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REVIEW

Traditional Chinese Medicine in Regulating Tumor Microenvironment

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Abstract: Tumor microenvironment (TME) is a complex and integrated system containing a variety of tumor-infiltrating immune cells and stromal cells. They are closely connected with cancer cells and influence the development and progression of cancer. Traditional Chinese medicine (TCM) is an important complementary therapy for cancer treatment in China. It mainly eliminates cancer cells by regulating TME. The aim of this review is to systematically summarize the crosstalk between tumor cells and TME, and to summarize the research progress of TCM in regulating TME. The review is of great significance in revealing the therapeutic mechanism of action of TCM, and provides an opportunity for the combined application of TCM and immunotherapy in cancer treatment.

Keywords: cancer, tumor microenvironment, traditional Chinese medicine, anti-tumor effects

Background

Cancer is currently one of the leading causes of human mortality. According to the latest statistics from Global Cancer in 2020, there are approximately 19.3 million new cancer cases and nearly 10 million cancer deaths worldwide.[1] Cancer treatment has always been a challenge for researchers. Since the beginning of the 20th century, researchers have come to realize that the interaction between cancer cells and tumor microenvironment (TME) plays an important role in promoting tumorigenesis and its progression, and that the TME consists of an immune microenvironment, mainly composed of immune cells, and a non-immune microenvironment, mainly composed of fibroblasts, which are both anti-tumorigenic, but also promote tumorigenesis and progression.[2,3] Targeting the balance of immune cells in the micro-environment and enhancing tumor immunity have been the focus of tumor immunotherapy. Current therapeutic approaches, like chemotherapy and targeted therapy, have also achieved remarkable results and prolonged patient survival time, but the adverse effects and drug resistance have limited their clinical use.[4–7]

Traditional Chinese medicine (TCM) has been applied in clinical as an adjuvant therapy for anti-tumor treatment, which can reduce the adverse effects of radiotherapy/chemotherapy, and have synergistic effects with anti-tumor drugs to prolong the survival of tumor patients. The occurrence and development of tumor diseases are closely related to the low immune function of the human body. Especially after surgery, radiotherapy and chemotherapy, the immune system of the body is seriously damaged.[8] More and more studies have confirmed that TCM can enhance anti-tumor effects by regulating the immune system.[9,10] The aim of this study is to introduce how immune cells and non-immune cells in TME promote tumor progression, and to summarize the research progress of TCM in regulating TME.

Crosstalk Between Cancer Cells and TME

The TME mainly consists of innate and adaptive immune cells, as well as stromal cells,including T and B lymphocytes, tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), tumor-associated neutrophils (TANs), natural killer cells (NKs), and dendritic cells (DCs).[11] In TME, several types of cells are closely associated with the promotion of tumorigenesis and progression (Figure 1 and Table 1).

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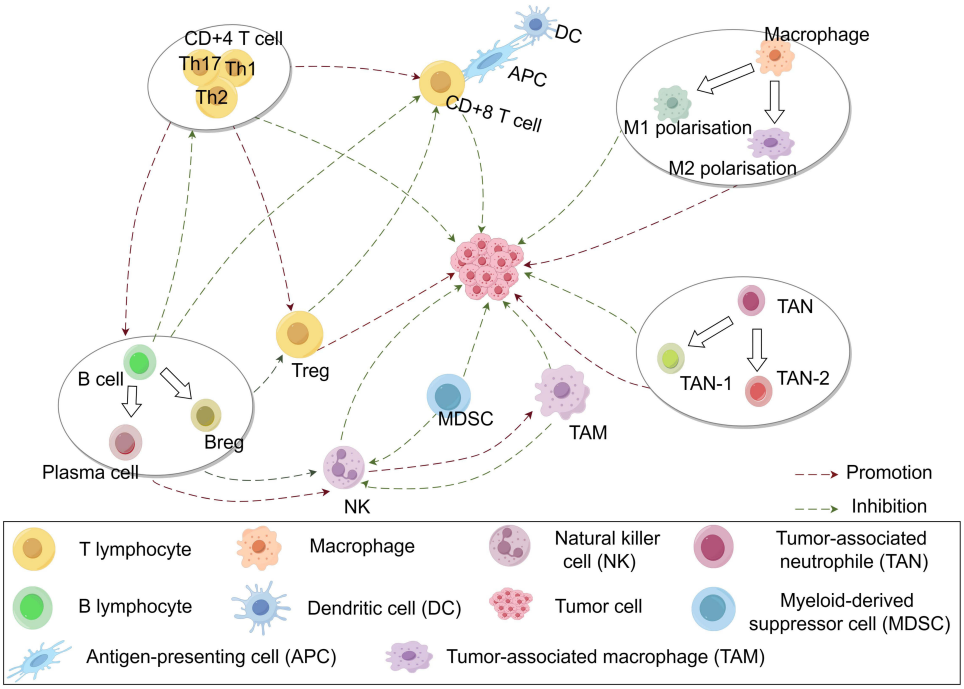

Figure 1 Crosstalk between cancer cells and TME cells. T lymphocytes mainly include CD4+ T cells, CD8+ T cells and Tregs, of which CD4+ T cells can differentiate into T helper 1 (Th1 cells) and T helper 2 (Th2 cells). Th1 cells can enhance the killing ability of T lymphocytes and activate macrophages; Th2 cells can assist B lymphocytes (B cells) to produce specific antigens and exert anti-tumor function; meanwhile, CD4+ T cells can recruit CD8+ T cells and promote tumor growth. Regulatory T cells (Tregs) can reduce NK cells and promote the depletion of effector T cells. TIL-Bs can reduce NK cells and promote the depletion of effector T cells. Secretion of IL-10 or TGF-β by regulatory B cells impairs antitumor immunity and converts quiescent CD4+ T cells into Tregs. NK cells secrete proinflammatory phenotypes that maintain tumor-associated macrophages (TAMs) and tumor-associated neutrophils (TANs). TANs differentiate into TAN-1 and TAN-2, of which TAN-1 inhibits tumor growth and TAN-2 promotes tumor cell proliferation and metastasis. Mature cells (DC cells) have strong antigen-presenting ability, and can block T cell cycle or apoptosis, and induce Treg cell differentiation. Macrophages are mainly polarized into M1 and M2 macrophages, most of which have antigen-presenting capacity.

Crosstalk Between Innate Immune Cells and Cancer Cells

Dual Roles of Nature Killer Cells (NK cells)

NK cells, mainly derived from thymic bone marrow lymphoid stem cells, act on TIME-associated cells by secreting cytokines such as IFN- γ and TNF- α to maintain the pro-inflammatory phenotype of TAMs and TANs. In addition, NK cells secrete perforin and granzyme, which target and destroy cancer cells through antibody-dependent cell-mediated cytotoxicity. In addition, they trigger an immune response by releasing of immunomodulatory cytokines, thereby inhibiting cancer cell metastasis.[12,13] However, it has been shown that TAMs and MDSCs release inhibitory cytokines such as TGF-β and IL-10, which prevent NK cells from migrating to TME and have anti-tumor effects.

Macrophages Subtypes and Their Opposite Roles

Macrophages are the most numerous group of immune cells in the TME, derived from monocytes, the progenitor monocytes in the bone marrow, and are present in almost all tissues with strong phagocytosis, killing ability, and pro-inflammatory responses.[14] They mainly contains M1 macrophages and M2 macrophages. The former can phagocytose and destroy cancer cells by releasing large amounts of proinflammatory substances, while the latter mainly produce vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), transforming growth factor–β (TGF-β), platelet derived growth factor (PDGF), and other vasculature-promoting cytokines.[14] TAMs, which are mainly composed of M2 macrophages, are immunosuppressive cells in TME.[15] These TAMs prevent T cell recruitment and activation by releasing cytokines and chemokines, and participate in multiple signaling pathways that promote angiogenesis, immunosuppression, and chronic inflammation. Thus, they contribute to tumor development.[15]

Table 1 Mechanisms of Action of Immune Cells

Immune Cells	Mechanism of Action
NKs[12,13]	Secreting perforin and granzyme to destroy cancer cells; Secreting cytokines such as IFN- γ and TNF- α to maintain the pro-inflammatory phenotype of TAMs and TANs.
Macrophages[14,15]	M1 macrophages phagocytose and destroy cancer cells by releasing large amounts of pro-inflammatory substances; M2 macrophages produce the cytokines to promote vascular development; TAMs prevent T cell recruitment and activation by releasing cytokines and chemokines, immunosuppression, and chronic inflammation.
DCs[16–18]	Mature DCs have a strong antigen-presenting capacity and the ability to stimulate B cells and T cells; DCs express IDO, leading to T cell cycle arrest or apoptosis and inducing Treg cell differentiation.
MDSCs[19–22]	NOS2 can promote the inhibitory activity of M-MDSCs, and the tumor can rapidly differentiate into TAMs due to the increased hypoxia.
TAN[23–26]	TANs-N1 release large amounts of cellular hydrolases that produce ROS, MPO, and other reactive oxides to destroy tumor cells; TANs-N1 also triggers the IL-18 activation and the IFN-β secretion, which activates NKs, DCs, macrophages, and other immune cells; TANs-N2 produce ROS, cytokines, proteases, MMP-9 to promote the proliferation and metastasis of tumor cells.
T lymphocytes[26–33]	CD4+T cells recruit CD8+T cells and promote their proliferation; CD4+T cells secretes IFN-γ-dependent chemokines and IL-2 to enhance the effector function of CD8+ T cells; CD8+ T cells destroy target cells through granzyme- and perforin-mediated apoptosis or Fas/Fasl-mediated cell death; Tregs reduced NK cells, promoted the depletion of effector T cells and inhibited the cytotoxic effect of effector T cells through the production of GF-β, IL-10 and IL-35; Th1 cells can enhance the killing ability of T cells and activate macrophages; Th2 cells can assist B lymphocytes to produce specific antigens to perform anti-tumor function.
B lymphocytes[34–36]	TIL-Bs have a strong antitumor response in TME; Regulatory B cells secrete IL-10 or TGF-β to impair anti-tumor immunity and converse resting CD4+ T cells to Tregs.

Dual Roles of Dendritic Cells (DCs)

DCs are the primary effector cells in the immune response. In the resting state, DC cells are usually immature with reduced level of expression of MHC and stimulatory molecules, and are therefore unable to activate T cells.[16] Mature DCs have a strong antigen-presenting capacity and the ability to stimulate B cells and T cells.[17] In tumor immunity, DCs cannot kill tumor cells directly, but monitor and kill tumors by recognizing tumor cell-specific antigens and presenting them to T cells.[18]

Immunosuppressive Effects of Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are immature populations of DCs, macrophages, and granulocytes that significantly suppress immune cell responses.[19] It has been found that MDSCs can be classified into different subtypes based on their specific functions. These subtypes include polymorphonuclear (PMN-MDSCs) and Monocyte-like MDSCs (M-MDSCs).[20,21] PMN-MDSCs account for more than 70% of the total number of MDSCs in peripheral lymphoid organs, whereas M-MDSCs account for a much higher proportion of tumors. Interferon-γ (IFN-γ) has been shown to stimulate the inhibitory activity of M-MDSCs by activating the transcription factor STAT1, which in turn promotes the transcription of NOS2, one of the main enzymes responsible for the inhibitory activity of M-MDSCs. Differentiation of M-MDSCs toward macrophages depends on tissue. M-MDSCs differentiate slowly into macrophages in spleen, but rapidly into TAMs in tumors, a phenomenon that is regulated by hypoxia.[20,22]

Dual Roles of Tumor-Associated Neutrophils (TANs)

Neutrophils are myeloid progenitor cells of the human body and are important component of peripheral blood cells and TME. They play an important role in promoting and inhibiting tumor cell growth.[23] TANs have a dual nature, and their functional diversity determines functional heterogeneity. In the early stages of tumor growth, TANs-N1 release large amounts of cellular hydrolases that produce reactive oxygen species (ROS), myeloperoxidase (MPO), and other reactive oxides to destroy tumor cells. It also triggers the activation of IL-18 and the secretion of interferon-β (IFN-β), which activates NKs, DCs, Macrophages, and other immune cells in the immune system and exert cellular immunity.[24,37] As the tumor develops, TANs gradually change into N2 phenotype and produce various products such as ROS, cytokines, proteases, and matrix metalloproteinase-9 (MMP-9), thus promoting the proliferation and metastasis of tumor cells.[25]

Crosstalk Between Adaptive Immune Cells and Cancer Cells

T Lymphocyte Subtypes with Different Functions

In TME, T cells are one of the most important tools against tumor. Depending on the surface antigen, they mainly include CD4+T and CD8+T lymphocytes.CD4+T cells recruit CD8+T cells and promote their proliferation. In addition, it secretes IFN-γ-dependent chemokines and IL-2, which enhances the effector function of CD8+ T cells. They mainly differentiate into helper T cells (Th), which mainly include Th1 and Th2, as well as regulatory T cells (Tregs). Th1 cells enhance the killing ability of T cells, and activate macrophages, which exert significant anti-tumor effects. Th2 cells exert anti-tumor functions mainly by assisting B lymphocytes in the production of specific antigens.[26,27]

The classical phenotype of Tregs is $CD4^{+}CD25^{+}Foxp3^{+}$, which belongs to the CD4+ T cell subpopulation, has low proliferative capacity, secretes cytokines such as IL-4, IL-10 and TGF-β, and acts mainly by suppressing immune response, maintaining immune homeostasis, and inducing immune tolerance, which is opposite to the role of helper T cells.[28] Based on their products and biological characteristics, Tregs can be categorized into natural regulatory T cells (nTregs) and induced regulatory T cells (iTregs). Compared with nTregs, iTregs are more closely related to tumorigenesis and progression than nTregs.[29,30] TGF-β, IL-10, and IL-35 produced by Tregs block anti-tumor immune response. TGF-β secreted by Tregs inhibits the cytotoxic effects of NK cells and cytotoxic T cells (CTLs), and promotes tumor growth. It also promotes depletion of effector T cells and inhibits the cytotoxic effects of effector T cells by producing IL-10 and IL-35.[29,30] CD8+ T cells differentiate into CTL and memory T cells (Tm). Through antigen presentation, the T cell receptor (TCR) binds to MHC expressed by cancer cells, thereby specifically recognizing cancer cells. Upon binding to the TCR, CD8+ T cells eliminate target cells through granzyme- and perforin-mediated apoptosis or Fas/Fasl-mediated cell death.[31] Nanotechnology promotes the expansion and infiltration of T cells, which significantly enhances the antitumor effect of T cells.[32,33]

B Lymphocyte Subtypes with Different Functions

B lymphocytes are the primary mediators of humoral immunity. In TME, B cells exert anti-tumor effects through antibody-dependent cytotoxicity and complement activation.[34] Many studies have shown that B cells reside in the tertiary lymphoid structures (TLSs) of TME. Infiltrating B cells and plasma cells (PCs) have been referred to as tumor-infiltrating B lymphocytes (TIL-B), which have a strong anti-tumor response in TME.[34,35] However, TIL-B rarely act alone, but are closely associated with T cells and promote T cell activation through antigen presentation.[36] In addition, B cells over-secrete anti-inflammatory and pro-angiogenic mediators that promote inflammation and immunosuppression, thereby supporting tumor growth. TIL-Bs are mainly composed of effector and regulatory B cells, where regulatory B cells are an important cell population in the immunosuppressive microenvironment, either directly impairing anti-tumor immunity through the secretion of IL-10 or indirectly destroying tumorigenic immunity through the production of TGF-β and the conversion of resting CD4+ T cells into Tregs.[36,38,39]

Regulation of tumor microenvironment (TME) by TCM

The immune system is a natural defense against tumorigenesis and development. We have described in detail how immune cells defend against tumorigenesis and development above. Therefore, targeted regulation of the balance of immune cells in the microenvironment has always been the focus of tumor immunotherapy. As an important adjunct to antitumor therapy, a number of previous clinical studies have shown that TCM can alleviate the adverse effects of radiotherapy, improve quality of patients' life, and work synergistically with anti-tumor drugs to prolong the survival time of cancer patients.[40,41] In addition, studies have demonstrated that TCM herbs and thier active ingredients (polysaccharides, alkaloids, flavonoids, terpenoids, etc.) can enhance anti-tumor efficacy by modulating the immune system.[42] In this section, the anti-tumor immunomodulatory mechanisms of representative TCM formulae (Table 2, Supplementary Table 1) and compounds (Table 3) will be discussed.

Table 2 TCM Formulae in Regulating Tumor Microenvironment

Formulae	Disease Type	Trial Type	Cell Line	Model	Drug Dose	Composition	Mechanism of Action
JYYZXZ[43]	GC	Animal vitro	MGC-803	-	Animal: 2 g/kg	Radix Codonopsis pilosulae, Rhizoma Atractylodis macrocephalae, Poria, semen coicis, Radix Angelicae sinensis, Rhizoma Dioscoreae, Radix Aucklandiae, Pericarpium Citri Reticulatae, Smilax Chi, Salviae Chinensis Herba, Radix Glycyrrhizae	TAM regulates the phenotypic transition of macrophages from M2 to M1
YYFZBJS[44]	CRC	Animal	HCT 116 MC 38	C57BL/6J ApcMin/$^{+}$mice	Animal: L: 3.825 g/kg, M: 7.65 g/kg H: 15.3g/kg	Semen Coicis, Radix Aconiti Lateralis, and Herba Patriniae	YYFZBJS can reduce the number of Treg cells, improve intestinal inflammatory response, and inhibit the occurrence and development of colon cancer.
FLP[45]	LC	Animal	Lewis	Nude mice	Animal: 0.2 mL/day (200 mL NS + 84 g FLP)	Astragalus, American ginseng, sand ginseng, wheat winter, white flower snake tongue grass, defeated sauce grass, fist ginseng, peach kernel, notoginseng	FLP can inhibit the expression of IL-2, and then inhibit the differentiation of T cells into Treg cells.
mBYD40[46]	GC	-	-	-		Radix astragali; Radix codonopsis pilosulae; Radix angelicae sinensis; Radix glycyrrhizae; Cimicifugae rhizoma; Radix bupleuri; Atractylodes macrocephala, Pericarpium citri reticulatae; Rhizoma Sparganii; Rhizoma	mBYD can promote the proliferation and activation of T lymphocytes, while inhibiting the up-regulation of CD8+PD-1+T cells.
FZJD[47]	Acute lung injury	Animal	-	ALI rats	-	Radix Astragali, Codonopsis pilosula, Atractylodes macrocephala, Polygonum multiflorum, Chinese wolfberry, Yunnan Chonglou, Hedyotis diffusa, Actinidia deliciosa	It promoted the transformation of TAM phenotype M2 to M1

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Table 3 Herbal Compounds in Regulating Tumor Microenvironment

Compounds	Source	Disease Type	Trial Type	Cell Line	Model	Drug Dose	Mechanism of Action
Astragalus polysaccharides[48–50]	Radix Astragali	Proctitis CRC LC	Cell Animal Clinic	H441; H1299; H1437; Lewis; THP;	C57BL/6 mice	Cell: 16 mg/mL Clinic: 500 mg	Increase the CD80 + M1 + M2 / CD206 ratio to accelerate the M1 MDSC polarization; Promote the surface molecules CD80 and CD86.
Lentinan[51]	Lentinus edodes	BC LC	Animal	EO771	C57BL/6 mice; FVB mice	1 mg/kg	Promote the proliferation of CD8 + T cells and activation; Induced TAN to N1 phenotype.
Licorice polysaccharide[52]	Licorice	CRC	Cell Animal Clinic	CT26	BALB/c mice	Animal: 500 mg/kg	Activate CD4 +T and CD8 + T cells; Increase the number of T lymphocytes; Increase the serum IL - 2, IL-6, IL-7.
Salvia miltiorrhiza polysaccharides[53]	Salvia miltiorrhiza	GC	Animal	-	Wistar rats	Animal: 200mg/kg	Improve the anti-inflammatory cytokine (IL-2, IL −4 and IL −10) level, Inhibit proinflammatory cytokines (IL - 6 and TNF alpha).
Asparagus polysaccharides[54]	Asparagus	CRC	Cell Animal	MC 38	C57BL/6 mice	Cell: 250 mg/kg 500 mg/kg	Reduce the production of MDSCs or promote the apoptosis of MDSCs; Inhibit the proliferation of MDSCs in MC38 colon cancer mice.
Berberine[55]	Coptis chinensis	CACRC	Cells Animal	IMCE; HCT116; RAW 264.7	C57BL/6J-ApcMin/$^{+}$ mice	100 mg/kg	Inhibit the production of pro-inflammatory cytokines such as IL-6. and IFN-α in colon macrophages; Reduce the activation of EGFR/ERK signaling pathway in colorectal cancer cells, thus inhibiting the growth of colorectal cancer cells.
Matrine[56]	Sophora flavescens	ALL	Clinic	-	-	340 mg/kg	Promote the production of ROS in B-cells; Up-regulated the expression ratio of Bax/Bcl-2 apoptotic genes; Enhanced their immune effects; Improved their anti-tumor effects.
Astragalosid[52,57]	Radix Astragali	CRC	Cell Animal	CT 26	Balb/c mice C57BL/6 mice	50 mg/kg	Increase the expression of NKG2D and IFN - gamma of NK cells; Enhance the killing ability of NK cells.
Ginsenosiderg3[58]	Ginseng	-	Cell Animal	-	Balb/c mice	-	Reduce the expression of PD-L1 induced by drug resistance and restore t cell toxicity; Promoted the differentiation of M2 macrophages into anti-tumor M1 phenotypes

Resveratrol[59–61]	Peanuts, grapes, Polygonum cuspidatum and other plants.	BC	Cell Animal	NK 92; BCap37; MDA-MB-231	C57BL/6 mice	-	Down-regulating PD-1 expression to enhance Th1 immune response; Promote the activation of CD8+T cells; Inhibiting the expression of c-Myc; Inhibiting the secretion of cytokines and the p-STAT2 to reduce the number of T cells and TAM; Inhibite the polarization of M2 macrophages.
Curcumin[62]	Turmeric	BC GC CRC	Cell Animal Clinical sample	4T1-Neu MKN-45 CT26	BALB/c mice nude mice	Animal: 50 mg/kg	Reducing in the number of MDSCs and promote its maturity; Promoting CD4+ and CD8+ T cells to produce IFN-γ.
Andrographolide[63]	Andrographis paniculata	Colon cancer	Cell Animal	CT 26	C57BL/6 mice	Animal: 5 mg/kg	Increase the CD4 + and CD8 + T cell infiltration and function.
Triptolide[64]	Tripterygium wilfordii	melanoma	Cell Animal	B16-F10	C57BL/6 mice	-	Inhibiting TGF - β, VEGF and the production of IL – 10; Reduce the proportion of Treg cells

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TCM Formulae

Jianpi Yangzhen Xiaozheng Decoction (JYYZXZ) Converts M2 Macrophages into M1 Macrophages

JYYZXZ is composed of Radix Codonopsis pilosulae, Rhizoma Atractylodis macrocephalae, Poria, semen coicis, Radix Angelicae sinensis, Rhizoma Dioscoreae, Radix Aucklandiae, Pericarpium Citri Reticulatae, Smilax Chi, Salviae Chinensis Herba, and Radix Glycyrrhizae. Sun et al analyzed the effects of JYYZXZ and its disassembled prescription on postoperative patients with gastric cancer. The results showed that JPYZXZ and its components could prevent the progression of gastric cancer. Compared with JPYZ (Radix Codonopsis pilosulae, Rhizoma Atractylodis macrocephalae, Poria, semen coicis, Radix Glycyrrhizae) and XZSJ (Radix Paeoniae Alba, Radix Angelicae sinensis, Rhizoma Dioscoreae, Pericarpium Citri Reticulatae, Smilax Chi, Salviae Chinensis Herba), JYYZXZ inhibits the Epithelial-Mesenchymal Transition (EMT) of gastric cancer more effectively, but JPYZ mainly regulated the phenotypic changes of macrophages from M2 subtype to M1 subtype.[43]

Fei Liu Ping (FLP) Inhibits the Differentiation of T Cells into Treg Cells

FLP is composed of astragalus, American ginseng, sand ginseng, wheat winter, white flower snake tongue grass, defeated sauce grass, fist ginseng, peach kernel, notoginseng. Fan et al discovered that FLP combined with cyclophosphamide chemotherapy reduced the proportion of localized Treg cells in the tumor and the expression of IL-2, which in turn inhibited the differentiation of T cells into Treg cells and immune escape of the tumor.[45]

Yi-Yi-Fu-Zi-Bai-Jiang-San (YYFZBJS) Reduced the Accumulation of CD4+CD25+Foxp3-Positive Treg Cells

YYFZBJS, as an important ancient formula, is mainly composed of Semen coicis, Radix Aconiti Lateralis, and Herba Patriniae. In intestinal adenomas, YYFZBJS can reduce the number of intestinal lymphatic vessels and mesenteric lymph nodes (MLN) and accumulate CD4+CD25+Foxp3-positive Treg cells, as well as improve the intestinal inflammatory response and inhibit the occurrence and development of colon cancer.[44]

mBYD40 Enhances the Cytotoxicity of T Cells

mBYD, composed of Radix astragali, Radix codonopsis pilosulae, Radix angelicae sinensis, Radix glycyrrhizae, Cimicifugae rhizome, Radix bupleuri, Atractylodes macrocephala, Pericarpium citri reticulatae, Rhizoma Sparganii and Rhizoma, has been shown to directly promote the proliferation, activation and cytotoxicity of T lymphocytes. Meanwhile, the upregulation rate of $CD8^{+}PD\text{-}1^{+}$T cells was decreased. In addition, this study confirmed that the PI3K/AKT pathway inhibited PD-L1 expression in gastric cancer tissues.[46]

Fu Zheng Jie Du Formula (FZJD) Reversed M2 Macrophage to M1 Macrophage

FZJD (Radix Astragali, Codonopsis pilosula, Atractylodes macrocephala, Polygonum multiflorum, Lycium barbarum, Yunnan leafy rhizome, tapeworm, and Aguta kiwifruit) not only reduced the expression of IL-10 and TGF- β, but also raised the ratio of iNOS/Arg2, which represents the ratio of M1/M2, which reversed TAM's phenotype from M2 to M1 of TAM, thereby suppressing tumor cells.[47]

Herbal Compounds

Polysaccharides increase the number of T cells and the maturation of DCs, and promote conversion of MDSCs to M1 macrophages

Astragalus-contained herbs are commonly used in TCM. Its main components are astragalus polysaccharide (APS), astragalus polysaccharide glycoside (AS-IV) and flavonoids. APS is a water-soluble heteropolysaccharide composed of hexanedioic acid, glucose, galacturonic acid and glucuronic acid. It has various health benefits such as enhancing the immune system, modulating anti-tumor, anti-stress and antioxidant effects. Studies have shown that APS can increase the ratio of CD80+M1/CD206+M2, promote MDSCs polarization towards M1, and activate CTL to exert anti-tumor effects. In addition, APS prevented the recruitment of SDF-1 Treg cells through CXCR4/CXCL12 axis, activated the TLR4 signaling pathway, and reduced the number of Treg cells.[48–50] Glycyrrhiza glabra is an important ingredient in many complementary and alternative medicine prescriptions, and is also commonly used in TCM for the treatment of various diseases. Licorice polysaccharide (Glycyrrhiza polysaccharide, GPS) is one of the main active components of licorice, which consists of rhamnose, glucan, arabinose and galactose.[52] Recent studies have shown that Glycyrrhiza increased the expression ratio of $CD3^{+}CD8^{+}$ and $CD3^{+}CD4^{+}$T lymphocytes, promoted the

maturation and phagocytosis of DCs, and enhance the cytokine production of IL-4 and IFN-γ.[65] Lentinan (LNT), a kind of polysaccharides extracted from Lentinus edodes, has been widely used in clinic to enhance patients' immunity. It was found to inhibit the growth of breast cancer and lung cancer, and promoted the proliferation and activation of CD8+ T cells and induced the polarization of TANs toward the N1 phenotype, resulting in an anti-tumor effect.[51] He et al explored the mechanism of Salvia miltiorrhiza Bunge polysaccharides to improve the immune function of rats with gastric cancer. It was found that compared with the gastric cancer model group, Salvia miltiorrhiza Bunge polysaccharides enhanced the killing ability of NK cells and CTLs, increased the expression levels of IL-2, IL-4, IL-10, IgA, IgG and IgM in serum, and decreased the levels of IL-6 and TNF-α, which enhanced the immune function of rats with gastric cancer.[53] Zhang et al found APS inhibited the migration, invasion and angiogenesis of HCC cells by down-regulating the HIF-1α/VEGF signaling pathway under normoxic conditions in *vitro*.[54]

Alkaloid inhibits the production of inflammatory factors and up-regulates apoptotic genes

A study on berberine for prevention and treatment of colitis-associated colorectal cancer (CACRC) found that berberine inhibits CACRC by inhibiting the production of pro-inflammatory cytokines (eg, IL-6 and IFN-α) in colon macrophages, leading to a reduced activation of the EGFR/ERK signaling pathway in colorectal cancer cells, and inhibited their proliferation.[55] Matrine is a unique tetracyclic quinoline alkaloid derived from Robinia pseudoacacia with anti-inflammatory properties. Aghvami M et al found that it promoted the production of ROS in B-cells, up-regulated the expression ratio of Bax/Bcl-2 apoptotic genes, enhanced thier immune effects and improved thier anti-tumor effects.[56]

Glycosides Balance Th1/Th2 Ratio and Promote M1 Polarization

Astragalus saponin inhibited the proliferation of tumor cells, increased the protein levels of IL-12, IL-12R and pSTAT4, activated the IL-12/STAT4 pathway, increased the expression of IL-12, IL-12R and STAT4 genes, and thus induced the transformation of Th1/Th2 to Th1 cells.[52] Xu et al also found that astragalus saponins inhibited M2 polarization of macrophages through the AMP-activated protein kinase (AMPK) signaling pathway, increased the proportion of M1 cells in TME, alleviated immunosuppression, and reduced the proliferation of lung cancer A549 cells and H1299 cells.[57] In another study, ginsenosideRg3, an active ingredient of Radix Ginseng reduced drug resistance-induced PD-L1 expression, restored T-cell cytotoxicity, and inhibited proliferation and cisplatin resistance in A549/DDP cells. Moreover, Rg3 regulated the differentiation of pro-tumor M2 macrophages into the anti-tumor M1 phenotype when used in combination with chemotherapy.[58]

Phenols Enhance the Killing Ability of NK Cells and Reduce the Number of MDSCs

Phenolic compounds are widely found in the human diet and plant foods, and their use in human health has been extensively studied. Resveratrol is a plant-derived phytoantitoxin widely found in berries, peanuts, mulberries, grapes and other fruits. However, resveratrol attenuated CTL response to PD-L1, thereby preventing suppression and exhaustion of antitumor immunity.[59] Another study showed that resveratrol induced mammalian target of rapamycin protein complex 2 (mTORC2)/Akt/cMyb signaling pathway to act on NK cells, which then exerted an anti-tumor effect.[60] In addition, it was found that the activation of NK cells required the upregulation of c-Myb.[60] In addition, resveratrol increased the expression of NKp30a, NKp30b and other ligands, which enhanced the cancer-killing ability of NK cells.[61] Curcumin reduced the number of MDSCs, promoted their maturation, and facilitated the production of IFN-γ by CD4+T and CD8+T cells. In addition, curcumin inhibited the activation of Stat3 and NF-κB pathway (activation of Stat3 and NF-κB regulated the expression of anti-apoptotic, pro-proliferative, and immune response genes) and reduced the level of IL-6 in MDSCs, thus exerting anti-tumor effects.[62]

Other Compounds Involved in T Cell Activation and Inhibition of Pro-Inflammatory Factors

Yang et al found that the combination of Andrographolide with PD-1 inhibitors resulted in greater therapeutic efficacy in a mouse CT26 colon cancer xenograft model.[63] Studies have shown that andrographolide combined with PD-1 blockade immunotherapy enhanced the infiltration of CD4+ and CD8+ T cells and co-activated T cell function.[63] In addition, Andrographolide inhibited the expression of inflammation-related genes and limited the immunostimulatory activity of cells by inducing COX2 gene transcription to increase PGE2 production.[63] Triptolide is a diterpene lactone with a variety of bioactive diterpene lactone extracted from the roots of Tripterygium wilfordii. It is the main active ingredient in preparations such as therapeutic rheumatoid tablets and wilfordii polyglucoside tablets. Triptolide inhibited the

production of IL-2 and IFN- γ, as well as activation of Naïve T cells and effector T cells, such as Tregs. Triptolide-treated DCs have also been reported to down-regulate the expression of Th1 cells and inhibited the maturation and migration of DCs.[64] In addition, studies have shown that glycyrrhizic acid (GL) and glycyrrhetinic acid (GA) modulated a variety of components involved in immune regulation and inflammation, such as inflammatory factor and acidophilic chemotactic protein secretion.[66]

Discussion

In 1889, Paget *et at.* first proposed the theory of "soil and seed", which suggested that tumor cells are equivalent to "seeds", and their unbridled proliferation is predicated on the need for "soil" with a suitable environment[67]. TME is a complex network of interactions that affect tumorigenesis and development. The significance of the immunosuppressive microenvironment lies in the fact that it can evade tumor-suppressing immune cells and molecules, escape immune surveillance, and promote the occurrence and development of tumor cells, and leaving the organism in a state of immunosuppression.[68] Since entering the 21st century, tumor immunotherapy has achieved remarkable results, but through the actual feedback from clinicians and patients, it has been found that its adverse reactions and drug resistance may be an important factor affecting its long-term efficacy. A single therapeutic target may not be enough to prevent and treat tumor progression, but also requires the combined application of multiple targets. TCM can improve the tumor immunosuppressive microenvironment and the progression of chronic inflammation from various aspects.

The mechanism of immunotherapy is to activate immune cells by lifting the "braking" effect of the immune system, restarting and maintaining the "tumor-immunity" cycle, restoring the normal anti-tumor immune response of the body, and controlling the occurrence and development of tumors. it is common with the "holistic concept" of TCM. TCM is a systematic means of treatment, characterized by the combination of multiple targets and pathways. Currently, doctors believe that TCM works on both "seeds" and "soil". The effects on tumor cells are mainly reflected in the following aspects: (1) Inhibiting tumor cell proliferation, inducing tumor cell differentiation and apoptosis. Among them, Lentinan is a potential drug expected to be used in clinic in the future[51]. (2) Reducing oncogene expression and inhibiting tumor angiogenesis. Among TCM compounds, Triptolide and Its derivatives have good therapeutic efficacy and deserve further study.[64] (3) Reversing the drug resistance of tumor cells. Andrographolide and ginsenosideRg3 are able to sensitize cancer cells to immunotherapy and platinum drugs, respectively, indicating their combined application to enhance the efficiency and reduce the toxicity.[58,63] The effects of TCM on TME are mainly manifested in two ways: to improving blood rheology index, activate blood circulation; and to improve the immune function and indirectly inhibit cancer cells.

Adjuvant alternative therapy is a form of medicine that combines TCM with other anti-tumor therapies to increase the sensitivity of tumor cells to radiotherapy, reduce adverse reactions, lower the risk of drug resistance and recurrence of tumors, and promote the reduction of toxicity and increase in efficacy. As we know, TCM is affordable, safe and reliable, and therefore favored by tumor patients. It helps reduce the economic burden of patients and is a widely accepted treatment option. However, according to the current literature review, the following problems still exist: 1) Most of the studies only verified the effects of TCM on immune cells, and the specific binding targets are not clarified. We can explore the mechanism of TCM intervention in TME from multiple perspectives and levels, such as protein expression, signal transduction, metabolomics, etc. 2) The effects of various TCM combinations/single formulas on immune cells tend to focus on T cells, MDSCs and DCs. However, the immune system includes innate and adaptive immunity. The body's defense system consists of many cells, and there are interrelationships among these cells. Therefore, it is important to study other immune cells as well. 3) In most studies, the molecular mechanisms of the efficacy of TCM formulae remains largely unknow. 4) The research of TCM on TME has been based on basic research, with a low rate of translation of the results, and its clinical efficacy has not yet been further verified. In addition, although TCM formulae or single herb have been proven to bring benefits to patients, the time of benefit has not been tracked, which should also be the research focus in the future.

Abbreviations

TME, Tumor microenvironment; TCM, Traditional Chinese medicine; TAM, Tumor-associated macrophages; MDSCs, Myeloid-derived suppressor cells; TAN, Tumor-associated neutrophils; NK, Natural killer cells; DCs, Dendritic cells;

VEGF, Endothelial growth factor; EGF, Epidermal growth factor; TGF-β, Transforming growth factor-β; PDGF, Platelet derived growth factor; PMN-MDSCs, Polymorphonuclear MDSCs; M-MDSC, Monocyte-like MDSC; ROS, Reactive oxygen species; MPO, Myeloperoxidase; IFN-β, Interferon-β; MMP-9, Matrix metalloproteinase-9; Th, Helper T cell; nTregs, Regulatory T cell; iTregs, Induced regulatory T cell; CTL, Cytotoxic T cell; Tm, Memory T cell; TCR, T cell receptor; TLSs, Tertiary lymphoid structures; PCs, Plasma cell; APS, Astragalus polysaccharide; LNT, Lentinan; CACRC, Colitis-associated colorectal cancer; AMPK, AMP-activated protein kinase; GC, Gastric cancer; CRC, colorectal cancer; LC, Lung cancer; ALL, acute lymphoblastic leukemia; BC, Breast cancer.

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Disclosure

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