Biomedicine & Pharmacotherapy 121 (2020) 109570

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Antitumor effects of immunity-enhancing traditional Chinese medicine

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ARTICLE INFO

Keywords:
Traditional Chinese medicine
Cancer
Antitumor immunity
Adaptive immunity
Innate immunity

ABSTRACT

Traditional Chinese Medicine (TCM) has been traditionally used to treat patients with cancers in China. It not only alleviates the symptoms of tumor patients and improves their quality of life, but also controls the size of tumors and prolongs the survival of tumor patients. While some herbs of TCM may exert therapeutic effects by directly targeting cancer cells or reducing side effects caused by antitumor drugs, others can control tumor growth and metastasis via enhancing antitumor immunity. In particular, TCM can exert antitumor effects by upregulating immune responses even in immunosuppressive tumor microenvironment. For instance, it reduces the number of M2-type macrophages and Treg cells in the tumor tissue. Although extensive reviews on directly killing cancer cells by TCM have been conducted, a review of anticancer activity of TCM solely based on its immunity-enhancing capacity is unusual. This review will summarize research progress of antitumor TCM that regulates the immune system, including both innate immunity, such as macrophages, dendritic cells, natural killer cells and MDSCs, and adaptive immunity, including $CD4^+$/$CD8^+$ T lymphocytes, regulatory T cells (Tregs) and B cells. As cancer immunotherapy has recently achieved certain success, it is expected that the clinical applications of immunity-enhancing TCM or traditional medicine for treating various cancer patients will be expanded. Further studies on the mechanisms by which TCM regulates immunity will provide new insights into how TCM controls tumor growth and metastasis, and may help improve its therapeutic effects on various cancers in clinic.

1. Introduction

Tumors are seriously threatening human health and life with morbidity and mortality increasing worldwide, and how to treat tumors has always been the urgent subject of modern medicine. Studies have shown that the occurrence and development of tumors are closely related to an individual's immunity or immune surveillance. Antitumor immune responses can be initiated through both the innate and adaptive immune system. Immunotherapy has been proved to be an effective method for the treatment of a variety of cancers [1]. At present, tumor immunotherapy has emerged from the simple adjuvant treatment to one of the most effective means, immune checkpoint blockade, which has dramatically advanced the field [2]. Cancer immunotherapy has been attracting more and more attention due to its obvious efficacy and relative safety, and was listed as one of the top ten scientific breakthroughs in 2013 by the journal Science [3]. Researches have shown that traditional Chinese medicine (TCM) can inhibit the proliferation and metastasis of tumor cells, including lung, breast and ovarian cancer cells etc., while promoting their apoptosis [4–6]. TCM has also been reported to suppress angiogenesis and tumor growth of Lewis lung or prostate cancer [7]. These tumor-repressing herbs can exert their effects by upregulating immune responses (Table 1), especially in the tumor microenvironment. This article will review the immunomodulatory effects of TCM in the context of tumor immunology, including innate immunity, adaptive immunity and tumor-associated immunoregulatory molecules (Fig. 1).

2. Innate immune system

The innate immune system is the body's earliest barrier against foreign pathogens and tumor cells and plays defensive and protective roles. Innate immune cells, such as macrophages (M), generate cytotoxicity by producing effector molecules and exerting phagocytosis, thus killing tumor cells; Dendritic cells (DCs), which process and

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https://doi.org/10.1016/j.biopha.2019.109570
Received 25 July 2019; Received in revised form 7 October 2019; Accepted 20 October 2019

Table 1
The immune cells impacted by TCM and its effects on cancers and tumor cell lines.

Traditional Chinese medicine(TCM)	Immune cells (Brief description of effects)	Repressed cancer types or tumor cell lines	Ref.
Bulbus fritillariae cirrhosae	Unknown	Lewis lung cancer	[7]
Rhodiola algida	↑Macrophages;↑ IL-2 secretion	Human breast cancer	[15]
Astragaloside IV	↓M2-type macrophages	A549 and H1299 cancer cells; Lewis lung cancer	[16]
Crassocephalum crepidioides	↑RAW264.7 macrophages	S-180 tumor cell growth	[17]
Soyasapogenols	↓M2-type macrophages; ↑M1-type macrophages	U373, SaOS2 and LM8 tumor cell growth in mice	[18]
Astragalus polysaccharides	↑DCs ↑T cell proliferation ↓MDSC proliferation	4T1 breast cancer in mice	[23,52]
Shikonin	↑DCs to activate Th1 cells	B16 tumor growth in mice	[24]
Achyranthes bidentata polysaccharides	↑DCs and DC-CIK	Colon cancer cell line: SW480	[30]
Lupanol	↑NK cells	Gastric cancer cell lines: BGC823, N87 and HGC27	[36]
Glycoprotein ZPDC from Chinese prickly ash	↑NK cells to secrete granzyme and perforin ↑cytotoxicity	Liver cancer cells in mice	[37]
Ganoderma polysaccharide	↑The number and killing activity of NK cells	Tumors in TLR4-deficient mice	[38]
Salviae miltiorrhizae polysaccharides	↑The function of NK cells and cytotoxic T lymphocytes (CTLs)	Gastric cancer in rats	[39]
Echinacea	↑Activity of NK cells and life span of leukemic mice	Leukemia in mice	[42,43]
Icariin (ICA); 3,5,7-trihydroxy-4'-methoxy-8 -(3-hydroxy-3-methylbutyl)-flavone (ICT)	↓Number and function of MDSCs; ↑DCs	4T1-Neu tumors in mice	[51]
Shugan Jianpi formula	↓CD8+ cell apoptosis ↓MDSC proliferation	Breast cancer in mice	[53]
Tetramethylpyrazine phosphate	↑Expression of IFN-γ and IL-2 ↓Expression of Th2 cytokines ;	Human lung cancer	[62]
Ginsenoside Rg3 Ginseng saponins	↑The differentiation of naive T cells into Th1 cells through activating DCs	H22 liver cancer in mice	[64,65]
Ganoderma lucidum polysaccharides	↑The differentiation of CTLs and granzyme B and perforin ↓Treg cells	B16-F10 melanoma cells Hepatocellular carcinoma in mice	[66] [81]
Astragalus polysaccharides	↓Number & proliferation of Tregs ↓The migration of Treg cells	Hepatocellular carcinoma	[78,79]
Radix glycyrrhizia polysaccharides	↓the proportion of Treg cells ; ↑Ratio of Th1/Th2 cytokines	H22 liver cancer in mice	[80]
Matrine	↑Apoptosis of B cells	Acute lymphoblastic leukemia in mice	[87]
Gambogic acid	↑The apoptosis of activated B-cell-like DLBCL	Large B cell lymphoma	[88]
Prunella vulgare	↑Apoptosis of thyroid carcinoma via Bcl-2-associated X protein/caspase-3 pathway	Human thyroid carcinoma cells	[89]
Qiyusanlong decoction	↓Both mRNA and protein levels of PD-1/PDL-1 in the tumor	Lewis lung cancer	[119]
Gegen-qinlian decoction	↑The effects of PD-1 blockade	Murine colorectal cancer	[120]

present antigens to T lymphocytes, activate adaptive immunity; Nature killer (NK) cells can directly identify and kill tumor cells [8]. However, myeloid-derived suppressor cells (MDSCs) are a group of heterogeneous cells derived from bone marrow and can inhibit the responses of other immune cells. In recent years, there have been many studies on the role of MDSCs in the tumor immunosuppressive environment and their molecular mechanisms of action. Thus, strengthening the innate immune system is one of the effective antitumor approaches.

2.1. Macrophages

Macrophages are mainly divided into M1-type and M2-type. M2-type macrophages mainly secrete epidermal growth factor (EGF), transforming growth factor (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), IL-10, IL-6, and arginase-1 to promote tumor angiogenesis and tumor progression [9]. Bingle et al. found that the infiltration of M2-type macrophages in tumor tissues promoted tumor angiogenesis, but that the infiltration of M2-type macrophages in tumor tissues with a much smaller number slowed down the tumor angiogenesis [10]. However, the function of M1-type macrophages is opposite to that of M2-type macrophages. The former can promote tumor cell death by releasing NO, IL-12, IL-23, TNF-α, IL-6 and ROS etc. Yuan R et al. found that M2-type macrophages played a dominant role in tumor-associated macrophages (TAMs) and promoted tumor growth, invasion and metastasis. The transformation of TAMs from M2-type to M1-type helps to induce specific anti-tumor immunity and inhibit tumor metastasis [11]. In recent years, it has also been found that TAMs can express PD-1 that in turn inhibits their phagocytosis and antitumor immune functions [12]. Therefore, activating M1-type macrophages or inhibiting M2-type macrophages has become one of the important antitumor strategies [13,14].

Many studies have shown that TCM controls tumor growth and metastasis via regulating M1-type/M2-type macrophages. Loo WT et al found that Chinese medicine Rhodiola increased the secretion of granulocyte-macrophage colony stimulating factor, IL-2 and IL-4, augmented their mRNA levels, and facilitated the proliferation of lymphocytes. Clinically, Rhodiola can improve the immunity in patients receiving postoperative chemotherapy for breast cancer and reduce the occurrence of chemotherapy-related oral ulcer. Rhodiola therefore has the potential to be used in conjunction with chemotherapy to reduce the incidence of oral ulcers [15]. Xu F et al. found that the active ingredient Astragaloside IV extracted from Astragalus significantly inhibited M2-type macrophage polarization induced by IL-13 and IL-4, as illustrated by decreased expression of CD206 and M2-related genes, and inhibited the invasion, migration and angiogenesis of A549 and H1299 cancer cells induced by M2-type macrophages. In vivo experiments showed that Astragaloside IV significantly inhibited the tumor growth and reduced the metastasis of Lewis lung cancer. The frequency of M2-type macrophages was decreased in tumor tissue after treatment with Astragaloside IV. In addition, Astragaloside IV also suppressed the activation of AMPKα in M2-type macrophages [16]. Tomimori, K et al found that Crassocephalum crepidioides extract delayed the tumor

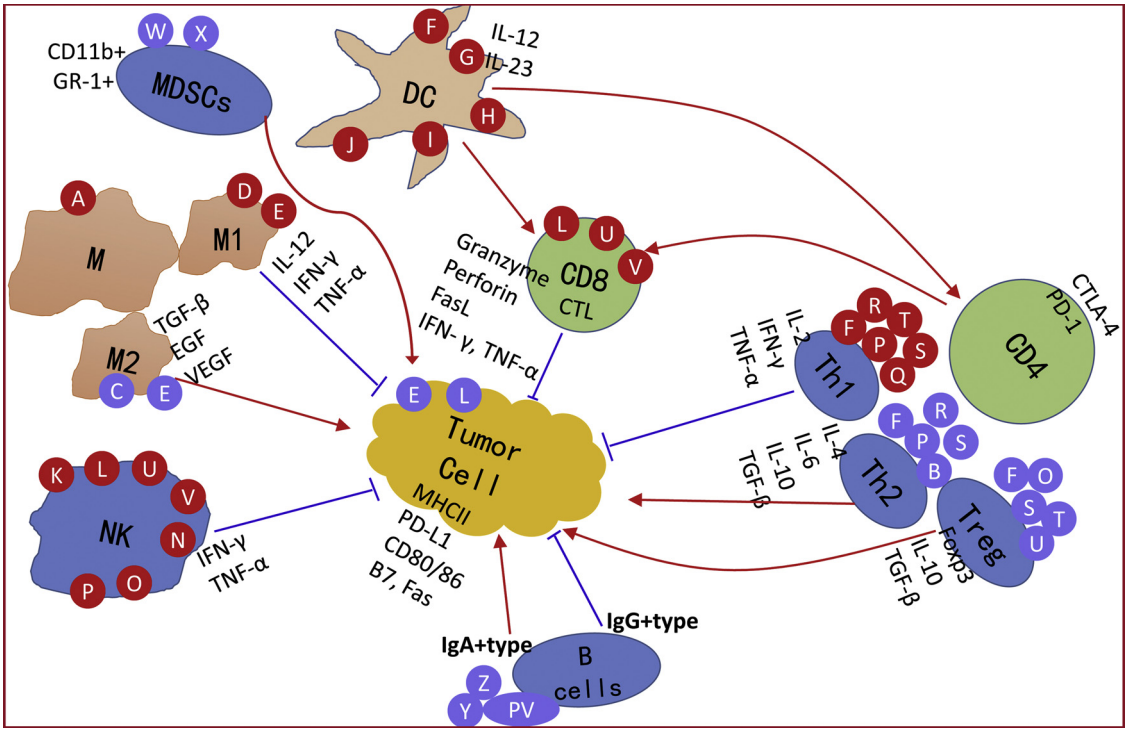

Fig. 1. A graphic summary of anticancer immunity: innate and adaptive immune cells regulated by a variety of anti-tumor traditional Chinese medicine and its components. Immune cells: **M**. Macrophage ; **NK**. Natural killer cell ; **DC**. Dendritic cell; **MDSC**. Myeloid-derived suppressor cell. Chinese medicine and its ingredients: **A**. Rhodiola; **B**. Astragalus embranaceus; **C**. Astragaloside IV; **D**. Crassocephalum Crepidioides extract; **E**. Soyasapogenols; **F**. Astragalus Polysaccharides; **G**. Codonopsis Polysaccharides; **H**. Shikonin; **I**. Achyranthes Bidentata Polysaccharides; **J**. Cordyceps Sinensis; **K**. lupanol; **L**. ZPDC, a glycoprotein extracted from Pepper; **U**. Ganoderma Polysaccharide; **V**. Salviae Miltiorrhizae Polysaccharides; **N**. ACNO, a Chinese herb formula, anti-cancer number one; **O**. Echinacea; **P**. Tetramethylpyrazine Phosphate; **Q**. Ginsenoside; **R**. HemoHIM, a herbal medicine preparation of three Chinese medicine herbs Cnidium officinale Makino, Angelica gigas Nakai, Paeonia japonica Miyabe; **S**. Glycyrrhizia Polysaccharide; **T**. Bushen Gubiao Recipe (BGR). **W**. Icariin; **X**. Asparagus Polysaccharide; **Y**. Matrine; **Z**. Gambogic Acid; **PV**. Prunella Vulgare. The red arrows represent activation while blue lines indicate suppression, with the letters inside red or blue dots representing traditional Chinese medicine or their ingredients. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

growth of S-180-cell-bearing mice, while Crassocephalum crepidioides extract stimulated the RAW264.7 macrophages to produce NO, which in turn had cytotoxicity to S-180 cells through the NF-κB pathway [17]. Fujiwara,Y et al. found that Soyasapogenols, a main component of soybean extract, significantly inhibited the polarization of M2-type macrophages, increased the secretion of IL-12 by M1-type macrophages, and suppressed the activation of STAT3 in macrophages and tumor cells as well as the proliferation of U373, SaOS2 and LM8 tumor cells. In addition, oral administration of Soyasapogenols B significantly inhibited the development of subcutaneous tumors and lung metastasis in LM8 tumor-bearing mice. Soyasapogenols B also induced anti-tumor immunity by promoting macrophage differentiation into M1-type phenotype [18]. The “DI” product is a multi-herbal formula composed of extracts from eight different Chinese herbs (Astragalus membranaceus, Codonopsis pilosula, Ganoderma lucidum, Eleutherococcus senticosus, Ligustrum lucidum, Schisandra chinensis, Atractylodes macrocephala and Glycyrrhiza spp.). The DI product stimulated the phagocytosis of macrophages, increased the release of NO by macrophage RAW264.7 in vitro, and strengthened the killing effects of macrophages on tumor cells [19]. Thus, TCM indeed controls tumor growth and metastasis via regulating the balance of M1-type/M2-type macrophages.

2.2. Dendritic cells

Dendritic cells (DCs) are professional antigen presenting cells, which play an important role in both innate and adaptive immune system. The functional state of DCs largely determines the strength of anti-tumor immunity. Enhancing the function of DCs in tumor patients to promote the activation of T cells is an effective means of anti-tumor immunotherapy [20–22] as mature DCs secret IL-12, which in turn acts on T cells and promotes Th1 cell differentiation. Chang WT et al. found that DCs treated with Astragalus polysaccharides and Codonopsis polysaccharides promoted the proliferation of CD4 + and CD8 + T cells in mice, and that DC-based tumor vaccine against 4T1 breast cancer in mice effectively enhanced anti-metastatic effects, with an increase in the expression of CD40, CD80 and CD86 molecules on the surface of DCs [23]. Shikonin is an anti-inflammatory, anti-tumor phytochemical extracted from some Chinese herbs. Chen HM et al reported that the B16 tumor cell lysate combined with shikonin could activate DCs to a highly mature state so that high levels of CD86 and MHC II were expressed on their surface, which then activated Th1 cells and enhanced their function. The shikonin-tumor cell lysate loaded dendritic cell vaccines strongly induced the cytotoxicity of splenocytes to tumor cells, delayed tumor growth and improved the survival of experimental mice [24]. Liu QY et al found that Astragalus polysaccharides induced differentiation of splenic dendritic cells into $CD11c^{high}CD45RB^{low}$ dendritic cells and transformed Th2 cells into Th1 cells, so as to enhance the immune function of T lymphocytes [25]. Immunotherapy using dendritic cells cocultured with cytokine-induced killer cells (DC-CIK) is a safe and effective method for adoptive immunotherapy of tumors [26–29]. DCs, which were jointly stimulated by Achyranthes bidentata polysaccharides extracted from Chinese medicine Achyranthes and tumor antigens of colon cancer cell line SW480 combined with CIK had the strongest killing effects on SW480 tumor cells, indicating that Achyranthes bidentata polysaccharides and tumor-specific antigen jointly stimulated DCs may synergize with CIK to improve cytotoxicity and enhance anti-tumor activity [30]. On the other hand, Cordyceps

Sinensis, a Chinese herb that has been widely used in China for a thousand years, promoted the activation and maturation of immature dendritic cells by stimulating their expression of costimulatory molecules and proinflammatory cytokines, and thus enhanced the proliferation of allogeneic T cells induced by the dendritic cells [31].

2.3. Natural killer cells

Natural killer (NK) cells are conventionally innate immune cells, known for their ability to rapidly recognize and clear infected cells. NK cells form the basis for host protection against viral infections and malignancies [32]. NK cells can generate antigen-independent immune responses to malignant cells. More and more experimental and clinical studies have shown that NK cell-based anti-tumor immunotherapies are promising [8,33]. Metastasis of malignant cells to distant anatomical sites is one prominent cause of cancer progression and patients' death. Metastasis is controlled by cancer-cell-intrinsic mechanisms that enable neoplastic cells to invade the local microenvironment, enter the circulation, and colonize distant sites, whereas NK cells play an important role in controlling the metastasis and proliferation of cancer cells [34]. NK cells can differentiate tumor stem cells or undifferentiated tumors by secreted or their membrane-bound IFN-γ and TNF-α, which prevent tumor growth by remodeling tumor microenvironment [35].

Many studies have shown that TCM or its ingredients can control tumor growth and metastasis via activating NK cells. Wu et al. proved that Lupanol induced the proliferation of human NK cells and inhibited the proliferation of human gastric cancer cell lines BGC823, N87 and HGC27. Further studies showed that lupanol promoted the proliferation and killing activity of NK cells by activating their PI3K/AKt and Wnt/β-catenin signaling pathways to increasingly express PFP, IFN-γ and CD107a [36]. Lee et al isolated a glycoprotein ZPDC from Chinese prickly ash, which has antioxidant and anti-tumor activities. The effects of ZPDC on liver cancer cells and NK cells were observed in a diethylnitrosamine-induced liver cancer mouse model. They have shown that ZPDC induces the secretion of perforin and granzyme B and the cytotoxicity of NK cells, increases the expression of apoptosis-related factors (cytochrome c and caspase-3) in liver cancer tissues, and enhances their antitumor activity [37]. Ganoderma polysaccharide could increase the number and killing activity of NK cells as well as the activity of CTLs in C3H/HeJ (TLR4-deficient) mice while reducing the tumor quality in C3H/HeJ mice and accelerating the apoptosis of tumor cells by increasing the activity of caspase-3 and caspase-9 [38]. On the other hand, Salviae miltiorrhizae polysaccharides significantly stimulated the splenocytes' proliferation in rats with gastric cancer, enhanced the function of NK cells and cytotoxic T lymphocytes (CTLs) [39] while Dendrobium polysaccharides were also found to increase the number of NK cells [40]. Li HF et al studied a Chinese herbal formula, called anticancer number one (ACNO), which could dose-dependently increase the number and activity of NK cells. They found that the increased activity of NK cells was mainly due to the increased cytotoxicity of each NK cell and increased number of circulating NK cells to some extent, while the mechanisms of its action were related to augmented secretion of NK-stimulating cytokines, such as IL-2, IL-12, and IFN-γ [41]. Finally, studies by Brousseau M and Currier NL et al also showed that Echinacea enhanced the activity of NK cells, and prolonged the survival of aging mice and life span of leukemic mice [42,43].

2.4. Myeloid-derived suppressor cells (MDSCs)

MDSCs are a heterogeneous group of cells composed of myeloid progenitors and immature bone marrow cells (IMCs). In normal individuals, IMCs differentiate into mature bone marrow-derived cells such as macrophages, dendritic cells or neutrophils. But when the body undergoes inflammation, infection or tumor pathology, the normal differentiation of IMCs is prevented while the inhibitory myeloid cells (MDSCs) are induced. MDSCs mainly consist of immature monocytes/macrophages, dendritic cells, granulocytes, and other bone marrow cells in early stage of the differentiation. MDSCs were identified in cancer patients 30 years ago [44] and were named "natural suppressor" cells, but MDSCs were linked to tumors only in the 1990s. It was the work done by Bronte et al. in 1998 [45] that aroused widespread interest. It was found that MDSCs expressed both CD11b and GR-1 in mice, and that they were expressed by only 2%～4% of monocytes in the spleen of normal mice, but by more than 50% of the same cells in tumor-bearing mice. Recent studies have demonstrated that murine MDSCs coexpress CD11b, GR-1, CD115, CD32/16, IL-4Rα and CD80. They were subdivided into two major groups according to different expression of Ly6C and Ly6G: granulocytic MDSCs (CD11b+ +Ly6G + $Ly6C^{low}$) and monocytic MDSCs (CD11b + Ly6G + $Ly6C^{high}$) [46,47].

MDSCs are one of the important components of tumor microenvironment and have strong immunosuppressive activity. They are produced in bone marrow, migrate to peripheral lymphoid organs and tumors in a tumor host, and promote the formation of immunosuppressive tumor microenvironment. MDSCs support tumor progression by promoting tumor cell survival, angiogenesis, and tumor cell invasion/metastasis to healthy tissues [48–50].

Recently, there have been some studies on the effects of TCMs on MDSCs. Icariin (ICA) is the main active component of Epimedium, while 3,5,7-trihydroxy-4′-methoxy-8- (3-hydroxy-3-methylbutyl)-flavone (ICT) is a novel derivative of ICA (Table 1). Zhou et al. [51] used ICA or ICT to inhibit tumor growth in mice bearing 4T1-Neu tumors and found that it also reduced the number of MDSCs in the spleen of these mice. Further, a restoration of IFN-γ production by CD8 + T cells in the tumor-bearing mice treated with ICA or ICT was observed. ICA or ICT significantly reduced the contents of nitric oxide and reactive oxygen species in MDSCs in vivo. When MDSCs were treated in vitro with ICT, they differentiated into dendritic cells and macrophages. Zhang et al. [52] found that Asparagus polysaccharide(AP) significantly inhibited the proliferation of MDSCs and induced their apoptosis via TLR4 pathway in vitro. In addition, AP enhanced the expression of Bax and caspase-9 and inhibited the expression of Bcl-2, suggesting that AP induces MDSC apoptosis. Thus, AP exhibits significant anti-MDSC activity by attenuating their suppression of antitumor immunity, indicating its potential usage in cancer therapy. In addition, Lu et al. demonstrated that Shugan Jianpi formula reduced the apoptosis of CD8 + T cells, suppressed the activity of tumor cells, and inhibited the proliferation of MDSCs, thus extending the survival time of the tumor-bearing mice [53]. Lin et al. found that Shenling Baizhu San reduced the infiltration of MDSCs and inhibited epithelial mesenchymal transformation and Wnt5a activation induced by TGF-β1 [54]. Taken together, TCMs may control tumor growth by suppressing MDSCs.

3. Adaptive immune system

Adaptive immune system is a highly specific immune response to a specific antigen, which is involved in the clearance of pathogenic bacteria and tumor cells [55]. Relevant studies have shown that the active components of TCM exert antitumor effects by regulating T cell subset differentiation and cytokine secretion [39,56].

3.1. CD4+/CD8+ T lymphocytes

Peripheral T lymphocytes are mainly divided into two subgroups: CD4+ and CD8+ T cells. Both CD4+ and CD8+ T cells play a crucial role in anti-tumor immunity. The main functional subgroup of CD8+ T cells is cytotoxic T lymphocytes (CTL) that directly kill tumor cells. CD4+ T cells can provide "help" by recruiting CD8+ T cells, increasing their proliferation, and enhancing their effector function through IFN-γ-dependent production of chemokines and IL-2 [57,58]. CD4+ T cells can differentiate into these functional subgroups: type 1 helper T cells (Th1), type 2 helper T cells (Th2) and type 17 helper T cells (Th17), Th9

cells, Tfh cells, and Treg cells etc. Th1 cells mainly secrete cytokines, such as IFN-γ, TNF-α and IL-2, and help to generate CTLs, thus playing a major role in antitumor immunity. Th2 cells are mainly involved in humoral immunity by secreting cytokines, such as IL-4, IL-6 and IL-13, and assisting B lymphocytes to produce specific antibodies. Th1/Th2 balance plays an important role in maintaining the healthy status of the homeostasis. Th17 cells produce IL-17 and IL-22 and are mainly involved in autoimmune diseases. In various malignant tumors, such as acute lymphoblastic leukemia and multiple osteoma, the number of Th1 cells is significantly reduced while the number of Th2 cells is increased [59]. Transcription factors T-bet, GATA-3 and RORγt are determinant for T cell differentiation into Th1, Th2 and Th17 cells, respectively [60,61]. Compared with healthy subjects, serum levels of Th1 cytokines, such as IFN-γ and IL-2, were decreased while serum levels of Th2 cytokines, such as IL-4, IL-6 and IL-13, were increased in lung cancer patients. Therefore, an imbalance of Th1/Th2 plays a role in the occurrence of cancers.

Some TCMs and their ingredients may exert antitumor effects by enhancing Th1 development. Wei H et al. conducted a comparative study after adding Tetramethylpyrazine phosphate extracted from a Chinese herb to the culture of peripheral blood monocyte cells (PBMC) from lung cancer patients and healthy subjects, and found that the addition of Tetramethylpyrazine phosphate increased the expression of IFN-γ and IL-2 but reduced the expression of Th2 cytokines in the cells from lung cancer patients, while it also enhanced the killing activity of macrophages [62]. Takei et al. found that Ginsenoside promoted the transformation of naive T cells into Th1 cells through acting on DCs, and thus increased the production of a large amount of IFN-γ. In CTL assays, the IFN-γ induced by Ginsenoside was more than that induced by mature DCs [63,64]. Therefore, the combination of Ginsenoside and DCs in the treatment of cancers may induce stronger Th1 immunity. In addition, Wu R et al. also found that Ginsenoside Rg3 treatment significantly increased the levels of IFN-γ and IL-2 in serum of H22 tumor-bearing mice compared with the tumor control group [65]. Sun LX et al. found that co-culture of Ganoderma lucidum polysaccharides with B16-F10 cells of malignant melanoma and splenic lymphocytes promoted the cytotoxicity of lymphocytes to melanoma cells by inducing the differentiation of CTLs and producing more granzyme B and perforin compared with the control group. Ganoderma lucidum polysaccharide also inhibited the tumor growth and reduced the tumor quality in melanoma-bearing mice [66]. HemoHIM is an herbal medicine preparation of three Chinese herbs: Cnidium officinale makino, Angelica gigas nakai and Paeonia japonica miyabe. An in vitro study showed that naive CD4+ T cells differentiated into more Th1 (IFN-γ+) but less Th2 (IL-4+) cells in the presence of HemoHIM in a dose-dependent manner [67]. Moreover, eosinophil numbers and cytokine levels of IL-4, IL-5 and IL-23 in BALF were decreased under HemoHIM treatment in a mouse model of airway inflammation, with a reduction in serum levels of OVA-specific IgE and IgG1. These results suggest that HemoHIM can regulate the balance of Th1/Th2, thus ameliorating allergic airway inflammation in the mouse model [67]. On the other hand, Astragalus could reduce eosinophils and excessive production of Th2 cytokines in the lung tissues of asthmatic model mice. After Astragalus treatment, the mRNA and protein levels of Th2 cytokines and GATA3/ T-bet ratio were all decreased. These results suggest that Astragalus corrects the imbalance between Th1 and Th2 cytokines [68].

Recently, cancer immunotherapies using engineered antigen-specific T cells, such as CAR-T and TCR-T cells, have achieved certain success. Chimeric antigen receptors (CARs) typically consist of a single-chain variable fragment (scFv), an extracellular hinge, a transmembrane region, and intracellular signaling domains [69]. CAR-T cells have been utilized for cancer immunotherapies. In particular, CAR-T cells targeting CD19 have been shown to be effective in treating hematological malignancies in both preclinical studies and clinical trials [70,71], and these CAR-T cells have already been authorized by US FDA for clinical usage. On the other hand, progresses have also been made in terms of using TCR-T cells to treat cancers [72]. However, TCR-T cells are MHC-restricted, likely limiting their potential application in clinic. Although there is currently no any report on cancer immunotherapy using both TCMs and CAR-T or TCR-T cells simultaneously, we do propose to use some TCMs to enhance anticancer function of CAR-T or TCR-T cells or reduce their side effects, including the cytokine storm.

3.2. Regulatory T cells

Regulatory T (Treg) cells are a subset of CD4+ T cells that control autoimmune responses and maintain immune homeostasis. Activated Treg cells can actively inhibit the immune function of T lymphocytes. Foxp3 is a specific marker of Treg cells, which is closely related to their development, peripheral expression and functional maintenance. It is considered as the "main regulator" of Treg cells [73,74]. FoxP3 expression in tumor tissue of colorectal cancer patients is positively correlated with the progression of malignant tumors [75]. During tumor development, tumor cells and macrophages in the local tumor microenvironment secrete chemokines that can recruit Treg cells from the peripheral blood to the tumor, which then escapes the attack of the host immune system due to Tregs' immunosuppressive function [76]. The occurrence, development and prognosis of tumors are closely related to Treg cells, and the treatment measures targeting Tregs in vivo are obviously conducive to the body's antitumor immunity [77].

TCM ingredients can improve antitumor immunity and inhibit the growth and metastasis of tumor cells by reducing the number and function of Treg cells and their secretion of immunosuppressive cytokines. In vitro studies demonstrated that Astragalus polysaccharides could inhibit the proliferation of Treg cells in a dose/time dependent manner, which might be related to the reestablishment of cytokine balance and the reduction of Foxp3 expression in the microenvironment of hepatocellular carcinoma [78]. Stromal cell-derived factor-1 (SDF-1) plays an important role in the recruitment of Treg cells into the microenvironment of hepatocellular carcinoma. Astragalus polysaccharides could block SDF-1 or its receptor through CXCR4/CXCL12 pathway, thereby inhibiting the migration of Treg cells [78]. Astragalus polysaccharides could also play an immunomodulatory role by activating the TLR4 signaling pathway to inhibit the expression of TGF-β, thus reducing the number of Treg cells [79]. He X et al. found that the polysaccharide from Radix glycyrrhizia also downregulated the proportion of Treg cells in the tumor microenvironment of H22 tumor-bearing mice, reduced the expression of Foxp3 in Treg cells, upregulated the ratio of Th1/Th2 in serum, and thereby inhibited the tumor growth [80]. Li et al. found that Ganoderma lucidum polysaccharides significantly inhibited the growth of tumors in tumor-bearing mice, increased the ratio of Teff/Treg cells, augmented the secretion of IL-2, and reduced the inhibition of Teff proliferation by Treg cells [81]. Another study found that Echinacea reduced the number of CD4+ CD25+Foxp3+ Treg cells, attenuated their inhibitory function and enhanced the presentation function of antigen-presenting cells with no any direct effect on the proliferation of Teff cells. It is speculated that Echinacea enhances the presentation function of antigen-presenting cells and thus improves the body's immunity by indirectly inhibiting Treg cells [82].

3.3. B cells

B cells are considered to be main immune cells mediating humoral immunity, and their role in tumor immunity has been neglected for a long time. Much of the work has focused on the role of T cell responses in antitumor immunity while little is known about the role of B cells in solid tumors. Recently, tumor infiltrating B cells have been found in a variety of solid tumors, including breast, ovarian, prostate, melanoma, and colorectal cancers. The role for B cells in solid tumors is controversial, with many studies reporting tumor-promoting effects, while others have shown that B cells can generate an antitumor immune

response [83,84]. Recent studies have revealed the differential roles of IgG+ and IgA+ B cells in antitumor immunity. IgG+ B cells exert antitumor effects because IgG mediates DC antigen presentation and activates antitumor T cell responses [85,86]. The allogeneic IgG has a stronger stimulating effect on DCs and T cells than homogenic IgG. However, IgA+ B cells have immunosuppressive effects through various tumor-promoting mechanisms. TGF-β from tumors can induce IgA+ B cell subsets. Tumor-infiltrating IgA+ B cells can release immunosuppressive cytokine IL-10 while they also express PD-L1, leading to T cell exhaustion [85,86].

There are few preliminary studies on the anticancer effects of TCMs involving B cells. Aghvami et al. found that Matrine promoted apoptosis of various cancer cells and inhibited their proliferation. Treating acute lymphoblastic leukemia with Matrine increased the production of ROS in B cells, caused mitochondrial swelling and a decrease in mitochondrial membrane potential, and significantly upregulated the pro-apoptotic protein Bax while downregulating the anti-apoptotic protein Bcl-2 [87]. Using Gambogic acid to treat diffuse large B cell lymphoma (DLBCL), Shi et al. discovered that Gambogic acid induced growth inhibition and apoptosis of activated B-cell-like DLBCL in vivo and in vitro [88]. As a traditional Chinese herb, Prunella vulgare (PV) has been proved to be rich in bioactive chemicals, which have anti-proliferative and pro-apoptotic effects on tumor cells. Yin et al. demonstrated that Chinese herb PV promoted the apoptosis of well-differentiated human thyroid carcinoma cells via the Bcl-2-associated X protein/caspase-3 signaling pathway [89].

4. Immune checkpoints

In recent years, immune intervention strategies targeting immune checkpoint molecules, such as PD-1 and CTLA4, have brought new hope for the treatment of related diseases, especially cancer. Initial studies have found that some immunosuppressive molecules expressed on effector T cells can prevent the excessive activation of T cells, thus preventing the occurrence of autoimmune diseases [90]. Therefore, the role for these checkpoint molecules in regulation of immune homeostasis has attracted widespread attention. Later studies have found that checkpoint molecules are also highly expressed and play an important pathological role in tumors, chronic viral infection and intracellular bacterial infection of immune cells [91,92]. At present, immune checkpoint molecules mainly include cytotoxic T-lymphocyte-associated antigen 4 (CTLA4), programmed death receptor 1 (PD-1), T-cell immunoglobulin mucin 3 (Tim3), and lymphocyte activation gene 3 (LAG3).

PD-1, as an important co-inhibitory molecule discovered in the recent decade, has been widely confirmed to play a role in controlling T cell function [93]. In addition, studies have found that PD-1 is also expressed on the surface of B cells, monocytes/macrophages, NK cells and DCs, and is involved in the negatively regulatory process of these cells [94–97]. Programmed cell death 1 ligand 1 (PD-L1) is one of the ligands of PD1, and the interaction of PD-L1 with PD-1 can generate a variety of immune regulation, such as inhibition of lymphocyte function, induction of lymphocyte apoptosis, and suppression of proinflammatory cytokine release, etc. [98–100]. In certain tumor microenvironment, tumor cells also highly express PD-L1 molecules, which bind to PD-1 molecules on the surface of tumor-infiltrating T cells to inhibit their activation, thus allowing the tumor to evade the killing by the immune system [2]. Monoclonal antibodies against PD-1 or PD-L1 can block their binding, thereby restoring antitumor function of T cells [101,102]. These findings have significantly advanced the field of cancer immunotherapy.

CTLA4, another important coinhibitory molecule that has a high structural homology with the costimulatory molecule CD28 and can bind to the B7 molecule on antigen presenting cells (APCs), is involved in the downregulation of T cell function. Its affinity and avidity are much higher than CD28 [103]. CTLA-4 was found to be a competitive antagonist of the CD28-B7 interaction because it effectively blocked this costimulation of the T-cell-APC interface, thereby disrupting T cell activation [104]. Scheipers et al. found that CTLA4 mediated the apoptosis of T cells in the Fas-independent pathway, resulting in a decrease in effector T cells, reduction in their secretion of cytokines, and inhibition of their function [105]. Other studies demonstrated that CTLA4 signaling also reduced the secretion of IL-2 and inhibited the gene expression of IL-2R, thereby suppressing T cell proliferation. In addition, CTLA4 could also control the progression of cell cycle by preventing it from developing into S phase from G0/G1 phase, resulting in the failure for T cells to proliferate and secrete cytokines [106,107]. Blocking CTLA4 with anti-CTLA4 antibodies prevented the occurrence of tolerance and promoted the proliferation of T cells and their expression of cytokines [108]. Recently, it has been reported that blocking CTLA4 significantly improves antitumor immunity [109].

Recent studies have found that other immune checkpoints, such as Tim3 and TIGIT, are also expressed in natural immune cells and affect immune homeostasis. Tim3 was found to be expressed in rat mast cells, macrophages, DCs, NK cells and NKT cells, as well as in human mononuclear macrophages [110–114]. TIGIT molecule, which was originally found on the surface of T cells, was also expressed on the surface of NK cells and DCs and involved in their functional regulation [115–118].

Recently, clinical trials using antibodies to block immune checkpoints for antitumor therapy have achieved certain success [101]. At present, however, there are only few studies on TCMs that may impact the immune checkpoints. Zhang X et al demonstrated that Qiyusanlong decoction inhibited the tumor growth in mice bearing Lewis lung carcinoma by reducing both mRNA and protein levels of PD-1/PDL-1 in the tumor [119]. Based on the fact that immune checkpoints are expressed on a variety of immune cells, and that TCM can stimulate the function of many immune cells, it is possible that some TCMs and its components may be able to regulate certain molecules of the immune checkpoints. Further research is needed to determine whether more TCMs have an impact on the immune checkpoints. On the other hand, a new study showed that Gegen qinlian decoction enhanced the effects of PD-1 blockade in colorectal cancer by remodeling the gut microbiota [120], indicating that a joint treatment combining TCM and PD-1 blockade may represent a promising strategy for treating human cancers.

5. Clinical application of TCMs

TCMs have been traditionally utilized to treat cancer patients in China for a long time. In particular, TCMs are often used in cancer patients who have finished conventional treatments, including surgery, chemotherapy or radiotherapy, and act as maintenance treatments or so called “alternative and complementary” treatments. The proportion of patients that were treated with at least one formula of alternative and complementary medicine increased from 25.7% in 2002 to 39.4% in 2007, an increase of 14.2% [121]. At present, we have mostly used “relatively safe” TCMs that have been administered for over a thousand of years, mainly including “tonic” and “heat-clearing” TCMs [122], but not toxic TCMs, although the exact toxicities of antitumor TCMs remain to be fully investigated. TCMs combined with chemoradiotherapy achieved certain curative effects on some cancers, prolonged the median survival time, improved the quality of life, and reduced adverse reactions [123]. Clinical analysis has shown that the most commonly used TCM formulas for patents with cancers are Fufang Banmao capsule, Huaier granule, and Jinlong capsule [124]. Astragalus polysaccharides repressed human hepatocellular carcinoma by suppressing CD4 + CD25+ Treg cells in the tumor microenvironment [78], and increased anticancer responses in patients with lung cancer by enhancing M1 polarization of macrophages and maturation of DCs [125]. Astragalus indeed has been the most commonly used single herb, whose ingredients mainly include polysaccharides, saponins and flavonoids. Astragalus exhibits antioxidant, anti-inflammatory and anticancer

properties, and it has been used alone or in combination with other TCMs [126]. The combined treatments with Astragalus and cancer chemotherapy reduced the toxicity induced by these chemical drugs [126]. There are also many of other TCMs that can be used as an adjunctive therapy for cancer treatment, such as Ginseng and Evodia officinalis etc [127,128]. More extensive studies are warranted to ensure both safety and efficacy of TCMs for the treatment of cancers.

6. Conclusion

The effects of TCMs on the immune system are diverse and complex, with different TCM acting on differential immune cells or even the same type of the cells. TCMs contain rich and diverse chemical components, including alkaloid, polysaccharide, glycosides, and flavonoids etc. These chemicals have multiple biological functions with broad impacts on the immune system, including both innate and adaptive immunity. In particular, TCMs can exert antitumor effects by upregulating immune responses in tumor microenvironment, such as reducing the number of M2-type macrophages and Treg cells in the tumor tissue. TCM has a long history of clinical application in China and is of great potential for further development. Thousands of years' clinical experience provides clues for pharmacological research into TCMs whereas the chemical composition of some of the antitumor traditional herbs used in clinical practice has not been fully determined. Thus further in-depth research is warranted. Facilitating antitumor immunity by some TCMs will provide a promising approach to treating cancers although studies on the mechanisms underlying the antitumor effects of TCMs are still in the early stage.

However, there are some limitations of TCMs in antitumor therapies since it's very difficult to know exactly which ingredient from TCMs is responsible for the net effects of the TCM. Further studies are required to identify the effective components or ingredients of TCMs with antitumor properties, to elucidate their mechanisms of action, to improve their biological efficacy, and to expand their applications in antitumor therapy in clinic. Although most of the TCMs are botanical and have been traditionally considered to be less toxic, some are indeed highly toxic. This area remains to be underexplored and should be studied more extensively in the near future. In particular, when herbs are grown in a polluted area, their toxicity could be increased dramatically. Further, some TCM formulas contain too many types of herbs and might generate additive toxicities. Finally, when a patient is diagnosed with cancer in the early stage, a more radical measure, such as surgery or a targeted biotherapy rather than TCMs, may be needed. Thus, more basic researches and clinical studies on TCMs are warranted in order to expand their clinical application for treating cancer patients.

Funding

This work was supported by the Specific Research Funds for TCM Science and Technology of Guangdong Provincial Hospital of Chinese Medicine, China (YN2016ZD01, YN2018ZD08 and YN2019MJ03).

Author contributions

YW, QZ and YC wrote a part of the manuscript; CLL, HL and FQ searched for the literature; ZD provided the general idea and extensively edited the manuscript.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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