Unveiling vitamin C: A new hope in the treatment of diffuse large B-cell lymphoma (Review)

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Abstract. Lymphoma is a malignancy of the immune system, which originates from lymphatic tissues and lymph nodes. Diffuse large B-cell lymphoma (DLBCL) is a common type of non-Hodgkin lymphoma, occurring in 30-40% of all cases, which has persistent clinical challenges. The treatment of DLBCL is challenging due to its diverse genetic and biological characteristics and complex clinical physiology. Despite advancements in overall prognosis, 20-25% of patients continue to experience relapse and 10-15% of patients experience refractory disease. Vitamin C is a water-soluble vitamin with antioxidant properties and notable pharmacological activity, with potential applications in cancer therapy. Pharmacological doses of vitamin C (1-4 g/kg) can induce apoptosis in malignant cells by inhibiting and/or reversing gene mutations that are associated with hematological malignancies. For example, 10-25% of patients with myeloid malignancies have tet methylcytosine dioxygenase 2 (TET2) gene mutations and vitamin C can regulate blood stem cell frequency and leukemia production by enhancing TET2 function. Consequently, pharmacological doses of vitamin C can inhibit the development and progression of hematological malignancies. Therefore, the present review aimed to investigate the role of vitamin C in the pathophysiology and treatment of DLBCL, whilst highlighting the potential challenges and future perspectives.

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Contents

1. Introduction

Diffuse large B-cell lymphoma (BCL) (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for 30-40% of all non-Hodgkin lymphoma cases (1). Although the majority of DLBCL cases are primary, DLBCL can also transform from various indolent lymphomas. For example, 6.78% of splenic marginal zone lymphomas, 5.55% of follicular lymphomas, 4.05% of nodal marginal zone lymphomas, 2.22% of lymphoplasmacytic lymphomas/Waldenström's macroglobulinemias and 1.62% of extra-nodal marginal zone lymphomas developed into DLBCL (2). Based on gene expression profiles, DLBCL can be classified into various subgroups, namely activated B-cell, germinal center B-cell and unclassified, with each exhibiting a distinct response to treatment (3). The rituximab (R)-cyclophosphamide doxorubicin vincristine prednisolone (R-CHOP) regimen, which includes a monoclonal antibody targeting CD20, represents an advancement in the initial treatment of patients with DLBCL (4,5). This regimen has improved the 10-year progression-free survival (PFS) rate of patients with DLBCL from 20 to 36.5% (6), and the 5-year overall survival (OS) rate from ~50% to 60-70% (7). However, despite this advancement, >40% of patients with DLBCL treated with R-CHOP or R-CHOP-like regimens will experience relapse or refractory disease (5). In addition, the majority of patients with relapsed or refractory DLBCL will have a shorter survival period compared with patients without relapsed or refractory DLBLC.

Previous studies have identified a number of risk factors for DLBCL, which are outlined in the present review. Clinical studies indicate that Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) and hepatitis viral infections are associated with DLBCL development (8-10). EBV is a cancer-causing virus that is associated with a number of lymphoproliferative disorders, such as DLBCL and Burkitt's

lymphoma. Furthermore, in individuals that are HIV-positive, the risk of EBV-associated cancers, including DLBCL, increases due to weakened immunity (8,9). Hepatitis C virus (HCV) is also associated with DLBCL, where co-infection with HCV and HIV further increases the risk of lymphoproliferative disorders due to combined immunosuppression and chronic inflammation (10). In addition, numerous studies indicate a positive association between autoimmune diseases, such as systemic lupus erythematosus and Sjogren's syndrome, and an increased risk of DLBCL (11-13). Furthermore, genetic factors are also considered to serve an important role in the biology and prognosis of DLBCL, and various studies reveal that DLBCL exhibits considerable genetic heterogeneity (14,15). The expression and rearrangement of *Myc*, *Bcl2* and *Bcl6* genes are useful for guiding treatment and predicting the prognosis of DLBCL (16,17). In addition, the tumor microenvironment (TME) and programmed cell death protein 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) are key factors that can determine DLBCL treatment outcomes, since they can enable tumor immune escape, and thus, recurrence or refractory disease (18). Consequently, the management of DLBCL is currently still challenging.

The influence of dietary nutrients, with a particular emphasis on vitamin supplementation, in the prevention and treatment of tumors is gaining interest in the present field of research. Previous empirical studies reveal that certain vitamins (vitamin D and E) can exert a substantial effect on tumor development and progression (19,20). In particular, a number of trials indicate that high doses of vitamin C (≥1 g/kg) exhibit both direct and indirect antitumor properties (21-30) (Table I). As a result, vitamins are regarded as an important agent in the prevention and therapeutic management of malignancies.

Ascorbic acid (AA), commonly known as vitamin C, is a water-soluble vitamin with potent antioxidant properties. Vitamin C is abundant in various fruits and vegetables, with concentrations differing among species. Citrus and kiwi fruits, mangoes, broccoli, tomatoes, and peppers have the highest levels of vitamin C (31). Numerous studies indicate that high doses of vitamin C (1-4 g/kg) can inhibit tumor cell proliferation through multiple mechanisms (30,32). These mechanisms include increased production of reactive oxygen species (ROS), activation of specific epigenetic regulatory factors [tet methylcytosine dioxygenase 2 (TET2)] and modulation of the antitumor immune response to either directly or indirectly eliminate tumor cells (30,32,33). Furthermore, previous clinical trials demonstrate that vitamin C treatment has a high level of safety and tolerability (34,35). The present review investigated the role of vitamin C in DLBCL and assessed its effects on the various pathogenic mechanisms of DLBCL. Additionally, the present review examined the future prospects and challenges associated with vitamin C-based antitumor therapy.

2. Properties and functions of vitamin C

Absorption, distribution and metabolism of vitamin C. Vitamin C is a weak acid that is comprised of six carbon atoms and is classified as an α-ketolactone. In the human body, vitamin C mainly exists in two active forms, dehydroascorbic acid (DHA) and AA, in an interconvertible manner (Fig. 1A and B) (36). Vitamin C is abundant in a wide variety of fruits and vegetables and can only be obtained by humans via ingestion through dietary means, since humans cannot synthesize it. Following oral intake, vitamin C is primarily absorbed in the duodenum and upper jejunum, with minimal absorption occurring in the stomach. It enters the bloodstream through passive and active transport, facilitating its transmembrane movement (37,38). However, the majority of vitamin C is absorbed via the sodium-dependent vitamin C transporter (SVCT)1 (39,40). Vitamin C typically moves slowly across the plasma membrane, even in the presence of a notable concentration gradient. AA is absorbed in the intestine through SVCT1 (40), whilst DHA may undergo transmembrane diffusion and absorption through glucose transporters (GLUT) (41). However, the mechanism underlying AA absorption into the bloodstream is yet to be elucidated (42). Once AA is absorbed into the bloodstream, it is subsequently transported to various organs through SVCT2. Vitamin C is widely distributed across various organs and cells, with particularly high concentrations in the brain and endocrine glands, such as the pituitary and adrenal glands (37,43). A schematic diagram illustrating intestinal vitamin C absorption and distribution is presented in Fig. 1C and D. However, the majority of vitamin C entering the body is excreted by the kidneys, with only a small proportion eliminated through feces (41).

Effect of vitamin C on the immune system. Via the SVCT2, vitamin C accumulates in key organs and cells, such as the skin, lymphocytes and neutrophils. The skin serves as the first line of defense for the body. Previous studies indicate that vitamin C reduces the synthesis and release of proinflammatory factors, such as IL-1β and TNF-α, by reducing the transcription of their genes (44,45). Additionally, vitamin C contributes to the tissue repair processes by promoting collagen synthesis and maturation, promoting the expression of angiogenic factors (such as VEGF), enhancing the expression of connective tissue regulators (such as connective tissue growth factor), increasing fibroblast activity, and activating important repair enzymes (such as heme oxygenase 1 and TGF-β) (44-46). In addition, preliminary evidence suggests that vitamin C can accumulate in neutrophils to an extent. Following infection, neutrophils can rapidly uptake DHA and convert it to AA within cells, leading to increases in its concentration. This concentration increase is calculated to be ~10 mM (36). *In vitro* and clinical studies also reveal that vitamin C can enhance the efficacy of phagocytosis and pathogen killing by promoting neutrophil chemotaxis (47,48). Lymphocytes, including T and B cells, are key types of immune cells that utilize SVCT2 for vitamin C storage. Although the precise mechanism by which vitamin C regulates lymphocyte physiology remains unclear (49), vitamin C can stimulate lymphocyte development, differentiation and maturation of immature cells, and regulate cytokine secretion (36,50,51). Additionally, when vitamin C is incubated with peripheral blood lymphocytes *in vitro*, it reduces the production of various inflammatory cytokines, such as TNF-α and IFN-γ, induced by lipopolysaccharide, whilst increasing the production of the anti-inflammatory cytokine IL-10 (50). Immunoregulatory T cells (Tregs), a subset of $CD4^+$ T cells, serve an important role in immune regulation. They serve to prevent the hyperactivation of the immune system and maintain immune homeostasis. A recent study demonstrates that

Table I. A summary of clinical and basic trials investigating the use of vitamin C in the treatment of tumors.

First author, year	Study type	Cancer model	Contents	Results	(Refs.)
Gillberg *et al*, 2019	Clinical study	Myeloid cancer	A randomized, double-blinded, placebo-controlled pilot trial (NCT02877277) in Danish patients with myeloid cancer using three cycles of DNMTi-treatment (100 mg/m^2/day of 5-azacytidine for 5 days in 28-day cycles) supplemented with an oral dose of 500 mg vitamin C (n=10) or placebo (n=10) daily during the last two cycles.	Normalization of plasma vitamin C byoral supplemen tation leads to an increase in the 5-hmC/5-mC ratio compared with the placebo-treated patients and may enhance the biological effects of DNMTis.	(22)
O'Leary *et al*, 2020	Clinical study	Pancreatic cancer	Determined the effects of P-AscH$^-$ on metastatic PDAC.	P-AscH$^-$ attenuates the metastatic potential of PDAC and may be effective for treating advanced disease.	(23)
Furqan *et al*, 2022	Clinical study	Lung cancer	Patients with naïve advanced stage NSCLC received chemotherapy of 75 g ascorbate twice per week intravenously with carboplatin (AUC 6[a]) and paclitaxel (200 mg/m^2) every 3 weeks for four cycles.	Adding P-AscH$^-$ to chemo-therapy notably improved the response rate to chemo-therapeutics in patients with NSCLC compared with those without P-AscH$^-$ treatment.	(24)
Bodeker *et al*, 2024	Clinical study	Pancreatic ductal adeno-carcinoma	Patients diagnosed with stage IV pancreatic cancer were randomized in a 1:1 ratio to either a gemcitabine and nab-paclitaxel only group (SOC; control) or a SOC group with 75 g P-AscH, three times weekly (ASC; experimental group).	P-AscH$^-$ infusions of 75 g three times per week in patients with metastatic pancreatic cancer increases the overall survival and progression free survival without a reduction in the quality of life nor an increase in the toxicity in the patient.	(25)
Paller *et al*, 2024	Clinical study	Prostate cancer	A randomized placebo-controlled phase II trial using a high-dose of intravenous vitamin C (1 g/kg, twice per week) combined with docetaxel (75 mg/m^2 i.v, every 3 weeks) in men with metastatic castration-resistant prostate cancer.	In the present patient cohort, combining a high dose of intravenous vitamin C with docetaxel did not improve the efficacy of treatment compared with docetaxel alone.	(21)
Su *et al*, 2019	Fundamental research	Thyroid cancer	The effect of vitamin C on thyroid cancer cell proli-feration and apoptosis was investigated.	Vitamin C kills thyroid cancer cells through a ROS-dependent inhibition of MAPK/ERK and PI3K/AKT pathways via distinct mechanisms.	(26)

Table I. Continued.

First author, year	Study type	Cancer model	Contents	Results	(Refs.)
Zhou *et al*, 2020	Fundamental research	Oral squamous cell carcinoma	The anticancer effects of vitamin C in oral squamous cell carcinoma was investigated.	Vitamin C had an anti-cancer effect in oral squamous cell lines. It was demonstrated to inhibit the growth and migration of xenograft tumors in nude mice.	(27)
Su *et al*, 2021	Fundamental research	Thyroid cancer.	The antitumor efficacy of PLX4032 combined with vitamin C against BRAF was investigated.	The PLX4032 and vitamin C combination may be a potential therapeutic approach to treat patients with $BRAF^{MT}$ thyroid cancer.	(28)
Zhao *et al*, 2024	Fundamental research	Breast cancer	The effect of high doses of vitamin C (1-2 g/kg) on the PD-L1 expression levels in triple negative breast cancer and its potential mechanism was investigated.	Vitamin C reduced the PD-L1 expression levels in breast cancer cell lines and enhanced the antitumor effects of T cells.	(29)
Lv *et al*, 2024	Fundamental research	Liver cancer	TET2-mediated tumor cGAS induces endothelial STING activation, which regulates vasculature remodeling and antitumor immunity in liver cancer.	Vitamin C increases TET2 activity, upregulates the expression of cGAS and activates the STING pathway in endothelial cells. It regulates the expression of VEGF and restores normal tumor vasculature. Furthermore, vitamin C increases the efficacy of anti-PD-L1 therapy, alone or with IL-2.	(30)

[a]Guidelines suggest dosing carboplatin according to plasma concentration multiplied by the AUC after a single dose (National Comprehensive Cancer Network guidelines; version 3.2025; https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450). DNMTi, DNA methyltransferase inhibitor; 5-hmC, 5-hydroxymethylcytosine; 5-mC, 5-methylcytosin; $P\text{-}AscH^-$, pharmacologic ascorbate; PDAC, pancreatic ductal adenocarcinoma; NSCLC, non-small cell lung cancer; SOC, standard of care; ASC, adjuvant systemic chemotherapy; PSA, prostate-specific antigen; ROS, reactive oxygen species; PD-L1, programmed cell death-ligand 1; TET2, tet methylcytosine dioxygenase 2; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; AUC, the area under the blood drug concentration curve.

TET2 enzymes are important for maintaining a stable population of Treg cells (52). Vitamin C can enhance the activity of TET enzymes, suggesting that targeting TET enzymes with vitamin C may improve the efficacy of Treg cell induction (53).

3. Mechanism of vitamin C in DLBCL

Mechanism of vitamin C in regulating BCL2. *Bcl2*, the first gene found in the BCL2 family, inhibits apoptosis or programmed cell death (Table II). *Bcl2* was named after it was found to be involved in follicular lymphoma, a cancer caused by a translocation between chromosomes 14 and 18, which increases the transcription of BCL2 (54). Previous studies demonstrate that the BCL2 family regulates cell death by inhibiting apoptosis and advancing the cell cycle, while also having antioxidant properties and participating in both pro-oxidant and antioxidant signaling pathways (55,56). The BCL2 family regulate the permeability of the mitochondrial membrane and induce the release of ROS to exert pro-oxidant effects (57). Additionally, the BCL2 family promotes the transcription of nuclear factor erythroid 2-related factor 2, which initiates an antioxidant response that reduces ROS levels, enhances cellular protection and growth, and contributes to tumor progression and drug resistance (58). Oxidative stress (OS) is caused by an

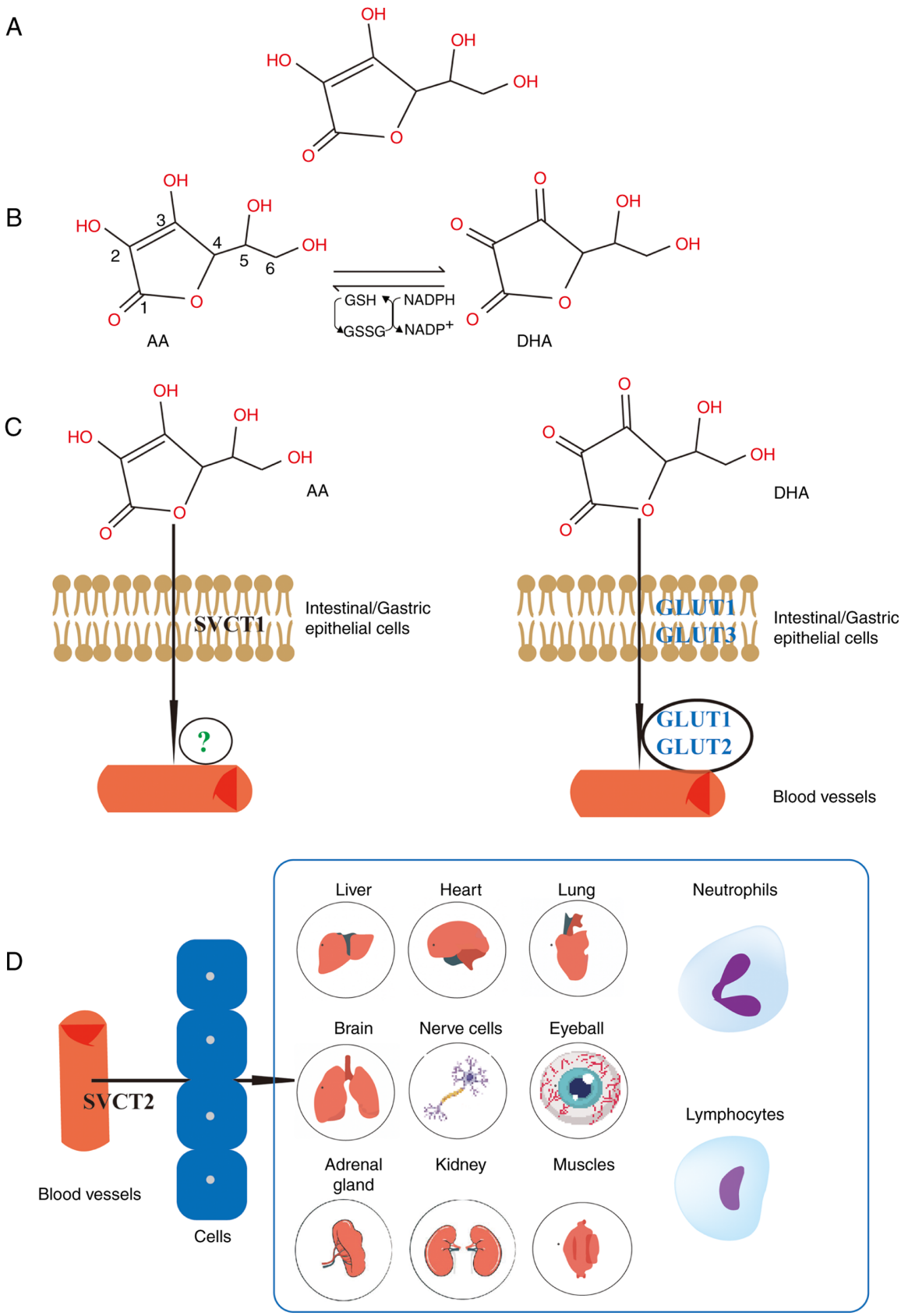

Figure 1. Structure, absorption and transport distribution of vitamin C *in vivo*. (A) Chemical structure of AA. (B) Vitamin C has two active forms in the body; AA and DHA. The two enol hydroxyl groups on carbon atoms 2 and 3 of AA are dissociated to release H^+, which oxidizes AA to form DHA. The oxidized DHA can be reduced to AA by GSH. (C) Absorption of AA and DHA. AA is transported in the intestine and absorbed into epithelial cells via SVCT1; however, the mechanism of AA transport into the blood is yet to be fully elucidated. DHA may diffuse into epithelial cells via GLUT1 or GLUT3. Once inside the cell, DHA is either converted into apoptosis-associated speck-like protein containing a caspase recruitment domain or transported into the bloodstream by GLUT1 and GLUT2, which are located in the basolateral membrane. This process maintains a low intracellular DHA concentration, which facilitates further DHA uptake. (D) Vitamin C is distributed to various organs via SVCT2. AA, ascorbic acid; DHA, dehydroascorbic acid; GSH, glutathione; GSSG, GSH disulfide; SVCT, sodium-dependent vitamin C transporter; GLUT, glucose transporter.

Table II. BCL2 family of proteins.

Subfamily	Members
Antiapoptotic proteins	BCL2
	BCL-XL
	MCL-1
	BCLW
	BFL-1
Proapoptotic proteins	BAX
	BAK
	BOK
	BIM
	BAD
	NOXA
	PUMA
	BID
	BIK
	HRK

MCL-1, myeloid cell leukemia-1; BCLW, BCL2 related protein W; BFL-1, BCL2-related gene expressed in fetal liver; BAK, BCL2 antagonist/killer; BOK, BCL2-related ovarian killer protein; BIM, BCL2 interacting mediator of cell death; NOXA, phorbol-12-myristate-13-acetate-induced protein 1; PUMA, p53 upregulated modulator of apoptosis; BID, BH3 interacting domain death agonist; BIK, BCL2-interacting killer; HRK, harakiri.

imbalance between oxidants and antioxidants, which can lead to cellular damage or even destruction (59). It has an important function in regulating the fate of a cell, especially during the early stages of tumor development. This is because the production of ROS in the body promotes damage to cellular DNA, and along with a decrease in antioxidants, can lead to tumor development. By contrast, at later stages of malignant progression, tumor cells can produce a large number of antioxidants that either reduce or neutralize the production of ROS in the body in order to promote immune escape (60-62).

The *Bcl2* gene is important in regulating programmed cell death or apoptosis. However, when the gene is mutated, the antiapoptotic and proapoptotic effects can become imbalanced, leading to various types of cancer, including lymphoma (63,64). DLBCL is particularly challenging in clinical management due to its heterogeneous nature. The BCL2 protein is overexpressed in ~10% of patients with DLBCL, which is associated with a reduced progression-free survival and a poor prognosis (65,66). In addition, the overexpression of BCL2 can reduce the production of oxygen-free radicals and lipid peroxides, creating a favorable environment for tumor cell proliferation (67-70). In oncogenic environments, pharmacological concentrations of vitamin C (0.3-20 mM) exerts a pro-oxidant effect by catalyzing the generation of hydrogen peroxide, which induces oxidative stress and selectively promotes the eradication of malignant cells, particularly in cases of liver, ovarian and breast cancer (71-73). A number of studies demonstrate that pharmacological doses of vitamin C (1-4 g/kg) can maintain the level of ROS in the body, preferentially killing various cancer cell lines whilst conferring minimal cytotoxicity to normal cells (29,32). In addition, vitamin C can increase the level of ROS, resulting in DNA damage and ATP depletion in tumor cells, promoting cancer cell apoptosis (27,74). Furthermore, vitamin C can inhibit the expression of BCL2, which activates the expression of the proapoptotic protein Bax, thereby further promoting the apoptosis of tumor cells (Fig. 2A) (27,75,76). Therefore, pharmacological doses of vitamin C may reduce the expression of BCL2 and increase the levels of ROS, leading to anticancer effects in DLBCL.

Mechanism of vitamin C in regulating BCL6 and p53. BCL6 is part of the antiapoptotic protein family and functions as a transcriptional repressor (77). The germinal center reaction pathway in mature B cells primarily uses BCL6, which serves an important role in promoting germinal center formation, regulating the cell cycle and participating in immune response signaling transduction. BCL6 inhibits the early activation and differentiation of germinal center B cells, rendering it an important regulatory factor for effective humoral immunity (77). In addition, BCL6 is indispensable for the development and function of T follicular helper cells and germinal center B cells (78,79). BCL6 was first identified in DLBCL. High expression of the BCL6 protein in germinal center B cells markedly inhibits the expression of the tumor suppressor *p53*. The inhibition of *p53* enables lymphoma cells to survive *in vivo* and inhibits tumor cell apoptosis (78).

The oncogenic role of BCL6 is reported in lymphoma (80). As a transcriptional repressor, BCL6 inhibits the expression of cell differentiation markers (such as B-lymphocyte-induced maturation protein 1) (81), high-fidelity DNA repair genes (such as radiation sensitive protein 51) (82) and tumor suppressors (such as PTEN) (83). Concurrently, BCL6 promotes the expression of genes associated with the inhibition of apoptosis, cell cycle arrest, tumor cell proliferation and cell differentiation (84,85). In germinal center-derived BCLs, BCL6 functions as an oncogene, and is frequently associated with chromosomal translocations or promoter mutations that results in an aberrant overexpression (86,87). Mutations in the *Bcl6* gene are frequently associated with a poorer prognosis and more aggressive disease course compared with cases with a non-mutated *Bcl6* gene. Numerous studies indicate that 7-10% of patients with DLBCL exhibit gene rearrangements involving *Myc Bcl2* and/or *Bcl6*, and that these are associated with an unfavorable prognosis (88,89).

As an important tumor suppressor gene, p53 regulates cell division, prevents DNA mutations and the proliferation of damaged cells, controls apoptosis, and inhibits tumor formation (90,91). Additionally, p53 halts the cell cycle and facilitates DNA repair (92). However, in DLBCL cells, vascular compression, due to rapid tumor cell proliferation, results in a hypoxic environment, which subsequently increases the expression of hypoxia-inducible factor-1 (HIF-1) in tumor cells. However, p53 competes with p300 proteins, which reduces the transcription of HIF-1α. Under sustained hypoxia, p53 induces the degradation of HIF-1α and triggers apoptosis, which are both important for inhibiting tumor growth (93-95). HIF-1 is expressed in most types of mammalian cell and primarily consists of the oxygen-dependent HIF-1α and the

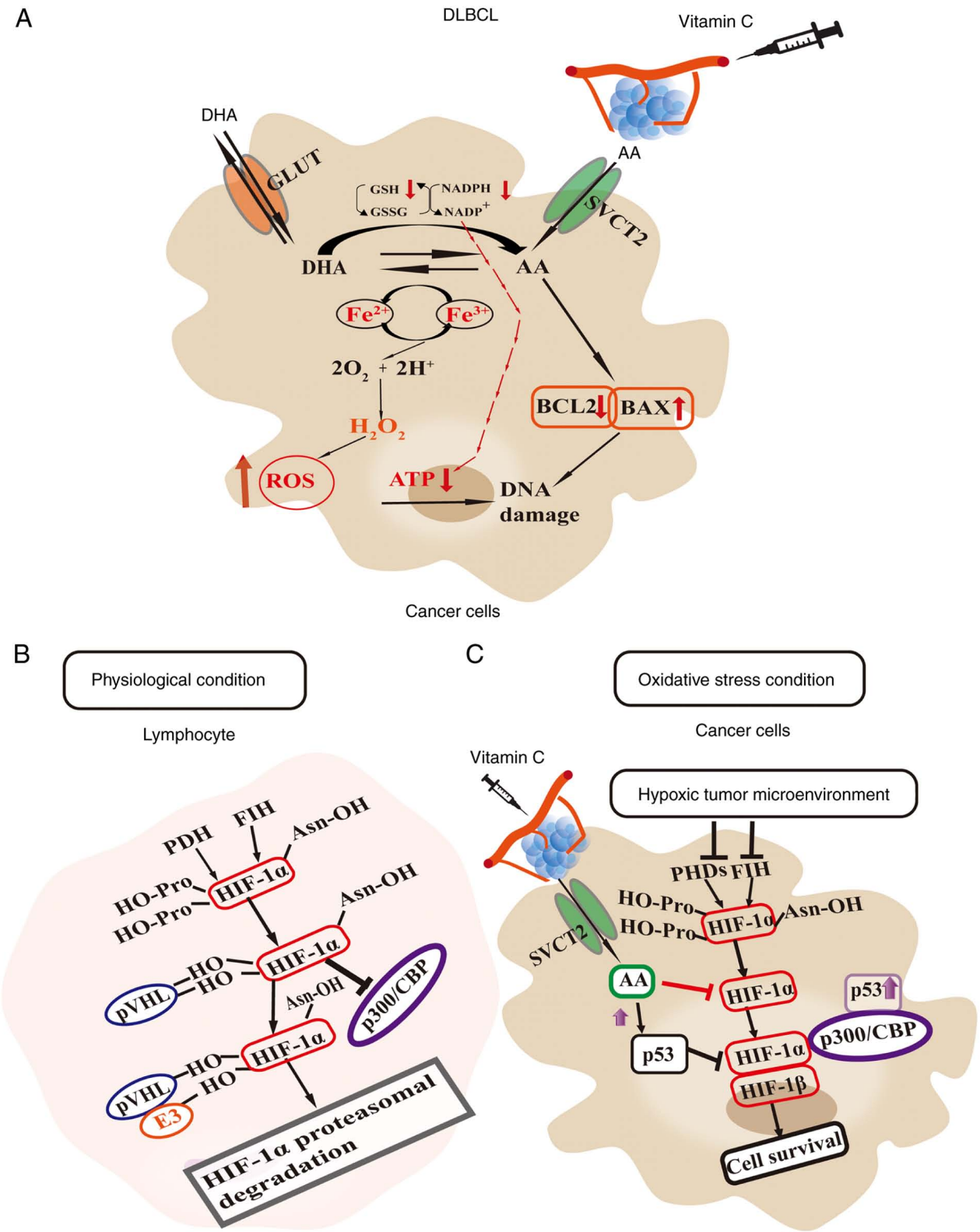

Figure 2. Mechanisms of vitamin C that promote oxidation and tumor cell apoptosis in hypoxic environments. (A) Pharmacological doses of vitamin C (1-4 g/kg) increase the oxidative stress in tumor cells, and thereby increase cytotoxicity. The conversion of DHA to vitamin C in cells leads to the consumption of GSH. Additionally, vitamin C promotes the reaction between Fe^{3+} and Fe^{2+}, which increases the consumption of ATP and the production of ROS. Vitamin C can also upregulate the expression of BAX and inhibit the expression of BCL2. (B) Under aerobic conditions, HIF-1α can be hydroxylated by PHD, resulting in ubiquitination after pVHL binds to HIF-1α. In addition, HIF-α is inhibited by the factor FIH, thereby preventing HIF-α from binding to the co-activator protein p300/CBP. (C) Under hypoxia, the activity of PHD and FIH is limited by substrates (for example, oxygen and α-ketoglutaric acid), leading to the rapid aggregation, nuclear translocation and dimerization of HIF-1α with HIF-1β, which promotes tumor growth. In DLBCL, pharmacological doses of vitamin C (1-4 g/kg) can upregulate the expression of wild-type p53, and compete with p300, which inhibits the transcriptional activity of HIF-1α. p53 protein also induces HIF-1α degradation and promotes apoptosis. AA, ascorbic acid; DHA, dehydroascorbic acid; GSH, glutathione; GSSG, glutathione disulfide; SVCT, sodium-dependent vitamin C transporter; GLUT, glucose transporter; ROS, reactive oxygen species; HIF-1α, hypoxia-inducible factor-1α; PHD, prolyl hydroxylase; pVHL, von Hippel-Lindau protein; FIH, asparagine hydroxylation of HIF-1; CBP, cAMP-response element binding protein; DLBCL, diffuse large B-cell lymphoma; E3, E3 ubiquitin ligase.

oxygen-independent HIF-1β. It can regulate the expression of genes that regulate metastasis, angiogenesis and tumor cell invasion. In DLBCL, BCL6 primarily inhibits p53, which in turn inhibits the effects of p53 on cell cycle arrest and apoptosis. Overexpression of BCL6 reveals reduced wild-type p53 expression levels, resulting in enhanced tumor cell proliferation and impaired apoptosis (79,96-98).

Vitamin C is a natural antioxidant. In normal cells, its antioxidant properties dominate because it directly reacts with superoxide anion radicals ($O\square^-$) and hydroxyl radicals (OH^-), which reduces the level of ROS within the cells (99). In tumor cells, vitamin C often acts as a pro-oxidant due to high metal ion concentrations in the cytoplasm of the cell (such as Fe^{2+}), which leads to oxidative stress due to reactions such as the Fenton reaction. In addition, cancer cells also have an increased expression of GLUT1, which enhances the cellular uptake of oxidized vitamin C (DHA). This depletes the antioxidants such as glutathione, NADPH and superoxide dismutase, and increases the levels of ROS in the cytoplasm of the cell (32). Previous studies indicate that, at pharmacological concentrations, vitamin C can function as a pro-oxidant, selectively inducing DNA damage in cancer cells (71-73). This targeting facilitates the elimination of cancer cells. In cases of breast and cervical cancer, studies indicate that vitamin C upregulates the expression of wild-type p53 and inhibits HIF-1α activity, thus inhibiting tumor development (Fig. 2B and C) (74,100,101). Additionally, in DLBCL, pharmacological doses of vitamin C can increase wild type p53 production, indirectly modulating the impact of BCL6 overexpression. Furthermore, vitamin C can also inhibit HIF-1α activity, promoting apoptosis in tumor cells (102). In conclusion, vitamin C may be a potential anticancer therapeutic agent.

Mechanism of vitamin C in regulating Myc. The *Myc* gene family, initially identified in Burkitt lymphoma, includes n-Myc, l-Myc and c-Myc (103,104). These genes promote cell proliferation, potentially leading to tumor formation. They exhibit distinct expression timelines and tissue specificity during development (105). c-Myc is broadly expressed across multiple types of tumors and during tissue development, and it is associated with tumorigenesis and prognosis (106). n-Myc is expressed in neural tissues and during the early phases of hematopoietic development, with important value in early tumor therapy (107). l-Myc is predominantly expressed in the lungs and is associated with tumor susceptibility and prognosis (106-108). Previous studies demonstrate the important role of *Myc* gene products, particularly c-Myc, in regulating cell death, proliferation, differentiation and malignant transformation (109,110).

c-Myc, a proto-oncogene, is located on chromosome 8q24. When overexpressed, c-Myc promotes cancer cells to re-enter the cell cycle and proliferate, which promotes tumor growth (111). Numerous studies demonstrate that the activation of Myc in cancer cells occurs through multiple mechanisms (112,113). For example, genetic mutations, chromosomal translocations and genomic amplifications can induce elevated Myc expression levels. Furthermore, alterations in an upstream regulatory pathway (such as Wnt/β-catenin) (114) can also increase Myc oncogene transcription levels. In addition, post-translational modifications of the Myc protein such as phosphorylation, proteasomal degradation and ubiquitination enhances its stability, resulting in the activation of the Myc pathway (115). As demonstrated in a conditional knockout mouse model, Myc is essential for hematopoietic system development (116). It regulates the balance between hematopoietic stem cell self-renewal and differentiation, and is also highly expressed in proliferating cells during lymph node development (117). In DLBCL, Myc is the third most frequently rearranged oncogene after *BCL2* and *BCL6*. In total, ~15% of newly diagnosed patients with DLBCL have Myc gene rearrangements, and these patients are frequently associated with an increased level of tumor cell invasion and a poorer prognosis (118-120).

Previous studies demonstrate that vitamin C, acting as a pro-oxidant, increases the levels of ROS, which inhibits the growth of tumor cells (74,121,122). Previous studies using tumors such as clear cell renal carcinoma and esophageal cancer suggest that the accumulation of ROS inhibits the expression of c-Myc, induces DNA damage and reduces tumor cell proliferation (123,124). Another study reveals that the combination of vitamin C with a respiratory complex I inhibitor effectively eradicated c-Myc-overexpressing cells and enhanced treatment outcomes in human BCL xenografts (125). However, further research is required to elucidate the effects of vitamin C on human and hematological tumors. In summary, vitamin C has potential benefits in cancer treatment and may promote tumor cell apoptosis via the ROS/c-Myc axis.

Effects of vitamin C on the TME. The TME is a dynamic and intricate cellular landscape in which tumor or cancer stem cells coexist with immune cells (myeloid and lymphoid), fibroblasts, blood vessels, the extracellular matrix and a range of signaling molecules (such as C-X-C motif chemokine ligand 12 and IL-6) (126,127). A previous study indicates that the TME is adaptable, continuously altering its characteristics throughout tumor development and serving a role in regulating cancer progression (128). For example, immune cells within the TME transition between antitumor and protumor states in response to cytokines secreted by the TME. Cells that suppress the antitumor response include Tregs, myeloid-derived suppressor cells (MDSCs) and M2 phenotype tumor-associated macrophages (TAMs; Fig. 3) (129). Numerous studies indicate that the composition of immune cells in the TME, particularly endogenous immune cells (such as MDSCs, Tregs and M2 macrophages), is directly associated with unfavorable tumor treatment outcomes (130-132).

Dendritic cells (DCs). DCs are immune cells that originate from pluripotent hematopoietic stem cells in the bone marrow. These cells can be categorized into the classical DC (cDC) and lymphoid DC subtypes, with the latter known as plasma cell-like DCs (pDCs). cDC1 and cDC2, two subtypes of cDCs, are differentiated by the abundance of antigen-presenting molecules on their surfaces. These cells are highly specialized and proficient in stimulating naive antigen-specific $CD4^+$ and $CD8^+$ T cells through the processing and presentation of antigens, including tumor-associated antigens. This function is critical for the initiation of an adaptive immune response (133).

Previous studies indicate that DCs serve a role in the antitumor immune response (134,135). Specifically, cDC1 can recognize tumors, secrete factors that modulate the

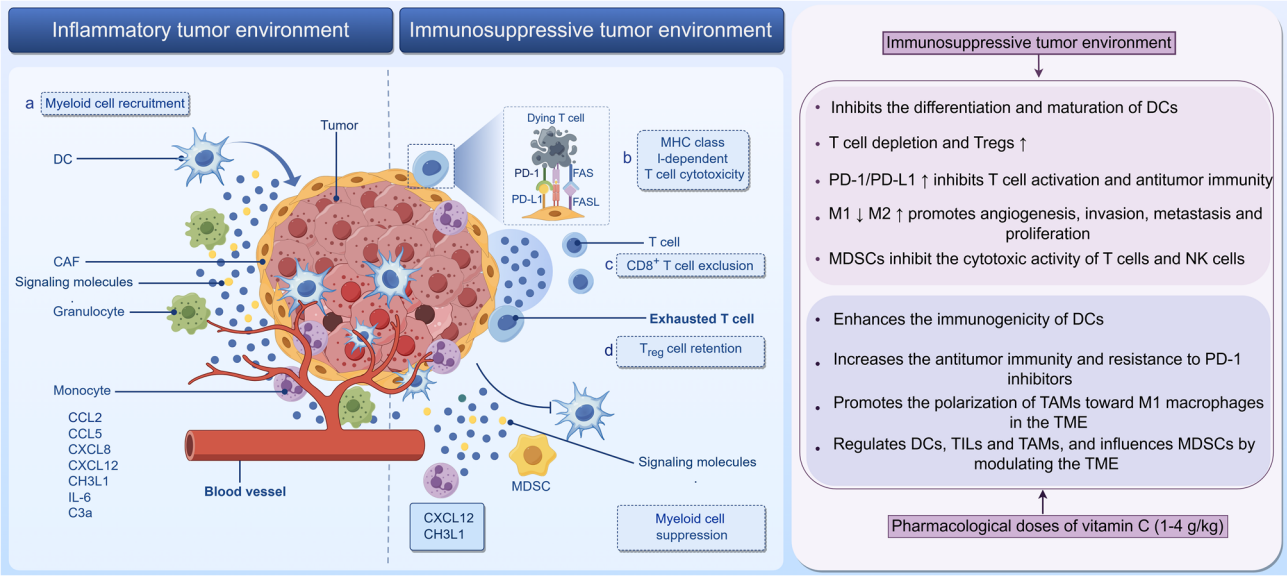

Figure 3. Composition of the tumor microenvironment and the role of individual immune cells. Surrounding immune cells (myeloid and lymphoid cells), fibroblasts, blood vessels, extracellular matrix and signaling molecules (such as CXCL12 and IL-6) compose the TME. Furthermore, vitamin C serves a multifaceted role in regulating elements within the TME. TME, tumor microenvironment; DCs, dendritic cells; CAF, cancer-associated fibroblast; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; FASL, Fas ligand; MHC, major histocompatibility complex; Treg, immunoregulatory T cell; MDSC, myeloid-derived suppressor cell; NK, natural killer; TAMs, tumor-associated macrophages; TILs, tumor-infiltrating lymphocytes; CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; CXCL8, C-X-C motif chemokine ligand 8; CXCL12, C-X-C motif chemokine ligand 12; CHI3L1, chitinase 3 like 1; C3a, complement component 3a.

TME, present tumor-associated antigens, activate $CD8^+$ T cell responses and enhance antitumor immune function (136-138). In addition, cDC2 can activate the $CD4^+$ T cell response, thereby augmenting the ability of $CD8^+$ T cells to kill tumor cells (139,140). IFN-I produced by pDCs serves an important role in the activation of stimulator of IFN response cGAMP interactor 1, which causes cell cycle arrest, regulates cell death and promotes the expression of proapoptotic proteins such as Bax and Bak. This increases the permeability of the mitochondrial membrane, which releases apoptotic factors such as cytochrome C, which in turn triggers the caspase cascade, leading to apoptosis (141). However, the TME in contrast can inhibit the differentiation and maturation of DCs (128), resulting in functional defects in their ability to stimulate T cells and drive antitumor immune responses, thereby promoting tumor growth (142-144). DC dysfunction occurs in various types of cancer, including colon cancer and melanoma (145,146), and is associated with a poor prognosis in patients with advanced-stage cancer (147,148). Consequently, activating DCs in the TME is advantageous for antitumor therapy, making it a promising target for immunotherapy.

DLBCL is a malignant lymphoma with a poor prognosis (18,149). Its TME is considered to serve a pivotal role in the development and prognosis of DLBCL. Various *in vitro* studies reveal that vitamin C can enhance the immunogenicity of DCs, improving their ability to secrete proinflammatory factors (such as IFN-γ and TNF-α) and promoting T cell differentiation (150,151). Furthermore, studies indicate that vitamin C can regulate the activity of the DNA demethylation enzyme TET2 and modulate the differentiation of DCs (152). Consequently, pharmacological doses of vitamin C can modulate DCs in the TME, enhance antitumor activity and mediate a synergistic effect with chemotherapy and immunotherapy (153).

Tumor-infiltrating lymphocytes (TILs) and PD-1/PD-L1. TILs are $CD4^+$ and $CD8^+$ T cells that mature in the thymus and have immune functions in various organs and tissues throughout the body (154). $CD8^+$ T cells initiate immune responses by killing cells through perforin and granzyme. They also produce a number of cytokines, such as TNF-α and IFN-γ, to enhance their activation (155). $CD4^+$ T cells regulate immune responses by producing cytokines and inducing T cell differentiation (155). By contrast, Tregs serve to prevent excessive activation of the immune system and serve a crucial role in regulating tumor immunity (156).

Tumor growth is typically a slow gradual process, where the interaction between tumor cells and the immune system can reshape the immune environment, impacting T cell differentiation (157). In patients with cancer, a notable number of T lymphocytes migrate to the tumor site to attack the malignancy. However, prolonged exposure can lead to exhaustion, T cell depletion, cytokine production and the reduced ability to destroy tumor cells (157). Contributing to this, Tregs in the TME obstruct antitumor effects through various mechanisms, including the secretion of inhibitory cytokines (such as IL-10 and TGF-β) to reduce the antigen-presenting ability of DCs, inhibiting $CD8^+$ T cells from targeting tumor cells and promoting immune evasion (158-160). This is observed in several types of solid tumors, including melanoma (161), hepatocellular carcinoma (162), lymphoma (163) and lung cancer (164).

Numerous studies reveal that the dysfunction of tumor-infiltrating T cells occurs gradually (165,166). Initially, a population of tumor-specific T cells is depleted during thymic maturation

due to negative selection, limiting the antigen recognition ability of the remaining auto/tumor-specific T cells (167). Subsequently, in a non-inflammatory environment, the lack of innate stimulators (such as lipopolysaccharide) results in the weak activation of antigen-presenting cells, leading to the poor activation of tumor-specific T cells (167). Finally, the TME induces and maintains T cell hypo-responsiveness (168). PD-1 is a marker of T cell failure (164). Tumor-infiltrating $CD8^+$ T cells express PD-1, which binds to PD-L1 on tumor cells, resulting in the inhibition of T cell activation and antitumor immunity. Treg cell-mediated immunosuppression is associated with the upregulation of PD-1 (169). Currently, PD-1 inhibitors are widely used in the treatment of various tumors (such as in lung and gastric cancer) and can effectively improve disease prognosis (170,171).

DLBCL is a prevalent type of non-Hodgkin's lymphoma. Study of the TME in DLBCL is becoming an increasingly popular research topic in the field of immunotherapeutics. Previous studies demonstrate immunological dysfunction in TILs and elevated PD-1 expression levels, both of which are associated with poor prognosis (172,173). Although PD-1 inhibitors (such as pembrolizumab and nivolumab) do not demonstrate objective remission rates in DLBCL, PD-1 inhibitors are considered safe, with good tolerance and promising prospects (174,175). Anti-PD-1 therapy is indicated to confer notable synergistic effects with vitamin C in a lymphoma mouse model (30,176,177). Vitamin C boosts antitumor immunity and improves anti-PD-1 therapy by increasing chemokine production and TIL (178). Vitamin C is known to enhance the activation of tumor-specific T cells by improving the antigen presentation ability of DCs (152). It also enhances T cell penetration into the tumor area to increase antitumor efficacy in combination with anti-PD-1 drugs (179). However, research on the role of Tregs in the antitumor effects of vitamin C remains warranted.

Tumor-associated macrophages (TAMs). Macrophages serve a key role in both innate and adaptive immunity. They are primarily derived from bone marrow-derived monocytes and their phenotype and function depend on the surrounding microenvironment. There are two types of macrophages: Classical activation (M1 macrophages) and alternative activation (M2 macrophages) (180). In different tissue environments, macrophages can differentiate into specific subtypes. M1 macrophages function to reduce inflammation, as well as to phagocytose and kill target cells (181). By contrast, M2 macrophages are involved in angiogenesis, tissue repair, and tumor progression (182).

TAMs are the most common immune cells that infiltrate the TME. Their role in promoting tumor growth has been extensively studied (183). Recent studies have shown that macrophages in the TME are continuously transitioning between two states: M1 and M2 (184,185). During the early stages of tumor growth, macrophages primarily differentiate into tumor infiltrating M1 macrophages to promote the antitumor immune response. However, in the latter stages, they primarily differentiate into the M2 subtype to counteract the antitumor effect. In the TME, TAMs are predominantly of the M2 variety (178). They primarily promote angiogenesis, invasion, metastasis and tumor cell proliferation (180). TAMs exert their antitumor effects through three main mechanisms: i) Secretion of inhibitory cytokines, which inhibit $CD8^+$ T lymphocytes from destroying tumor cells, such as TGF-β and IL-10 (181); ii) regulation of the epithelial-mesenchymal transition (EMT) and extracellular matrix remodeling, which contributes to the malignant biological characteristics and migration of tumor cells (182,183); and iii) tumor angiogenesis, in which growth factors (such as platelet-derived growth factor and VEGF) released by TAMs aid in tumor angiogenesis, creating blood vessels that promote tumor cell spread. These effects were indicated in several malignant types of tumor, including prostate, bladder and breast cancer (186). Therefore, TAMs serve a critical role in tumor development.

In DLBCL, TAMs are associated with disease progression. Their expression is inversely associated with DLBCL prognosis (187). A number of experimental studies reveal that vitamin C can induce the transformation of M2 macrophages into M1 macrophages to markedly enhance the oxidative toxicity of M1 macrophages, promoting the infiltration of tumor-killing T cells and enhancing antitumor effects (188-190). In summary, pharmacological doses of vitamin C, acting as a pro-oxidant, can promote the polarization of TAMs towards the M1 subtype in the TME. This promotes antitumor effects and facilitates TME remodeling.

MDSCs. MDSCs form a heterogeneous population of cells that suppress the immune system within the TME. They primarily inhibit the cytotoxic activity of T cells and natural killer cells, serving a role in tumor-mediated immune escape (127,191). MDSCs are primarily immature myeloid cells, consisting mainly of monocytes (M-MDSC) and polymorphonuclear cells (PMN-MDSC). Studies demonstrate that M-MDSC and PMN-MDSC are expanded in the majority of solid tumors, such as hepatocellular carcinoma (192) and melanoma (193). Although PMN-MDSC forms the predominant subgroup, a study by Azzaoui *et al* (194) demonstrates that M-MDSC is the most inhibitory subgroup, with the absence of PMN-MDSC not altering the tumor incidence. In colorectal and breast cancer, monocytes/M-MDSC can differentiate into TAMs within the TME and interact with TAMs to inhibit antitumor effects (195-197). This suggests that targeting MDSCs may enhance antitumor effects. It has been observed that a notable number of MDSCs can effectively impair T cell responses in DLBCL (194). Previous studies suggest that MDSCs serve a key role in early drug resistance following R-CHOP treatment for DLBCL (198,199). At present, to the best of our knowledge, the direct impact of vitamin C on MDSCs has not been studied. However, it is likely that vitamin C can mediate regulatory effects on DCs, TILs and TAMs within the TME to influence MDSCs by modulating the TME (200).

4. Challenges and perspectives

AA is a water-soluble vitamin with various chemical and physical properties. It should be stored in a shaded environment. When administered at high doses (1-1.5 g/kg), vitamin C exhibits pro-oxidant properties and may be beneficial in antitumor therapy (201,202). Previous studies indicate that when taken orally, vitamin C reaches lower plasma concentrations compared with intravenous (IV) administration (33,74). The

majority of existing *in vivo* studies indicate that high doses of AA (1-4 g/kg) administered through IV or intraperitoneal injection can inhibit tumor growth by 40-60%.

The present review investigated the role of vitamin C in treating DLBCL, but several challenges remain that limit its clinical application. These challenges include determining the optimal dose and blood concentration of vitamin C, in addition to its concentration at the tumor site. High-dose vitamin C has demonstrated antitumor effects in various studies, with doses ranging from 1.5 g/kg (32,202), 10 g/day (203) and 50-100 g per dose (2-3 times a week) (204). However, no conclusive data support an ideal dose and/or frequency of administration that would maximize its antitumor benefits. It is also unclear whether the antitumor effect is dose-independent or associated with the appropriate blood concentration (205,206). Therefore, further research is needed to determine the optimal vitamin C treatment strategy to maximize cellular uptake whilst preventing cytotoxicity.

Another challenge is understanding the role of SVCT2 in the transport of vitamin C. SVCT2 has low saturation and high affinity (207), but its involvement is crucial for effective drug distribution. In addition, the growth and hypoxic environment of tumor blood vessels in DLBCL can reduce the permeability and concentration of antitumor drugs in the TME (208), blocking the access of vitamin C to the tumor site. SVCT2 protein cannot be detected in the cell membranes of renal cell carcinoma and breast cancer cells, but it is unclear whether this affects the transport of vitamin C (209). There is insufficient information on how SVCT2 is distributed and expressed in tumor cells. Therefore, further research is needed to elucidate how SVCT2 is expressed and distributed in tumor cells to enhance the concentration of vitamin C in the TME. Numerous studies have reported that vitamin C has anticancer properties and can enhance the efficacy of antitumor treatments (33,153). However, relevant *in vitro* and *in vivo* experiments involving DLBCL are currently lacking. Therefore, further research is needed to clarify the anticancer efficacy of vitamin C in DLBCL, its associated signaling pathways and its impact on the TME. The present paper aimed to establish a theoretical and empirical foundation for the clinical application of vitamin C as a supplementary agent in cancer therapy.

5. Conclusions

DLBCL is the most common subtype of non-Hodgkin's lymphoma and is distinguished by its aggressive nature and unfavorable prognosis. The present review investigated the mechanisms through which vitamin C may influence the efficacy of DLBCL treatment, proposing a potential association between vitamin C and DLBCL, which may enhance the antitumor effectiveness of pharmacological therapies through various mechanisms or pathways. However, further research is required to clarify the specific mechanisms involved and to investigate the potential therapeutic implications within the framework of DLBCL management.

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Authors' contributions

CR took part in the conceptualization, figure curation and writing of the original draft. YW and ML took part in the conceptualization, supervision and editing and reviewing the manuscript. YL took part in the conceptualization and figure curation. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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