and after adjuvant therapy, in comparison to the group receiving only standard anti-cancer therapies [32]. In addition, a prospective study including 39 patients with metastatic cancer showed that treatment with 10 g intravenous vitamin C together with 4 g oral vitamin C daily induces a significant enhancement in the quality of life of the patients [33]. Yet, the clinical use of vitamin C for cancer patients is not known and further studies are needed to confirm its beneficial effect and to determine the best treatment regimen.

## 3. Mechanism of anti-tumor activity of vitamin C

### 3.1. Modulation of tumor microenvironment

Tumor microenvironment plays a crucial role in tumor growth, invasion, and metastasis. It has been shown that vitamin C can affect the structure of the tumor microenvironment by regulating immune cells activity as well as other mechanisms including pro-oxidation and epigenetic modulation. Indeed, there is an utmost need to understand the role of vitamin C in modulating the tumor microenvironment in order to predict its impact on the therapeutic responses to ICB.

### 3.2. The pro-oxidant effect of vitamin C

While at physiological levels vitamin C acts as an antioxidant, it may promote oxidative stress and subsequent cell death when used at high concentrations. Vitamin C exerts its pro-oxidant effect via metal ions such as iron. Moreover, the excess of iron in the tumor microenvironment can contribute to tumor initiation, tumor growth, drug resistance and immune evasion [34,35]. For those reasons, cancer cells need labile iron to survive and grow. In breast cancer cells, the pool of intracellular labile iron is twice as high as in normal breast epithelial cell [36]. In tumor microenvironment, labile iron reacts with vitamin C to produce hydrogen peroxide ($H_2O_2$), which generate the damaging hydroxyl radical (•OH) via the Fenton reaction. Vitamin C effectively donates electrons to $Fe^{3+}$ to regenerate redox-active $Fe^{2+}$, thereby continuously generating ROS and contributing to cell death [37,38] (Fig. 1). Extracellular $H_2O_2$ obtained after vitamin C oxidation can diffuse into cells and react with intracellular labile iron generating •OH which can be lethal for cancer cells. As results, the extracellular $H_2O_2$ can increase the level of extracellular dehydroascorbic acid (DHA) which would enter the cells and increase the intracellular oxidative microenvironment. Several studies showed that the antitumor potential of vitamin C depends on the extracellular conversion of vitamin C into DHA, which generates extracellular $H_2O_2$, leading to the cytotoxic activity [7,39,40]. Taken together, targeting the iron metabolism by vitamin C might provide new strategy for cancer therapy.

Tumor cells expressing high amounts of glucose transporter 1 (GLUT1) internalizes DHA and generates intracellular oxidative stress due to the reduction of DHA back to vitamin C. This reaction induces oxidative damage and glutathione (GSH) depletion inside the cells and increases the levels of endogenous ROS causing DNA damage followed by cell death. It has been shown that human colorectal cancer cells carrying Kirsten rat sarcoma (KRAS) or B-Raf murine sarcoma (BRAF) mutations were selectively killed in vitro when treated with high-dose vitamin C via intracellular accumulation of ROS [41]. It has been also suggested that the active anti-tumor agent for vitamin C toxicity was actually DHA, which could infiltrate cancer cells because of their high expression of GLUT1 [41].

The cytotoxicity of vitamin C in the tumor microenvironment is associated with the expression of the sodium-dependent vitamin C transporters 1 (SVCT1) and 2 (SVCT2) [42–44]. Indeed, a significant cytotoxic activity was observed after treating cancer cells with high expression levels of SVCT-2 with vitamin C. However, in low SVCT-2 expressing cell lines, only high dose vitamin C (>1 mM) showed anti-cancer effects while low-dose treatment (<10 μM) induced cancer cells proliferation [44]. In addition, a study in breast cancer has suggested that SVCT-2 may be considered as an indicator for launching vitamin C treatment [45]. Furthermore, the same study showed that SVCT2 knockdown in breast cancer cells resulted in resistance to vitamin C treatment [45]. These observations can explain why cancer patients will not similarly benefit from vitamin C therapy [15,16]. In this context, vitamin C could be used as a personalized therapy for cancer patients with high GLUT1 and SVCT2 expression.

### 3.3. The effect of vitamin C on epigenetic mechanisms

Vitamin C acts as a potent epigenetic regulator. Indeed, it has been demonstrated that vitamin C activates the ten eleven translocation (TET) enzymes which are responsible for the removal of methyl groups from DNA and histones leading to a regulation of DNA demethylation [22,46]. Moreover, vitamin C causes genome-wide demethylation and increases the hydroxy-methylation fraction in cancer cells by enhancing the activity of the TET enzymes [23,47]. Interestingly, it has been shown

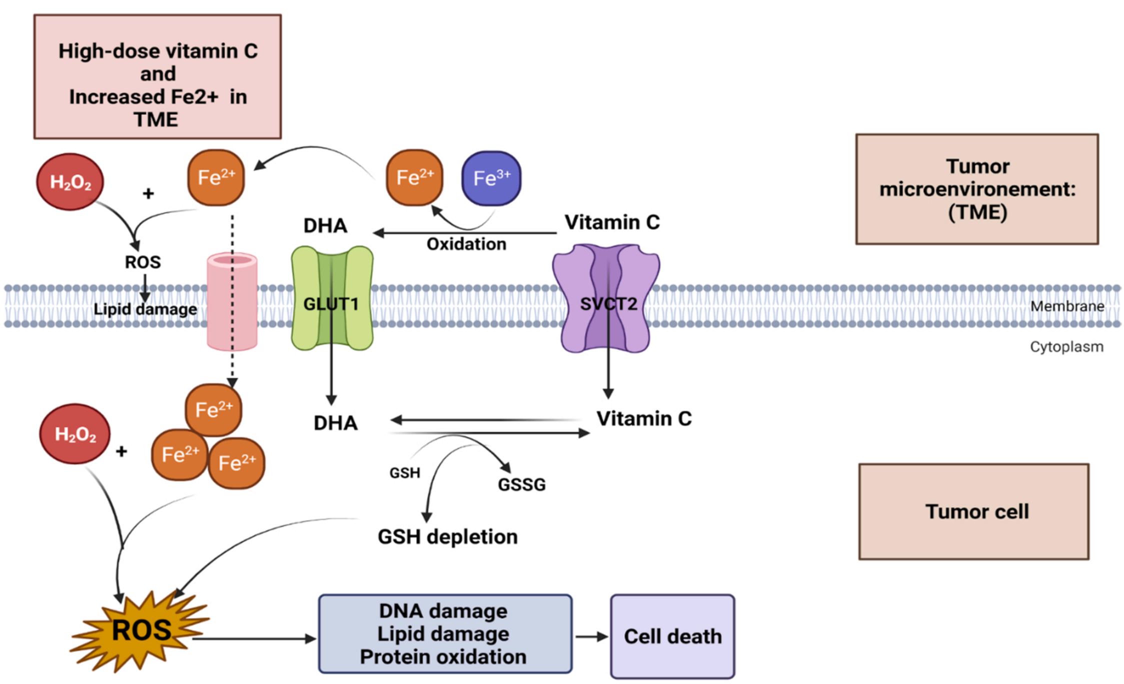


**Fig. 1.** Vitamin C cytotoxicity and its effect on tumor microenvironment. High-dose vitamin C induces cytotoxic effect against cancer cells by increasing oxidative stress via two mechanisms: generation of DHA and of $Fe^{2+}$ upon oxidation in the tumor microenvironment. Increased levels of labile ferric iron, $Fe^{3+}$ in the tumor microenvironment can facilitate the oxidation of vitamin C, resulting in the generation of DHA and ferrous iron $Fe^{2+}$.$H_2O_2$ reacts with the generated $Fe^{2+}$ to produce highly reactive hydroxyl radicals (•OH) that can induce direct damage to cell membrane via lipid peroxidation. Vitamin C can enter the cancer cell either directly through SVCT2 or as DHA through GLUT1 receptor. In the cytoplasm, DHA is converted to vitamin C and this will result in GSH depletion and consequently in an increased risk of oxidative damage. Additionally, high levels of vitamin C in the cells may promote the release of $Fe^{2+}$ from ferritin. Therefore, $H_2O_2$, which can enter the cells by diffusion, will also react with intracellular $Fe^{2+}$ leading to intracellular generation of ROS. The accumulation of ROS provokes cell death due to protein oxidation as well as DNA damage and lipid peroxidation.

that vitamin C is able to enhance TET activity in lymphoma cells leading to induction of DNA demethylation, increased expression of the tumor suppressor gene small mother against decapentaplegic (SMAD1) and enhanced chemo-sensitivity of lymphoma cells [9].

It has been shown that vitamin C is able to regulate the expression of the nuclear factor kappa B (NF-κB), a transcription factor with a primordial role in cancer development and progression [48]. Indeed, intracellular vitamin C inhibits tumor necrosis factor alpha (TNF-α) induced activation of NF-κB in various human cell lines (Cervical cancer (HeLa), myeloid leukemia (U937), myeloid leukemia HL-60, breast cancer and primary endothelial cells (HUVEC)) in a dose dependent manner [49]. Additionally, vitamin C inhibited NF-κB and interleukin 8 (IL-8) activation in response to TNF-α in endothelial cells. It has also been shown that the inhibition of the NF-κB was due to the direct inhibition of IκB kinase α/β (IKKα/β) [50]. Vitamin C is also suggested as a co-factor of hypoxia inducible factor hydroxylases. Indeed, cancer cells treated with different concentrations of vitamin C showed decreased protein levels of the hypoxia inducible factor 1 alpha (HIF-1 α), a transcriptional factor that controls the adaptation of cells to hypoxic conditions [51–53]. In addition, some retrospective studies showed inverse relationships between vitamin C and HIF-1α activity in tumor tissue. Interestingly, it has been demonstrated that cancer patients having the highest HIF-1α activity were those who had lower vitamin C levels in the tumor cells [54,55]. Few studies focused on the effect of vitamin C on the expression of inhibitory immune checkpoints such as PD-1 and its ligand PD-L1. PD-L1 is a member of the B7 family of cell surface ligands expressed on cancer cells surfaces, which binds the PD-1 inhibitory receptor expressed on T cells [56]. The PD-1/PD-L1 pathway regulates anti-tumor T cells activity and is considered as excellent target in cancer immunotherapy [57]. Recently, it has been shown that vitamin C could suppress PD-L1 expression in pancreatic cancer cells by affecting the histone acetyltransferase 1 (HAT1) level [58] which is known to regulate the expression of genes involved in cell differentiation, proliferation, metabolism and apoptosis [59,60]. It has been shown that vitamin C is able to downregulate HAT1 though activation of the TET-mediated DNA hydroxymethylation pathway [61]. Moreover, it was reported that HAT1 overexpression in cancer cells from patients with pancreatic ductal adenocarcinoma was correlated with PD-L1 expression [58]. This data suggests that vitamin C might play a potential role in overcoming tumor cells immune escape by downregulating their PD-L1 expression. However, a study performed using lymphoma cell lines showed that although vitamin C treatment enhanced the activity of the TET enzymes, it had no effect on PD-L1 expression in these cells [23].

Vitamin C could also affect the expression of microRNAs (miRNAs), a set of non-coding small RNA molecules in control of gene expression at post-transcriptional/translational level. Several miRNAs are commonly dysregulated in human diseases, including cancer. Indeed, in breast tissues, vitamin C inhibited carcinogenesis via suppression of oncogenic miR-93 associated with increased nuclear factor erythroid 2- related factor 2 (NRF2) expression [62]. It has also been shown that vitamin C treatment downregulated the expression of the oncogenic promoter miR-153 in breast carcinogenesis [63]. Moreover, vitamin C is able to inhibit the activity of DNA methyltransferases and up-regulate the expression of several miRNAs involved in tumor suppression, drug resistance, epithelial–mesenchymal transition and invasion in cancer cells (miR-596, miR-630, miR-422a, miR-490–5p, miR-375, miR-708, miR-345, miR-125b-2, miR-516a-3p, miR-135a, miR-1228, miR-1915, miR-134, miR-663). High expression of miR-596, miR-630, miR-490, miR-375 and miR-708 was associated with an increased overall survival when compared to low expression of these miRNAs in cancer patients [64]. For instance, it was reported that vitamin C regulates the expression of several genes which play a prominent role in the extracellular matrix (ECM) remodeling pathways, including TIMP3 (metallo-peptidase inhibitors) and GPRIN family member 3 (G protein-regulated inducer of neurite outgrowth 3) [64,65]. Overall, there is growing evidence indicating that vitamin C might play a role in the modulation of miRNA expression. However, additional research studies are needed to further confirm and characterize this effect.

### 3.4. The effect of vitamin C on immune cells activity and cytokines production

The role of vitamin C as a modulator of immune response is well documented. It has been shown that vitamin C can modulate multiple immune cells functions and therefore might exert beneficial effects in the context of cellular immunotherapy. I*n vitro* and in vivo studies reported that vitamin C promotes regulatory T cells (Tregs) functions through TET-dependent demethylation of the fork headbox P3 (FoxP3) regulatory elements [66,67]. Thus, the induction and activation of TET enzymes in Tregs by vitamin C might be an attractive method for Tregs-mediated adoptive immunotherapy. It has also been shown that vitamin C increases in vivo and in vitro the proliferative capacity of human natural killer (NK) cells [68]. Interestingly, a recent study has demonstrated that vitamin C enhances the activation and differentiation of human Vγ9Vδ2 γδ T cells [69]. Therefore, vitamin C treatment can be considered as a novel strategy to optimize the in vitro generation of effective NK and Vγ9Vδ2 T cells for adoptive transfer for cancer patients. Moreover, vitamin C was shown to stimulate dendritic cells (DCs) to secrete more interleukin-12 (IL-12) and thereby drive naïve CD4 + T cells to differentiate into T helper 1 cells (Th1) [70]. Finally, treatment of mouse bone marrow-derived DCs with vitamin C led to an enhanced CD8 + memory T cell production in vivo [71].

Vitamin C is able to regulate plasma cytokines levels and consequently to affect anti-inflammatory mechanisms. Indeed, a significant reduction of pro-inflammatory cytokines, including some interleukins (IL-1α, IL-2, IL-8) as well as TNF-α, when intravenous vitamin C was administered after chemo-radiotherapy to patients with various cancers (prostate cancer, breast cancer, bladder cancer, pancreatic cancer, lung cancer, thyroid cancer, skin cancer and B-cell lymphoma) [72,73]. Moreover, it has been shown that vitamin C inhibited IL-6 and TNF-α producing monocytes, and induced a downregulation of IL-2 secreting lymphocytes in vitro [74]. Furthermore, the production of pro-inflammatory cytokines is associated with the activation of NF-κB, which plays a major role in cancer development [75]. Subsequently, vitamin C might affect NF-κB activation and prevent the development of tumors through modulation of cytokines release.

Few studies focused on the role of vitamin C in immunotherapy. Luchtel et al. showed that vitamin C had a significant synergistic effect with anti-PD-1 therapy in a lymphoma mouse model [23]. The results of this study showed that vitamin C increases the intra-tumoral infiltration of $CD4^+$ and $CD8^+$ T cells and macrophages into the tumor microenvironment with increased production of granzyme B and interleukin-12 [23]. Moreover, it was shown that high-dose vitamin C can modulate the immune cells infiltration into the tumor microenvironment, enhance the cytotoxic activity of adoptively transferred CD8 + T cells and cooperate with anti-PD-1 and anti–CTLA-4 treatments in mice bearing syngeneic tumors [24]. Interestingly, vitamin C could also synergize with anti-PD-L1 by increasing the levels of chemokines (CXC Ligand 9, 10 and 11), promoting tumor-infiltrating lymphocytes and improving anti-tumor immunity [25].

## 4. Challenges for using vitamin C as potential adjuvant for cancer immunotherapy

The study of the effect of vitamin C in cancer has recently gained a major interest. Growing evidence indicates that vitamin C is a powerful molecule with pleiotropic functions (Fig. 2). As described above, different mechanisms could contribute to the anti-tumor activity of vitamin C 1) generation of ROS, 2) epigenetic regulation via downregulation of HIF-1 α and HAT-1, modulation of TET2 and specific microRNAs, 3) modulation of cytokines expression and of immune cells

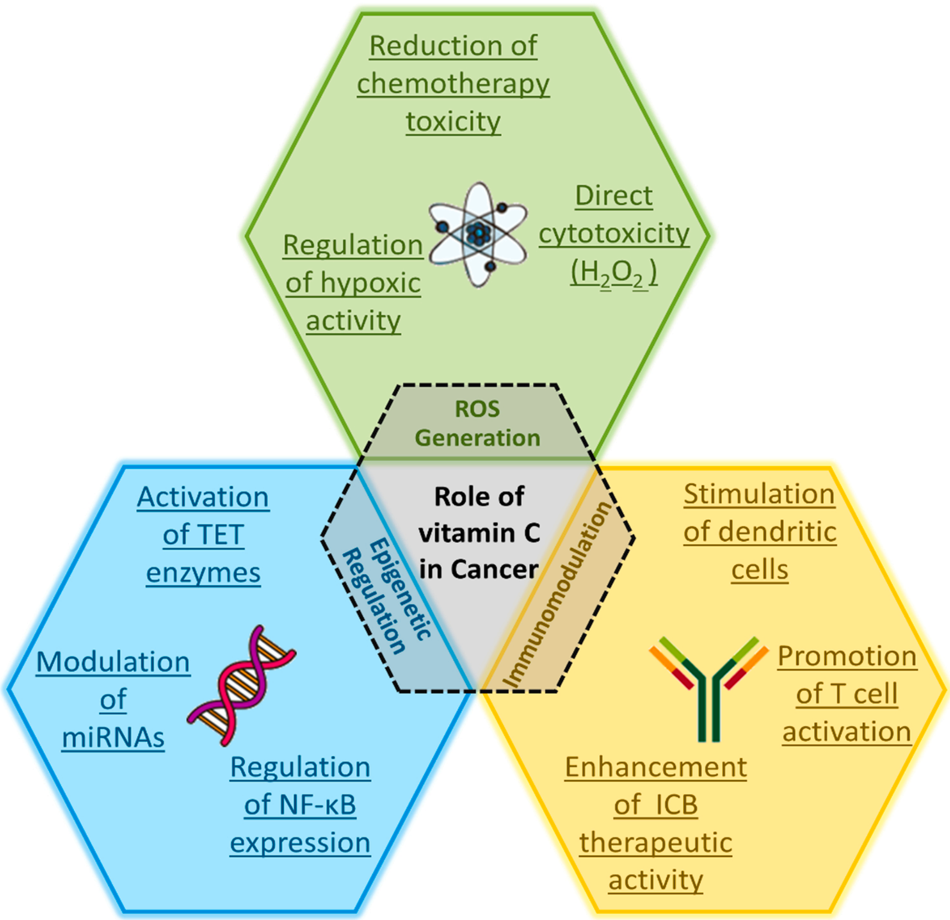


**Fig. 2.** Role of vitamin C in cancer: The anti-cancer effect of vitamin C is related to its pro-oxidant capacity and its ability to modulate epigenetic mechanisms in cancer cells and to stimulate the anti-cancer immune response.

activity. Moreover, several studies have investigated the role of vitamin C on the anti-tumor immune response and, subsequently, on cancer immunotherapy. Some of these studies are summarized in Table 1.

Vitamin C exerts its pro-oxidant action via ROS generation in vivo and in vitro. ROS are known to play an important role in tumorigenesis and to affect multiple biological processes such as cell proliferation, genomic instability, inflammation, resistance to apoptosis and metabolic reprogramming [76]. Moreover, ROS exert a significant effect on the expression of PD-1 and PD-L1. However, the mechanisms of crosstalk between ROS and PD-L1 are not yet clearly determined. Indeed, recent studies showed that ROS generation can induce both up and down-regulation of PD-L1 expression in cancer cells depending on their targets and mechanisms of activity [77]. Nevertheless, an enhanced generation of ROS often promotes PD-L1 expression [78–80] and, conversely, ROS scavenging can repress PD-L1 [81,82]. Yet, some drugs can induce ROS production while reducing PD-L1 expression and vice versa [77]. The effect of vitamin C on PD-L1 expression via generation of intracellular ROS has to be further investigated.

Moreover, in the tumor microenvironment, high levels of intracellular ROS can stimulate the secretion of IL-6, a pro-inflammatory cytokine that facilitates proliferation, migration and metastasis of several types of tumors [83,84]. Interestingly, it has been shown that IL-6 also plays an important role in suppressing the anti-tumor immune response to anti-PD-L1 treatments in colorectal cancer, pancreatic cancer, and melanoma [85,86]. In conclusion, exploring the specific role of ROS in the PD-1/PD-L1 pathway across cancer types is one of the key strategies to understand the role of vitamin C in the regulation of the immune response in cancer patients receiving ICB therapy.

In acute myeloid leukemia cells, vitamin C promoted TET2 activity and mimicked its restoration. The restoration of TET2 activity confers an emergent vulnerability in leukemia cells, rendering them more sensitive to poly ADP ribose polymerase inhibitors (PARPi) [87]. Moreover, TET2 mutations are known to play a primordial role in tumorigenesis. Recently, it has been shown that loss of TET2 expression resulted in an up-regulation of IL-6 in myeloid cells, including DCs and macrophages [88]. Moreover, vitamin C enhanced TET2 catalytic activity in B16-OVA melanoma cells, markedly improving chemokines secretion and PD-L1 expression. The up-regulation of chemokines levels (CXC-Ligand 9, 10 and 11) and of PD-L1 expression were associated with increased numbers of tumor-infiltrating lymphocytes, limited inflammation and improved anti-tumor immunity, as well as enhanced efficacy of anti-PD-L1 therapy [25]. Thus, vitamin C might be considered as an adjuvant to ICB therapy in cancer patients with TET2 mutation.

A number of transcription factors that are known to be down-regulated by vitamin C treatment, such as NF-κB andHIF-1α have been found to modulate PD-L1 transcriptional activation [89]. NF- κB is constitutively active in many human malignancies and it regulates apoptosis, tumor cell invasion, tumor angiogenesis, proliferation and metastasis [90]. It has been shown that NF-κB directly induces PD-L1 gene transcription by binding to its promoter, and that it can also regulate PD-L1 post-transcription through indirect pathways. One study showed that TNF-α can induce the NF-κB pathway and consequently promote the expression of demethylated PD-L1 promoter during epithelial-mesenchymal transition signaling in NSCLC [91]. Therefore, vitamin C therapy might downregulate PD-L-1 expression through inhibition of NF-κB.

**Table 1**
Studies investigating the effect of vitamin C on immune responses and cancer immunotherapy.

| References | Model | Dose of vitamin C | Combination/Single treatment | Effect on immune markers | Outcomes of vitamin C treatment |
|---|---|---|---|---|---|
| Magrì et al. [24] | • Syngeneic mouse models including colorectal (CT26 and MC38), breast (TS/A and 4T1), melanoma (B16-F10), and pancreatic (PDAC) models<br>• MMRd tumor models (colorectal and breast cancer murine cells)<br>• Adoptive T cell transfer model of breast cancer (CD4 + and CD8 + T cells) | 4 g/kg per day | Combination vitamin C with anti–PD-1 and anti–CTLA-4 | Activates CD69 and CD44 markers | • Increases T cells production of IFN-γ<br>• Increases CD4 and CD8 T lymphocytes activation and infiltration<br>• Enhances therapy in mice with increased mutational/neoantigen burdens<br>• Did not improve the activity of anti–PD-1 therapy<br>• Enhances the efficacy of anti–CTLA-4 as a monotherapy |
| Xu et al.[25] | • In vivo tumor progression and immunotherapy models (B16-OVA cells or MC38 cells)<br>• Adoptive T cell immunotherapy model (OT-I CD8 + T cells)<br>• Anti–PD-L1 immunotherapy model | 4 g/kg/mouse | Combination vitamin C with anti- PD-L1 | Induces PD-L1 expression | • Stimulates TET activity to enhance tumor-infiltrating lymphocytes and efficiency of adoptive T cell therapy<br>• Stimulates TET activity to enhance tumor-infiltrating lymphocytes and anti–PD-L1 immunotherapy. |
| Luchtel et al. [23] | Lymphoma cell lines (SU-DHL-6, OCI-Ly1, OCI-Ly7 and OCI-Ly3)<br>A20 lymphoma mouse Model | 1 mM<br><br>1.5 mM | Combination vitamin C with anti-PD-1 | Dose not increase PD-L1 expression | • Increases CD8 + T Cell and macrophages tumor infiltration<br>• Enhances granzyme B production by cytotoxic T cells and NK cells<br>• Induces interleukin 12 production by Antigen-Presenting Cells |
| Gustafon et al.[107] | Metastatic melanoma cell line (A2058) | 0.1 mM | Vitamin c monotherapy | Induces MAGE4 and TMP3 expression | • Inhibits cell migration and anchorage-independent growth |
| Fan et al. [59] | Pancreatic cancer cell lines (PANC-1, BxPC-3 and MIA PaCa-2) | 0, 20, 50 μmol/l | Vitamin C monotherapy | Decreases of PD-L1 expression | • Induces PD-L1 downregulation trough histone acetyltransferase 1 |
| Cimmino et al.[88] | Acute myeloid leukemia cells (HL60, MOLM13, K562, KG1, THP1 and KASUMI1) | 0, 125, 250,500 and 1000 μM | Vitamin C monotherapy | Not studied | • increases TET activity in human acute myeloid leukemia cell sand drives DNA hypomethylation<br>• Mimics effects of TET2 restoration<br>• TET-mediated oxidation of DNA by vitamin C in combination with PARP inhibition enhances AML cell death |

Furthermore, it has been shown that HIF-1α can stimulate the transcription of PD-L1 after binding to the PD-L1 proximal promoter. Indeed, several studies have reported that increased HIF-1α levels were associated with the up-regulation of PD-L1 expression on tumor cells, leading to cancer immune evasion [92,93]. This correlation in HIF-1α and PD-L1 expression levels were observed in cancer patients with hepatocellular cancer, follicular thyroid cancer and advanced oral squamous cell carcinoma [94–96]. Up-regulation of HIF-1α and PD-L1 expression could be one of the mechanisms used by cancer cells to develop resistance to chemotherapy and immunotherapy [97,98]. Indeed, it has been shown that targeting HIF-1α helped in improving cancer immunotherapy [99]. Interestingly, some recent studies showed that pharmacological dose of vitamin C induced a down-regulation of HIF-1α transcription in cancer cells [52,100,101]. Moreover, cancer patients who had the highest HIF-1α activity were those who had ascorbate deficiency [54,55]. Therefore, it is of utmost importance to explore the effect of vitamin C treatment in cancer patients with ascorbate deficiency [102]. Moreover, silencing of HIF-1α has been shown to promote the induction of TET2 activity and of 5-hydroxymethylcytosine (5 hmC) levels in melanoma cells treated with vitamin C [103]. Taken together, HIF-α degradation by vitamin C might result in the downregulation of immune checkpoint markers such as PD-L1.

In metastasis melanoma cells, physiological dose of vitamin C induced a differential expression of several cancer biomarkers genes including melanoma-associated antigen 4 expression (MAGEA4) and TIMP metallopeptidase inhibitor 3 (TIMP3) [104]. MAGEA4, a tumor antigen that belongs to the cancer-testis antigens (CTA) family, is considered as a promising target for cancer immunotherapy and it is frequently silenced by epigenetic mechanisms. TIMP3 is a biomarker which is down-regulated or deregulated in cancer [105]. Considering these finding, it would be interesting to examine the role of vitamin C on cancer-testis antigens expression and. other biomarkers that would affect tumor growth, cancer apoptosis, and immune cell infiltration and activation.

The tumor suppressor gene p53, frequently mutated in many cancer types, is known to negatively regulate PD-L1 expression. Interestingly, in NSCLC, patients who expressed high PD-L1 and low p53 levels had lower survival rates than those with low PD-L1 and high p53 levels [106]. Another study has also reported that PD-L1 and p53 protein levels are correlated in patients with lung adenocarcinoma [107]. It has been shown that vitamin C treatment induces an up-regulation of p53 [108].

The mechanisms by which vitamin C modulates cytokines expression is mostly unknown. Few studies showed that vitamin C treatment reduces the secretion of pro-inflammatory cytokines including IL-6, IFN-γ and TNF-α [72,73]. In parallel, many of those cytokines, found in an immune-reactive tumor microenvironment, may induce PD-L1 expression on tumor cells through distinct signaling mechanisms [109,110]. Additionally, a recent study demonstrated that vitamin C potentiates ICB by enhancing the intra-tumoral infiltration of macrophages and CD8 + T lymphocytes and secretion of IL-12 and granzyme B, which are considered as biomarkers of response to immunotherapy [23]. Furthermore, vitamin C treatment decreases the plasma C-reactive protein (CRP) levels [72,111]. CRP is a pro-inflammatory protein, considered as predictive biomarker in immunotherapy [112–114]. In this respect, it has been shown that CRP expression is well correlated with low levels of CD4 + T lymphocytes which play a crucial role in ICB mediated antitumor immune response [115]. Recently, it has been shown that vitamin C stimulates the tumor infiltration of lymphocytes and enhance the antitumor immunity [25]. Vitamin C can stimulate anti-cancer adaptive immunity and enhance the efficacy of ICB in mouse cancer models carrying mismatch repair-proficient (MMR-P) and mismatch repair deficient (MMR-D) tumors [24]. These data provide compelling rational for testing the combination of vitamin C and ICB in preclinical models and in patients with different cancer types.

Treatment with vitamin C is able to modulate microRNAs such as the miR-200 family. MiR-200 is a family of tumor suppressor miRNAs consisting of five members (miR-200a, miR-200b miR-200c, miR-429 and miR-141), which are significantly involved in inhibition of epithelial-to-mesenchymal transition, repression of cancer stem cells self-renewal and differentiation, modulation of cell division and apoptosis, and reversal of chemo-resistance [116–118]. Interestingly, miR-200 inhibits angiogenesis through direct and indirect mechanisms by targeting IL-8 and chemokines (CXC-Ligand 1) secreted by the tumor endothelial and cancer cells [119]. Moreover, miR-200b represents a potential regulator of PD-L1 expression. The correlation between the expression levels of miR-200b and PD-L1 on tumor and immune cells was reported in NSCLC [120]. Additionally, decreased miR-200b levels in mutant mouse model of lung adenocarcinoma led to increased expression of PD-L1 on tumor cells, causing an inhibition of CD8 + T lymphocytes activity [121]. Furthermore, significant downregulation of miR-200 C expression was observed in patients with PD-L1 positives malignant pleural mesothelioma [122]. It should be also noted that increased levels of ROS might also have an impact on the cellular profile of the miR-200 family [123]. For instance, it can be speculated that vitamin C would regulate PD-L1 expression via ROS generation and miR-200 family modulation. Nevertheless, the mechanisms by which vitamin C regulates the expression of PD-L1 via micro-RNAs need to be further investigated.

In conclusion, the evidence raised by different pre-clinical and clinical studies, suggest that there is a rational to investigate the potential use of vitamin C as an adjunct treatment for cancer immunotherapy especially for its lack of toxicity and for its low cost. However, the effect of vitamin C on the regulation of PD-L1 expression is yet not well determined. Therefore, further studies are needed to explore and clarify the effect of vitamin C on PD-L1 expression across different cancer types in order to specifically predict the clinical benefit of a combination strategy including vitamin C and ICB therapy.

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## CRediT authorship contribution statement

TB wrote the initial draft. TB and QF prepared the figures. MM designed and revised the manuscript. VI, SM, SU, NB and SD provided intellectual input and critical review of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

## Conflict of interest statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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