

The roles of curcumin in regulating the tumor immunosuppressive microenvironment (Review)

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Abstract. Cancer is a harmful threat to human health. In addition to surgery, a variety of anticancer drugs are increasingly used in cancer therapy; however, despite the developments in multimodality treatment, the morbidity and mortality of patients with cancer patients are on the increase. The tumor-specific immunosuppressive microenvironment serves an important function in tumor tolerance and escape from immune surveillance leading to tumor progression. Therefore, identifying new drugs or foods that can enhance the tumor immune response is critical to develop improved cancer prevention methods and treatment. Curcumin, a polyphenolic compound extracted from ginger, has been shown to effectively inhibit tumor growth, proliferation, invasion, metastasis and angiogenesis in a variety of tumors. Recent studies have also indicated that curcumin can modulate the tumor immune response and remodel the tumor immunosuppressive microenvironment, indicating its potential in the immunotherapy of cancer. In this review, a brief introduction to the effects of curcumin on the tumor immune response and tumor immune microenvironment is provided and recent clinical trials investigating the potential of curcumin in cancer therapy are discussed.

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1. Introduction

Cancer remains one of the diseases with a poor prognosis, which results in a high mortality rate (1). According to the 2019 American Cancer Annual Report, approximately 1,762,450 new cases of cancer and 606,880 cancer-associated deaths were predicted in the United States in 2019, with no significant improvement compared with the previous year (1,2). The prevalence of cancer and associated death statistics are also not optimistic in China; in 2015, 4,292,000 new cases of cancer were estimated and more than half of the cases were predicted to result in cancer-associated death in 2016 (3). Enormous economic burdens have been placed on nations and society in response to the increasing numbers of patients with cancer. For example, health care spending on patients with breast cancer in the United States has increased in recent years and the cost of treating patients with human epidermal growth factor receptor-2-positive breast cancer is predicted to rise from \$2.7 billion in 2012 to \$3.6 billion in 2035 (4). Therefore, cancer prevention and treatment is currently a major problem. Identifying natural food ingredients with low toxicity and minimal adverse side effects that can effectively target tumors may be valuable to cancer prevention and early treatment.

Curcumin, also known as diacetylmethane, is a bioactive lipophilic flavonoid polyphenol compound extracted from turmeric, the rhizome of the ginger family. Curcumin is an orange-yellow crystalline powder and its molecular weight is 368.38 (5). Curcumin is almost insoluble in water but soluble in ethanol and dimethyl sulfoxide (5). In addition to the use of curcumin as a food flavoring, curcumin has also been used in India and South Asia to treat a variety of diseases, including fever, gastrointestinal disorders, skin diseases, rheumatism, hepatitis, arthritis and burns due to its non-toxic, anti-oxidant, anti-inflammatory and anti-infection properties (6-9).

Previous findings have shown that curcumin also has significant anticancer effects. Curcumin has been shown to inhibit proliferation, invasion, metastasis and angiogenesis, weaken chemoresistance and inhibits the immortalization of cancer cells. Curcumin has been shown to modulate signaling pathways involving Janus kinase (JAK)/signal transducers and activators of transcription (STAT), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), Wnt/ β -catenin, vascular endothelial growth factor (VEGF)/vascular endothelial growth factor

receptor (VEGFR) and genes such as *cyclin D1*, *TP53*, *BAX*, *BCL-2*, *hTERT* and *MMPs* (10-14); these pathways have been confirmed to modulate the proliferation, migration and invasion, cell cycle and cell apoptosis of tumor cells (15-17).

During tumor progression, the tumor immunosuppressive microenvironment is considered to serve a crucial role in immune escape and subsequent progression of tumors (18). In addition to curcumin inhibiting tumors through the abovementioned mechanisms, curcumin also enhances the anticancer immune response, remodels the tumor immunosuppressive microenvironment and exerts influence on lymphocyte infiltration, such as cytotoxic T cells (CTL) (19), Foxhead p3 (FOXP3)+ regulatory T cells (FOXP3+Tregs) (20) and natural killer (NK) cells (21), and the M1 to M2 macrophage transformation in the process of innate immunity (22).

The present review briefly summarizes the important roles of curcumin in the treatment of tumors, with a focus on the functions of curcumin in tumor immunity regulation, and describes recent clinical trials investigating the potential of curcumin in cancer therapy.

2. Anticancer effect of curcumin

Curcumin can inhibit various malignant biological behaviors of tumor cells, including tumor proliferation and growth, invasion, metastasis, neoangiogenesis and chemoresistance, as summarized in Fig. 1.

Curcumin and tumor proliferation. Previous studies have shown that curcumin can regulate tumor proliferation and growth through multiple signal pathways (10,23). Human trophoblastic surface antigen-2 (Trop2) is a cell surface glycoprotein, which serves an essential role in tumor progression and tumorigenesis (24). A recent study in bladder cancer showed that Trop2 abolished the increased expression of p27 caused by curcumin, thereby mediating tumor proliferation (25). Therefore, Trop2 may be an intermediate link in the inhibition of the tumor proliferation signal pathway by curcumin, with potential for therapeutic targets. However, curcumin has also been shown to inhibit pancreatic cancer cells proliferation through p21 or the p27/Cyclin D1/PI3K/Akt signaling pathway (26).

The Wnt/ β -catenin signaling pathway is involved in the mechanisms underlying the function of curcumin in hindering tumor growth and proliferation. Wang *et al* (27) and Srivastava and Srivastava (28) demonstrated that curcumin inhibits the proliferation of lung cancer cell lines. Wang *et al* (27) also demonstrated that curcumin inhibited tumor oxidative stress with subsequent inactivation of the Wnt/ β -catenin signaling pathway. Moreover, phosphorylation-mediated inactivation of the JAK2/STAT3 signaling pathway is also involved in the anti-proliferation effect of curcumin on osteosarcoma cells (29). Interestingly, in lung cancer, increased expression levels of long non-coding RNA (lncRNA) UCA1 counteracted the anticancer proliferation effects of curcumin, suggesting that lncRNA UCA1 may be involved in curcumin-mediated inactivation of Wnt and mTOR signaling pathways (30).

Curcumin and tumor apoptosis. Apoptosis is the process of programmed cell death that is caused by damage to DNA

or other organelles, such as mitochondria and endoplasmic reticulum, when cells are externally stimulated (31). Apoptosis can be induced by several exogenous pathways, including pathways mediated by death receptor Fas and the tumor necrosis factor receptor family (32,33), cytokine-mediated endogenous pathways and caspase-12 activation caused by endoplasmic reticulum stress (34). Curcumin is hypothesized to mediate tumor cell apoptosis through these exogenous pathways. Synthetic curcumin non-spherical mesoporous silica nanoparticles can increase the carrying capacity and saturability of curcumin (35). In-depth studies have shown that curcumin binds apoptotic proteins, such as caspase-3 (36), phosphatase and tensin homolog deleted from chromosome 10 and poly ADP-ribose polymerase (37), inducing mitochondrial damage and thereby promoting tumor cell apoptosis (35). Another synthetic nanomaterial, chitosan nanoparticles loaded with demethoxycurcumin in combination with cisplatin, down-regulates the expression levels of thymidine phosphorylase required for DNA self-repairing pyrimidine salvage pathways and induces apoptosis in non-small cell lung cancer (NSCLC) cell lines (38). Moreover, Wang *et al* (27) demonstrated that in NSCLC, curcumin decreases the mitochondrial transmembrane potential and increases the accumulation of reactive oxygen species (ROS) in cells, inducing DNA and mitochondrial damage-mediated apoptosis (39).

Curcumin, tumor invasion and metastasis. The invasion and metastasis ability of tumor cells is a common cause of tumor treatment failure (40) and curcumin can significantly inhibit these activities in tumor cells. A study of oral squamous cell carcinoma showed that curcumin reduced cell adhesion and inhibited proliferation of tumor cells with mesenchymal features (41). In addition, tumor growth factor- β 1 (TGF- β 1) is an important promoter of the epithelial-mesenchymal transition (EMT) in tumor cells. In liver cancer, curcumin can decrease the expression levels of TGF- β 1, inhibit the phosphorylation and nuclear translocation of Smad2, reduce the specific binding of Smad2 to the Snail promoter, downregulate Snail expression levels and inhibit EMT by competing with TGF- β 1 (42). A moderate amount of ROS accumulation has been reported to be beneficial to tumor progression (43). Curcumin reversed the effect of H₂O₂ and ROS on pancreatic cancer cell invasion and metastasis by specifically inhibiting the extracellular regulated protein kinase (ERK)/nuclear factor kappa-B (NF- κ B) signal pathway (44).

Curcumin and tumor neoangiogenesis. The growth of a solid tumor depends on tumor neovascularization (45). Angiogenic factors such as VEGF, hypoxia-inducible factor-1 α , angiopoietin-1 and -2 and interleukin-2, -8 and -17 are closely associated with tumor neovascularization (46,47). These factors can be modulated by curcumin to remodel tumor neovascularization. VEGF is a crucial target for curcumin to regulate tumor angiogenesis (48). Curcumin inhibits the expression levels of VEGF, reduces its extracellular secretion and binds to the VEGF receptor, inhibiting the VEGF downstream signaling pathway (48). Curcumin can block hepatocyte growth factor induced EMT in lung cancer cell lines and the angiogenesis of human umbilical vein endothelial cells through targeting c-Met/PI3K/Akt/mTOR signaling

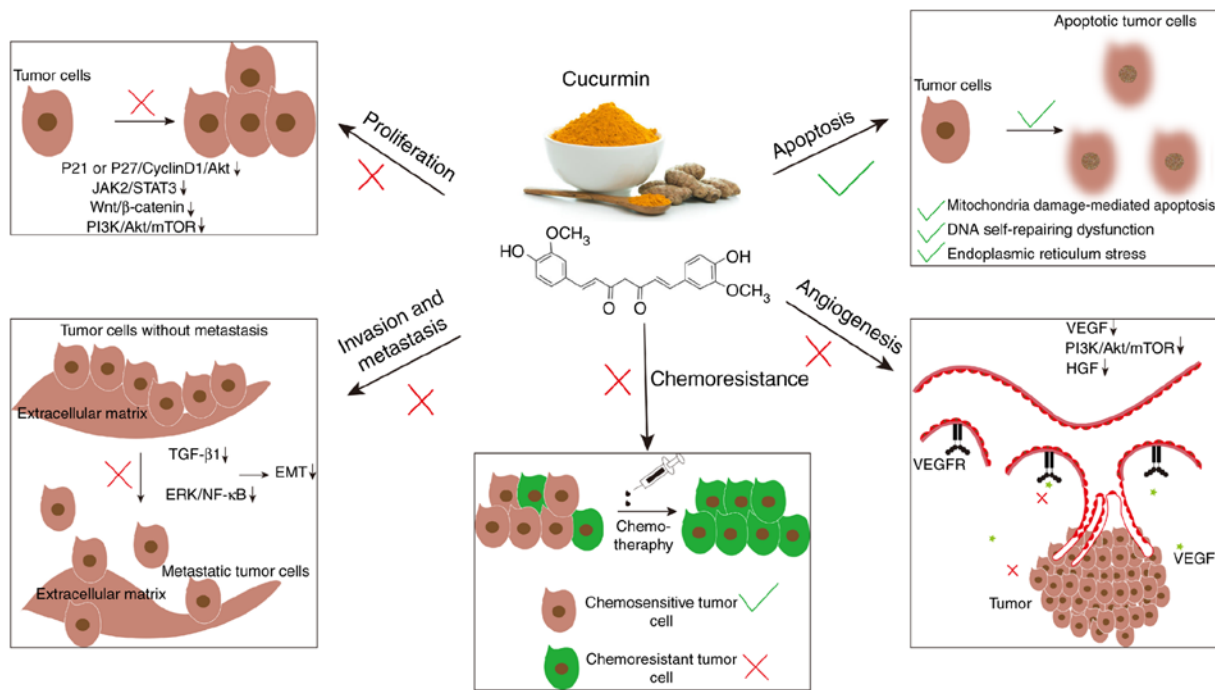


Figure 1. Curcumin exerts various effects on the malignant activities of tumor cells. Curcumin inhibits tumor cell proliferation through p21 or p27/CyclinD1/PI3K/Akt, JAK2/STAT3, Wnt/β-catenin and PI3K/Akt/mTOR signal pathways. Curcumin induces tumor cell apoptosis by mitochondria damage-mediated apoptosis, DNA self-repairing dysfunction and endoplasmic reticulum stress. Curcumin inhibits tumor cell EMT, which prevents tumor cell invasion and metastasis through downregulation of TGF-β expression and inactivation of TGF-β downstream signaling pathways. Neoangiogenesis is blocked by curcumin through decreasing the expression of VEGF and HGF, inactivating the PI3K/Akt/mTOR signaling pathway. Chemoresistance can be overcome by curcumin, which mediates cancer stem cell apoptosis. PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; mTOR, mammalian target of rapamycin; TGF-β1, tumor growth factor β1; ERK, extracellular regulated protein kinase; NF-κB, nuclear factor-κB; EMT, epithelial-mesenchymal transition; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; HGF, hepatocyte growth factor.

pathway, which indicated the anti-metastasis and anti-angiogenesis ability of curcumin in cancer treatment (49). The PI3K/Akt/mTOR signaling pathway is blocked by curcumin targeting c-Met, and curcumin abolishes the angiogenesis of human umbilical vein endothelial cells induced by hepatocyte growth factor.

Curcumin and tumor chemoresistance. The intrinsic resistance and adaptive resistance of tumors to chemotherapeutics are important reasons for chemotherapy failure (50). Therefore, identifying efficient chemotherapy sensitizers is important to address this problem. Curcumin has been demonstrated to exert specific functions in resensitizing certain types of cancer to chemotherapy, such as colorectal cancer and ovarian cancer. Chemotherapeutic drugs, such as irinotecan, 5-fluorouracil and capecitabine, show a decline in efficacy during colorectal cancer therapy and cancer stem cells (CSCs) are considered to influence this process (51). Curcumin increases the sensitivity of colon cancer cells to capecitabine by inducing apoptosis of CSCs (51). In addition, the combination of mitomycin C and curcumin downregulates the expression levels of anti-apoptotic proteins Bcl-2 and Bcl-w and induces the apoptosis of breast CSCs (52). Zhang *et al* (53) demonstrated that curcumin restores lncRNA MEG3 function in ovarian cancer cells and exosomal vesicles via demethylation, reduces the expression levels of miR-214, which can induce cell survival and cisplatin resistance through targeting the PTEN/Akt pathway (54).

3. The tumor immunosuppressive environment

The tumor microenvironment is complex and heterogeneous (55). O'Donnell *et al* (56) classified the tumor microenvironment into four types according to tumor mutation burden and the degree and subgroup of tumor infiltrating T cells. The different types of immune microenvironments, such as those that suppress and enhance the microenvironment, correspond to specific types of tumors and different tumor immunotherapeutics should be administered according to the different types of immune microenvironment (56). Immunosuppressive cells in the tumor microenvironment can facilitate the progression of tumors through generating tumor immunosuppressive microenvironment (57). Previous research has suggested that in the early stage of tumors, both innate and adaptive immunity are active in immune surveillance, thereby suppressing spontaneous tumorigenesis, which is usually transient (58,59). Tumor-associated antigens are considered to be a necessary component in stimulating the tumor immune response. Innate immune cells, such as dendritic cells (DCs) (59), macrophages and NK cells (21), recognize tumor-associated antigens and stimulate cytotoxic effects thereby killing the tumor cells. Moreover, antigen-presenting cells also present tumor-associated antigens to adaptive immune cells, such as CTLs or Th1 cells, to stimulate specific killing pathways against tumor cells (19). If a tumor is regenerated, the memory of adaptive immunity can exert the same killing effect (60). However, the mechanisms *in vivo* are

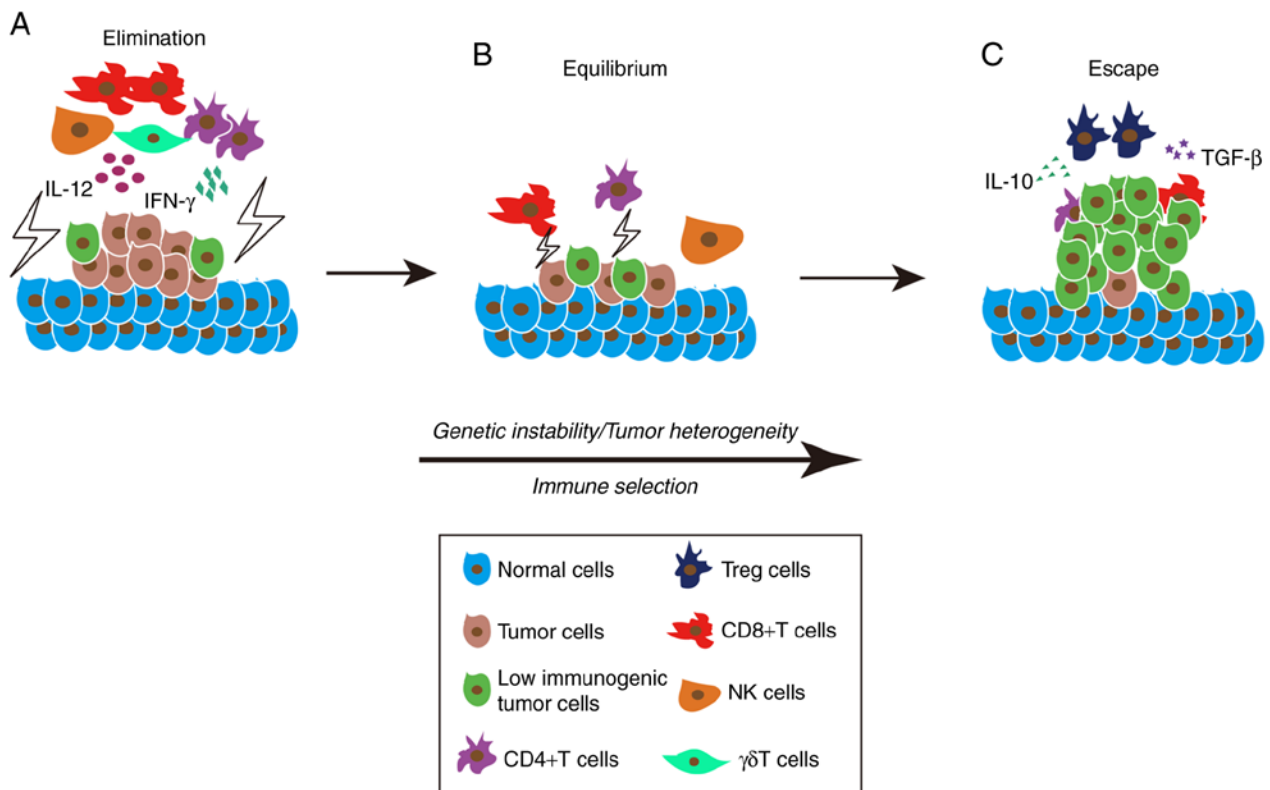


Figure 2. The three 'E's of cancer immunoediting. (A) Elimination: IFN- γ , IL-12 and other tumor suppressive cytokines are released by NK cells and $\gamma\delta$ T cells mediate perforin, granzyme, FasL and Trail-dependent cytotoxic effects in the early stage of tumor progression. Antigen-presenting cells present tumor-specific antigens to CD4+T cells, thereby recruiting specific CD8+ T cells to further kill tumor cells. (B) Equilibrium: Adaptive immunity prevents tumors from continuing to grow and confers immunogenicity to tumor cells to mediate immune recognition. Tumor cells can also block the constant immune system killing mechanism by gene mutations, which confer the ability of some tumor cells to escape from immune recognition. Therefore, tumor cells and the immune system reach an equilibrium state. (C) Escape: Tumor cells regulate the immune response of T cells and promote their apoptosis through releasing immunosuppressive cytokines, such as TGF- β and IL-10. In addition, increased intratumoral infiltration of CD4+CD25+FOXP3+Treg cells upregulates TGF- β and IL-10 expression levels and downregulates IL-2 expression levels. IFN, interferon; IL, interleukin; NK cells, natural killer cells; TGF- β , tumor growth factor β ; Treg, regulatory T cell.

more complex. First, tumor cells mediate immune escape by altering the composition of tumor infiltrating immune cells by recruiting multiple immunosuppressive cytokines, which induce increased production of Treg cells, antigen-tolerant M2 macrophages and DCs, and reducing the infiltration of CTLs, NK cells and NKT cells, resulting in loss of tumor immune surveillance function (61). Second, tumor-associated antigens can be non-tumor-specific and normal cells occasionally also produce the same antigen, mediating innate immune tolerance and leading to dysfunction of immune system recognition of tumor-associated antigens (62). Third, the lack of major histocompatibility complex class I on the surface of tumor cells can lead to the inability of the immune recognition of CD8+ cytotoxic T cells to mediate immune tolerance (63). In addition, upregulated expression of immunosuppressive ligands, such as programmed cell death-ligand 1, also mediates tumor immune tolerance (64). Subsequently, the immune cells in both innate and adaptive immunity become apoptotic due to the lack of stimulation of tumor-associated antigens and the inability to specifically recognize tumor cells, leading to the immune escape of tumors (65,66).

In addition, post-transcriptional modifications of some tumor-specific antigen genes, such as GIL1 in multiple myeloma (67) and hPMS1 in oral squamous cell carcinoma (68), may result in their downregulated expression or

complete silencing. The cancer-testis family is expressed on a variety of cell surfaces and hypomethylation of the cancer-testis family promoter facilitates gene expression and thus expression on the tumor cell surface; however, in contrast, demethylation of this promoter occurs in tumor cells mediating tumor immune tolerance (69). DNA methyltransferase or histone deacetylase activity can restore the gene expression of tumor-specific antigens to a certain degree, mediating anticancer immunity (70,71). However, Rosenthal *et al* (72) indicated that hypermethylation of gene promoters of mutant neoantigens was also a possible mechanism leading to tumor immunoediting in early stage NSCLC.

Increasing studies have shown that the interaction between the immune microenvironment and tumor cells is a process of dynamic equilibrium, which was called immunoediting by Dunn *et al* (73). Immunoediting is the entire process of editing and shaping the immunosuppressive microenvironment and is also a Darwinian selection process. Immunoediting consists of three phases: Elimination (also called immunosurveillance); equilibrium (also called cancer dormancy); and escape and collectively these are referred to as the 3 'E's' of immune editing (73). In the first phase, a growing tumor recruits innate immune cells such as NK cells and $\gamma\delta$ T cells, which mediate perforin, granzyme, FasL and Trail-dependent cytotoxic effects through releasing interferon- γ (IFN- γ),

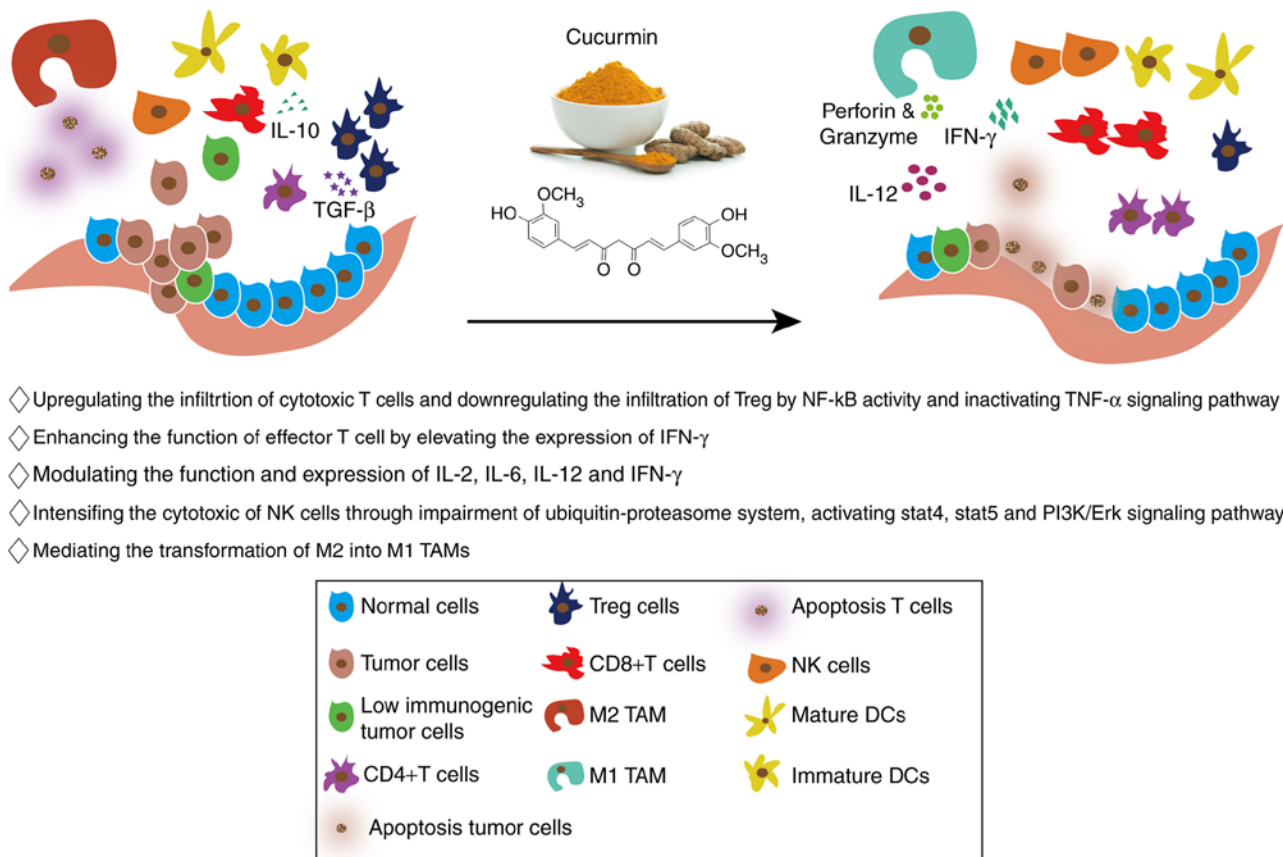


Figure 3. The role of curcumin in tumor immunomodulation. The shaping of the tumor immunosuppressive microenvironment is induced by tumor cell secretion of immunosuppressive cytokines, such as IL-10 and TGF-β, apoptosis and malfunction of effector T cells and the infiltration of Treg cells. Curcumin remodels the tumor immunosuppressive microenvironment by: Regulating the infiltration of cytotoxic T cells and Treg by restoring NF-κB activity, inactivating the TNF-α signaling pathway; enhancing effector T cells function by elevating the expression of IFN-γ; modulating the function and expression of IL-2, IL-6, IL-12 and IFN-γ; intensifying the cytotoxic of NK cells through impairment of ubiquitin-proteasome system, activating STAT4, STAT5 and PI3K/Erk signaling pathway; and mediating the transformation of M2 TAMs into M1 TAMs. Treg, regulatory T cell; NK cells, natural killer cells; DCs, dendritic cells; TAM, Tumor-associated macrophage; TGF-β, Tumor growth factor β; IL, Interleukin; IFN, interferon.

IL-12 and other tumor suppressive cytokines (74,75). In addition, antigen-presenting cells present tumor-specific antigens to CD4+T cells thereby recruiting specific CD8+ T cells to kill tumor cells (76). In the second phase, adaptive immunity, rather than innate immunity, prevents tumors from continuing to grow and confers immunogenicity to tumor cells to mediate immune recognition (77). Tumor cells hijack the various mechanisms mentioned above to inhibit the immune system killing mechanisms allowing some of the less immunogenic tumor cells to survive (77). In addition, tumor cell instability caused by gene mutations also confers the ability of some tumor cells to escape from immune recognition (78). Thus, tumor cells and the immune system can reach an equilibrium state, and tumor proliferation and tumor apoptosis also reach an equilibrium state (77). This balancing process may be inclined toward tumor cell elimination or tumor cell escape depending on the progression of tumor and may last for months to years (79). In the third phase, the tumor further grows and becomes a clinically detectable tumor, which gradually suppresses the immune system and shapes the immunosuppressive microenvironment (80). Tumor cells regulate the immune response of T cells and promote their apoptosis through releasing immunosuppressive cytokines, such as TGF-β, IL-10, galectin and indole

2,3-dioxygenase (81). In addition, intratumoral infiltration of CD4+CD25+FOXP3+Tregs in tumor cells increases TGF-β and IL-10 expression levels, IL-2 expression level knockdown, and reduces co-stimulation and activation of DCs (82). The three phases of immune editing ultimately lead to the immune escape of tumor cells as summarized in Fig. 2.

4. The role of curcumin in tumor immunomodulation

Curcumin not only inhibits tumors by affecting the biological behaviors of tumor cells, but it also regulates the composition of different components in the tumor immune microenvironment, so that the immune microenvironment is conducive to tumor killing (83). The detailed roles of curcumin in tumor immunomodulation are shown in Fig. 3.

Curcumin regulates the number of various infiltrating T cells. In the tumor immunosuppressive microenvironment, due to the lack of effective presentation of tumor-specific antigens and the influence of various inhibitory cytokines, a large number of inactivated CD4+ and CD8+ T cells and CTLs undergo apoptosis (78). Curcumin has been shown to effectively reverse this process. During tumor generation, tumor cells can induce atrophy of the thymus, reduce the

production of mature T cells and enable escape from the adaptive immune response. Tumor cells induce apoptosis of T cells by interfering with the production of NF- κ B in T cells, making T cells susceptible to TNF- α -mediated apoptosis (84). Curcumin neutralizes oxidative stress of tumor cells, restores NF- κ B activity and reactivates the TNF- α signal pathway, thereby enhancing the ability of T cells to resist apoptosis (84). Bhattacharyya *et al* (84) found that mechanisms of tumor cell immune escape included loss of effector T cells and memory T cell subsets, secretion of type II cytokines and increased proliferation of Treg cells. In Ehrlich's ascites carcinoma-bearing nude mice treated with curcumin, curcumin inhibited the apoptosis of T cells, expanded the number of central memory cells and effector memory T cells and disabled the functions of Treg cells, thus successfully reversing the tumor immunosuppressive microenvironment (84). A clinical trial also demonstrated that in patients with colon cancer, transcription and expression of the *FOXP3* gene was inhibited by curcumin, thereby permitting the conversion of FOXP3+Treg cells into Th1 cells (85). Curcumin also abolished the induction of IFN- γ secretion from CD4+ T cells by inhibiting Treg cell function (85). Zou *et al* (86) also demonstrated the inhibition of Treg function by curcumin in lung cancer.

Curcumin enhances the function of effector T cells. The effect of curcumin on T cells not only increases the number of effector T cells or to induce the infiltration of Treg cells, but more importantly, enhances the cell killing function of effector T cells inhibited by tumor cells (87). A novel nanocurcumin significantly increased the expression levels of co-stimulatory molecule CD86 on the surface of DCs and decreased the levels of pro-inflammatory factors secreted by effector T cells *in vitro* (87). Moreover, curcumin was also reported to increase effector T cell-induced cytotoxicity against esophageal cancer cells (87). Adoptive T-cell therapy has become an important research field of tumor immunotherapy. Autologous reinfusion of effector T cells, which proliferate *in vitro*, can increase the number of exogenous effector T cells and induce tumor apoptosis in humans (88). However, due to the numerous immunosuppressive cytokines in the tumor immunosuppressive microenvironment, the efficacy of adoptive T-cell therapy is often transient and prone to failure (89). In the E.G7 mouse T lymphoma model, the combination of adoptive T-cell therapy and curcumin led to increased intratumoral infiltration of CD8+ T cells at the end of the course and curcumin increased the levels of IFN- γ secreted by CD8+T cells (90). These results showed that combination therapy had greater efficacy compared with adoptive T-cell therapy alone. Different doses of curcumin were administered to mice bearing tumors derived from the 3LL breast cancer cell line and a low dose of curcumin led to delayed tumor growth and prolonged survival of the mice. An *in vitro* study also demonstrated that low doses of curcumin increased the number of CD8+T cells and enhanced their IFN- γ secretion capacity (91). Administration of high doses of curcumin, however, reduced the number of CD8+ T cells, indicating that the anti-tumor effect of curcumin may be dose-dependent (91). Moreover, the combination of an intravenously administered polyethylene glycol curcumin coupler, rather than an oral formulation, and a tyrosinase-related peptide vaccine for the treatment of mela-

noma significantly increased the CTL response and IFN- γ expression levels compared with the vaccine alone, while the combination therapy also decreased the levels of tumor immunosuppressive cells, such as marrow-derived suppressor cells and Treg cells (92).

Curcumin modulates the function of cytokines. During the gradual shaping of the tumor immunosuppressive microenvironment, various cytokines are considered to serve a crucial role in regulating the composition and proportions of the cancer-promoting immune cell component and the cancer-suppressing immune cell component (93). Curcumin, as a tumor inhibitor, not only facilitates the secretion of cancer-promoting cytokines, but also inhibits the secretion of cancer-suppressing cytokines, thereby remodeling the tumor immunosuppressive microenvironment (94). IL-2 plays a dual role, stimulating and inhibiting the tumor immune response. Since high-affinity IL-2 receptor (IL-2R) is highly expressed on the surface of Treg cells, IL-2 is a tumor promoter activating Treg cells (95). Curcumin directly inhibits the interaction between IL-2 and IL-2R α (CD25), thus inhibiting the activation of Treg cells (96). A previous study reported that curcumin inhibits tumor cell apoptosis by downregulating the levels of the tumor immunosuppressive cytokine IL-10, resulting in JAK/STAT signal pathway malfunction (97). Curcumin also downregulates the levels of TGF- β and IL-10 in Treg cells, reduces their ability to stimulate Treg cells and decreases the Treg cell infiltration in tumors (86). An increased expression level of IL-6 in triple-negative breast cancer is considered to mediate the tumor immunosuppressive microenvironment, leading to tumor vaccine therapy failure (98). Curcumin is a specific inhibitor of IL-6, and the combination of curcumin and breast cancer vaccine Listeriaat-Mage-b resulted in decreased IL-6 expression levels and increased IL-12 and IFN- γ levels, resulting in greater anti-tumor efficacy compared with using vaccine alone (99). However, Bill *et al* (100) showed different results. Although previous reports showed that curcumin promoted tumor apoptosis (36-38), curcumin-pretreated human A375 melanoma cells led to STAT1 phosphorylation inhibition and decreased downstream IFN- γ and IFN- α expression levels. In addition, co-culture of NK cells and these curcumin-pretreated melanoma cells also reduced IL-12-induced IFN- γ expression, which indicated curcumin may also inhibit the expression of cancer-suppressing cytokines.

Curcumin intensifies the cytotoxicity of NK cells. Curcumin not only influences adaptive immunity through regulating T cell proliferation and apoptosis, but it also influences NK cell-mediated innate immunity (101). In a study of breast cancer, exosomes secreted by tumor cells abolished the activation of NK cells via IL-2 by inhibiting the JAK3/STAT5 signal pathway (102). Curcumin may inhibit the cytotoxicity of exosomes to circulating immune cells by disrupting the ubiquitin protease system and increasing the ubiquitinated exosomal proteins that interfere the function of normal exosomal proteins (102). Another study in breast cancer showed that curcumin increased the expression of CD16+ and CD56^{dim} on the surface of NK-92 cells (103). In addition, the effect of curcumin on promoting cytotoxic ability of NK cells

Table I. Curcumin as an anticancer agent or adjuvant agent in clinical trials.

Cancer type	Trial status	Trial	Institution	Identifier no.	Last updated
Pancreatic Multiple myeloma	Completed	Gemcitabine with curcumin for pancreatic cancer	-	NCT00192842	2010
	Completed	Curcumin (diferuloylmethane derivative) with or without bioperine in patients with multiple myeloma	M.D. Anderson Cancer Center	NCT00113841	2011
	Completed	Curcumin bioavailability in patients with glioblastoma	Department of Neurosurgery, Johann Wolfgang Goethe-University	NCT01712542	2013
Advanced cancer	Completed	Phase I study of surface-controlled water soluble curcumin (THERACURMIN CR-011L)	M.D. Anderson Cancer Center	NCT01201694	2015
Head and neck	Completed	Curcumin biomarker trial in head and neck cancer	Shreveport and Feist-Weiller Cancer Center	NCT01160302	2016
Endometrial	Completed	Effect of curcumin addition to standard treatment on tumor-induced inflammation in endometrial carcinoma	University Hospital KU	NCT02017353	2016
Prostate	Completed	Comparison of duration of treatment interruption with or without curcumin during the off treatment periods in patients with prostate cancer undergoing intermittent androgen deprivation therapy	Leuven Campus Gasthuisberg	NCT03211104	2017
Breast	Ongoing	Curcumin in combination with chemotherapy in breast cancer	National Center of Oncology, Yerevan, Armenia	NCT03072992	2017
Colorectal	Ongoing	Combining curcumin with folfox chemotherapy in patients with inoperable colorectal cancer	Dept Oncology, Leicester Royal Infirmary	NCT01490996	2017
Rectal	Ongoing	Radiation therapy and capecitabine with or without curcumin before surgery in treating patients with rectal cancer	M.D. Anderson Cancer Center	NCT00745134	2018
Prostate	Ongoing	Trial of curcumin to prevent progression of low-risk prostate cancer under active surveillance	The University of Texas Southwestern Medical Center	NCT03769766	2019
Bladder	Ongoing	Curcumin and piperine in reducing inflammation for ureteral stent-induced symptoms in patients with cancer	Mayo Clinic	NCT02598726	2019
Lung	Ongoing	Phase II trial to modulate intermediate endpoint biomarkers in former smokers	H. Lee Moffitt Cancer Center and Research Institute	NCT03598309	2019

is also associated with the activation of STAT4 and STAT5 in NK cells and the suppression of pERK and PI3K expression in curcumin-induced breast cancer cells (103). In a study of pancreatic cancer, curcuminoids enhanced the ability of NK cells to secrete IFN- γ and promoted the killing effect of NK cells in pancreatic cancer cell lines (104).

Curcumin mediates the transformation of M2 into M1 macrophages. Tumor-associated macrophages (TAMs) are classified into inducible nitric oxide synthase (NOS) (+) M1 macrophages and ARG1 (+) M2 macrophages according to their function following a strict binary classification, which was proposed by Mills *et al* (105). The former exhibit tumor-suppressing functions while the latter show tumor-promoting ability. M1 TAMs show high expression levels of IL-12 and low expression levels of IL-10, whereas M2 TAMs exhibit the opposite expression (106). In a study of HPV+ tumors, injection of TriCurin, a synergistic formulation of curcumin, resveratrol and epicatechin gallate into tumor-bearing mice transformed ARG^{high}, IL-10^{high}, iNOS^{low}, IL-12^{low} M2 TAMs into ARG^{low}, IL-10^{low}, iNOS^{high}, IL-12^{high} M1 TAMs. Subsequently, M1 TAMs induced STAT1 and NF- κ B (p65) expression, subsequently increasing the expression levels of IL-12 and thereby activating NK cells and CTLs, resulting in cytotoxicity (107). The same mechanism of action was also demonstrated in malignant glioma (108,109).

5. Recent clinical trials on curcumin

Since 1987, when Kuttan *et al* (110) first conducted a clinical trial of curcumin for the treatment of external cancerous cancer, several clinical trials of curcumin alone or in combination with other cancer therapeutics have been widely carried out. At present, randomized, controlled, double-blind clinical trials of curcumin are mainly concentrated on pancreatic cancer (111), colorectal cancer (112), prostate cancer (113) and breast cancer (114), whereas clinical trials for other tumors are currently underway. Curcumin is being investigated in clinical trials of pancreatic cancer as a chemosensitizer because of the very low response rate (<10%) of pancreatic cancer to traditional chemotherapeutic drugs and targeted drugs, such as gemcitabine and erlotinib (115). As early as 2008, a clinical trial of 25 patients with advanced pancreatic cancer showed that despite the low bioavailability rate of the curcumin oral formulation, the formulation can be tolerated and had good clinical biological activity in several patients (116). One of the patients had a progression-free survival of >18 months, which was longer compared the longest survival (12 months) in the prior study (115). In addition, administering curcumin significantly downregulated the expression levels of NF- κ B, cyclooxygenase and phosphorylated STAT3 in peripheral blood mononuclear cells (116). By contrast, in another study, 17 patients with unresectable pancreatic cancer were administered oral curcumin (8 g/d) and intravenous gemcitabine, but the results were unsatisfactory due to severe abdominal discomfort and abdominal pain caused by the oral curcumin formulation (117). However, in another later phase I/II clinical trial, the same oral dose of 8 g of curcumin combined with gemcitabine resulted in a median survival of 161 days for pancreatic cancer patients and a 1-year survival rate of 19%

and most patients were able to tolerate this dose without serious adverse effects (118). Therefore, an oral dose of 8 g/d curcumin is considered as a chemosensitization dose for pancreatic cancer.

To address the low bioavailability of curcumin, a recent clinical trial investigated the combination of phospholipid-coated curcumin using nanotechnology and gemcitabine (111). Although the patient quality of life was not significantly improved during treatment, the patient drug response rate reached 27.3%, which was higher compared with the rate of 12% of gemcitabine alone, and the average progression-free survival and overall survival also reached 8.4 and 10.2 months, respectively (111). Therefore, curcumin combined with gemcitabine is may be a safe and effective therapy for wider application for pancreatic cancer treatment; however, before the combination of curcumin and gemcitabine therapy can become routine therapy for pancreatic cancer large multicentric randomized controlled trials need to be conducted. The recent ongoing and completed clinical trials of curcumin in diverse tumors are summarized in Table I by referring to clinicaltrials.gov.

6. Conclusions and future prospects

Curcumin, a traditional food ingredient, has been identified to serve versatile roles in the prevention and treatment of several diseases (119-121). Curcumin has also been identified to inhibit a variety of biological functions of tumors, including growth, proliferation, invasion, metastasis, apoptosis, angiogenesis and drug resistance of tumor cells (122). In the present review, highlighted the role of the tumor immunosuppressive microenvironment in tumor progression and the functions of curcumin in modulating and remodeling the tumor immunosuppressive microenvironment have been highlighted. Curcumin increases the number of effector T cells (78), reduces the infiltration of FOXP3+Tregs (85), inhibits cytokine-induced apoptosis of effector T cells and the expression of tumor immunosuppressive cytokines (87,94), enhances NK cell cytotoxicity and mediates M2 TAM transformation to M1 TAM (101,105), which can change the tumor immunosuppressive microenvironment and lead to the killing of tumor cells. Therefore, given the multiple functions and good biosafety of curcumin in inhibiting tumor progression, as a tumor-preventing food and tumor-assisted therapeutic drug, curcumin has potential in tumor treatment potential in combination with multimodal anticancer therapies. However, curcumin has several limitations in clinical practice such as its low bioavailability, drug dose-effect disproportion and poor water solubility (123). To address these problems, an increasing numbers of studies are focusing on how to enhance the tolerance of curcumin, improve the targeting of curcumin delivery, overcome low bioavailability and obtain better therapeutic effects (124,125). A variety of nano-curcumin formulations have been introduced, which have improved the anti-cancer effects of curcumin (126,127). It is considered that curcumin will serve a more important role in the prevention and treatment of cancer in the future.

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Authors' contributions

In this review, the concept and design was conducted by YW and JG. YW and JL drafted the manuscript. Tables and diagrams were generated by JL and BJ. Critical revision of the manuscript for important intellectual content was conducted by YW, JL and BJ. JG provided the funding support. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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