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Current Research Status and Molecular Mechanisms of Traditional Chinese Medicine Combined with Anti-Tumor Therapy Targeting Tumor-Associated Macrophages

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Abstract: Tumor-associated macrophages (TAMs) are a key component of the tumor immune microenvironment, and their function depends on their polarization state. M1 macrophages are generally associated with anti-tumor immune activity, while M2 macrophages are linked to immunosuppression, tumor progression, and metastasis. Recent studies have shown that Traditional Chinese Medicine (TCM) may regulate TAM polarization in cancer. Both experimental and clinical evidence suggest that TCM monomers and formulas can influence this process, although the strength of evidence varies. Compounds such as artesunate, matrine, and celastrol may shift macrophages toward the M1 phenotype, involving pathways including PI3K/Akt/mTOR, STAT6, and NF-κB. TCM formulas such as Bufei Decoction and Danggui Buxue Decoction have also been reported to enhance chemotherapy or immunotherapy effects, possibly through reducing immunosuppressive interactions in the tumor microenvironment. Clinically, Jianpi Yangzheng Xiaozhong Decoction has shown potential survival benefits in gastric cancer and has been included in integrated treatment guidelines. However, current evidence remains limited, with issues such as small sample sizes and lack of standardization. In addition, poor bioavailability of some TCM components continues to limit clinical application. Overall, TCM may regulate TAM polarization and reshape the tumor immune microenvironment through multiple targets, but further well-designed clinical studies are still needed for translation into practice.

Keywords: TAMs; TCM; Traditional Chinese Medicine anti-tumor therapy; Integrated Traditional Chinese and Western Medicine anti-tumor therapy; Research status; Molecular mechanisms

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1. Introduction

Tumor-associated macrophages (TAMs) are a major immune cell population in the tumor microenvironment. They are involved in several processes related to cancer, including tumor growth, metastasis, and anti-

tumor immune responses. Because of these roles, TAMs have been studied more frequently in recent years, although their functions are still not fully understood in different tumor types.

At the same time, there has also been increasing interest in how Traditional Chinese Medicine (TCM) might affect these cells. Some studies have reported that extracts and active compounds from TCM can influence macrophage behavior, especially the polarization process of TAMs, which may be related to anti-tumor effects [1].

Research on the relationship between TAMs and tumor progression is still developing. In this context, this review looks at what is currently known about TAMs in cancer, and then focuses on how TCM may regulate them. Studies involving both single compounds and herbal formulas are considered, particularly those related to signaling pathways in macrophage polarization. Some work has also explored combining TCM with chemotherapy or immunotherapy, and this topic has gained attention recently, although the evidence is still limited.

Overall, while the idea of targeting TAMs is becoming more discussed, many mechanisms are still unclear. Even so, it may provide a possible direction for integrating traditional Chinese and Western medicine in cancer treatment.

2. Research progress on core molecular mechanisms of tumor-associated macrophages

2.1. Relationship between TAM polarization phenotypes (M1/M2) and tumor progression

Tumor-associated macrophages (TAMs) are generally described as existing in two main polarization states, M1 and M2, although in reality the situation may be more flexible and not always strictly divided. The balance between these two types is thought to influence tumor progression, but this balance can look different depending on tumor context.

M1-type macrophages are usually linked with anti-tumor immune activity. They are known to produce inflammatory mediators such as CD86, IL-1β, TNF-α, and IL-12, which are involved in activating Th1-type immune responses and supporting recruitment of $CD8^+$ T cells into tumor tissues. However, the strength of this response can vary in different tumor environments.

On the other hand, signals in the tumor microenvironment tend to push macrophages toward an M2-like state. Cytokines such as IL-4, IL-13, and IL-10 are often mentioned in this process. These M2-like macrophages show higher expression of markers including CD206, Arg1, Fizz1, and Ym1, and they also release immunosuppressive factors like IL-10 and TGF-β. Once this phenotype becomes dominant, effector T-cell activity tends to decrease, and tumor cells can more easily survive and expand. In addition, processes such as angiogenesis and invasion are promoted, partly through VEGF and matrix metalloproteinases (MMPs) [2].

Clinical observations more or less support this general pattern. Higher infiltration of M2-type TAMs has been reported in cancers such as lung cancer, gastric cancer, and hepatocellular carcinoma, and these cases are often associated with poorer outcomes. Still, the relationship is not completely identical across all tumor types, and different studies report some variation. Overall, it is generally accepted that the M1/M2 balance is related to tumor progression, even if the exact mechanism is not fully consistent across cancers.

2.2. Key signaling pathways of TAM-mediated immune suppression and their roles in tumor proliferation and metastasis

The regulation of TAM polarization is not controlled by a single pathway, but rather by several interconnected signaling networks. PI3K/Akt/mTOR is often mentioned first in this context, mainly because it is closely associated with M2 polarization. When cytokines such as IL-4 are present, this pathway becomes activated and M2-related genes are upregulated. There are also reports showing that blocking PI3Kγ can shift macrophages back toward a more inflammatory state, partly restoring M1-like activity.

STAT6 is usually discussed together with IL-4 signaling. After phosphorylation, it enters the nucleus and triggers transcription of genes such as Arg1 and Fizz1. Some experimental studies have shown that when STAT6 is inhibited, tumor metastasis can be reduced, although the exact effect seems to depend on tumor type and model used.

Beyond the two major pathways mentioned above, PI3Kγ seems to play a wider regulatory role in macrophages. It has been reported to suppress NF-κB activity while at the same time enhancing C/EBPβ signaling, which overall pushes macrophages toward a more immunosuppressive state. IL-10 produced by TAMs may further strengthen this tendency. Some studies suggest that IL-10 can upregulate PD-L1 expression on tumor cells, and this then reduces $CD8^+$ T-cell activity through the PD-1/PD-L1 axis. There is also another pathway that has been discussed more recently: the NLRP3/Caspase-1/IL-1β pyroptosis pathway. The situation here does not seem completely straightforward. In some experimental models, overactivation of this pathway may cause pyroptosis in M1 macrophages, which could weaken anti-tumor immune responses. On the other hand, inhibition of NLRP3 has been reported to help maintain M1 function, and this might improve the effect of immunotherapy, although this is still being explored [3].

Apart from immune-related regulation, TAMs also have more direct effects on tumor cells themselves. M2 macrophages can release growth factors such as EGF, TGF-β, and IL-6, and these factors activate several downstream signaling pathways in tumor cells, including MAPK, PI3K/Akt, and Wnt/β-catenin. This is generally associated with increased proliferation and maintenance of stem-like characteristics, although the strength of these effects may vary in different tumor models.

During metastasis, molecules like TGF-β and IL-10 are often mentioned in relation to epithelial-mesenchymal transition (EMT), which is linked to increased migration and invasion ability. At the same time, processes such as matrix degradation and angiogenesis also play a role. MMPs contribute to the breakdown of the extracellular matrix, while VEGF supports the formation of new blood vessels. All of this together makes metastatic spread easier in many cases. TAMs can also reduce $CD8^+$ T-cell infiltration and function, mainly through IL-10 and PD-L1-related mechanisms [4]. Figure 1 gives a general overview of these pathways and their effects.

Overall, TAMs are involved in different stages of tumor development, including immune escape, growth, and metastasis. Because of this, they are often considered a potential target in cancer therapy. Recently, TCM has been discussed in this context since it may influence several signaling pathways at the same time rather than acting on just one target.

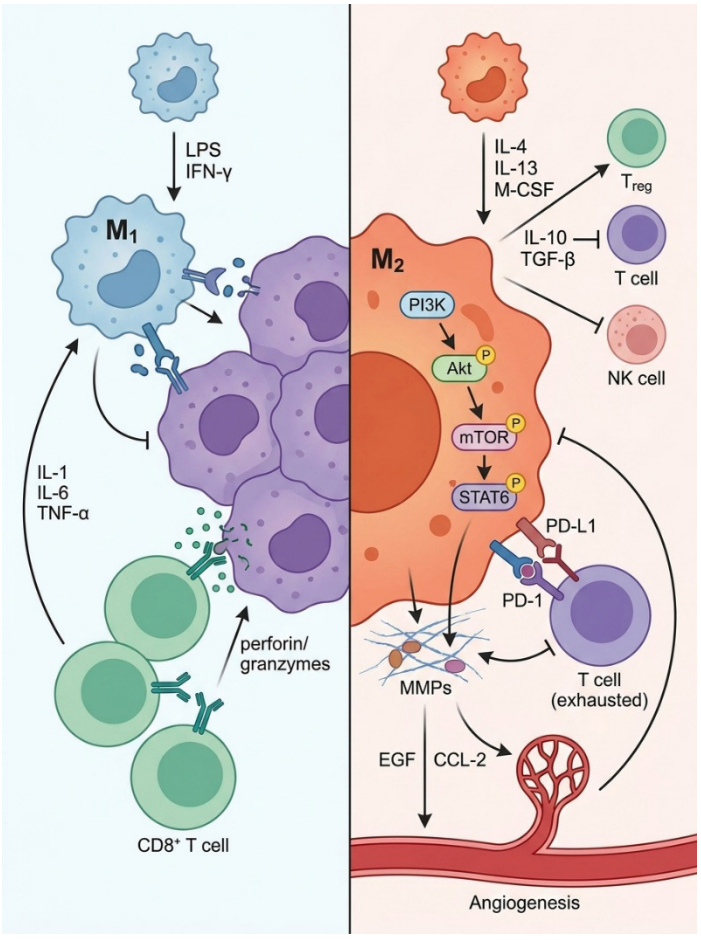

Figure 1. TAMs polarization.

2. Molecular mechanisms of anti-tumor effects of traditional Chinese medicine by regulating TAMs

2.1. Regulatory effects of TCM monomers on macrophage polarization

There is increasing evidence that several compounds derived from Traditional Chinese Medicine (TCM) can influence the polarization state of tumor-associated macrophages (TAMs). Most of the studies point in a similar direction, that is, shifting macrophages from the M2 phenotype toward M1, although the specific pathways involved are not always the same.

For instance, a water extract containing ginseng and Astragalus was reported to increase M1-related markers while reducing M2-type polarization. In that study, immune activity within the tumor environment appeared to be enhanced after treatment [5]. Compound Kushen Injection shows a somewhat similar trend, but through a different mechanism. It activates the TNFR1/NF-κB/p38MAPK signaling pathway, and this activation is accompanied by increased proliferation and cytotoxic function of $CD8^+$ T cells [6].

Some single compounds have also been studied at the molecular level. Lobeline, for example, has been shown to bind MAPK14 and regulate the p53/Slurp1 pathway. This does not directly act only on macrophages, but seems to indirectly push the balance toward M1 polarization, and there are also reports that it may work better when combined with anti-PD-1 therapy [7]. Bezoar (Calculus bovis) has been reported to

inhibit M2 polarization, possibly through suppression of the Wnt/β-catenin signaling pathway, although the exact downstream process is still not fully clear.

Matrine has been studied in Lewis lung cancer models and is often described as suppressing M2-type TAM polarization. The effect is generally linked with inhibition of the PI3K/Akt/mTOR pathway. In the same context, changes in epithelial–mesenchymal transition (EMT)-related proteins have also been observed, including increased E-cadherin and decreased N-cadherin, Vimentin, and Snail. These changes correspond with reduced migration and invasion of tumor cells, suggesting a broader anti-tumor effect [8].

Pulsatilla saponins (PS) mainly act through the STAT6 pathway. In IL-4-induced macrophage models, PS were found to reduce M2 polarization and downregulate markers such as Arg1, Fizz1, Ym1, and CD206 [9]. One study on vinegar-processed frankincense (PF) water extract reported a different pattern. Instead of acting directly on macrophages, its effect seems to be linked with the gut microbiota and related metabolites. This microbiota–immune interaction may also influence TAM behavior, although the mechanism is still not well defined. It adds a slightly different angle to how TCM might regulate immune responses in tumors [10].

2.2. Reprogramming of TAMs by TCM compounds

Compared with single compounds, more recent studies have started to focus on TCM formulas and how they affect TAM reprogramming in a more complex way. Some of the findings suggest that these formulas may not only act on signaling pathways, but also influence macrophage metabolism, which in turn affects the tumor immune environment.

One example is the Wenxia Changfei Formula. Yin et al. reported that it suppressed the activation of the PPAR-γ/CD36 pathway in M2 macrophages. As a result, fatty acid uptake and lipid accumulation were reduced, and fatty acid oxidation was also affected. These metabolic shifts were linked with a change in macrophage state, from M2-like toward M1-like phenotype. In the same experimental model, reduced migration and metastasis of Lewis lung cancer cells were also observed [11].

Xihuang Pills (XHP) show a somewhat different mechanism. Based on network pharmacology combined with metabolomic analysis, one study found that XHP decreased kynurenine levels in a mouse model of pancreatic ductal adenocarcinoma. This was accompanied by inhibition of AKT/mTOR signaling and promotion of M1 polarization, together with stronger anti-tumor immune responses. In that work, β-boswellic acid was identified as one of the key components that may be responsible for regulating both kynurenine metabolism and macrophage polarization [12].

Overall, these studies suggest that TCM formulas do not act through a single target. The effects seem to involve multiple components and different biological layers, especially metabolic regulation in macrophages. By shifting the balance from M2 toward M1 phenotype and changing the tumor immune environment, they may help slow down tumor progression, although the exact contribution of each pathway is still not fully clear.

3. Strategies and research progress of traditional Chinese medicine in anti-tumor therapy

3.1. Preclinical research applications of TCM combination treatment strategies

Combination therapy has become an important approach in cancer treatment because it can simultaneously target multiple biological pathways and may improve the limitations of single-agent therapy. Traditional

Chinese Medicine (TCM) has attracted considerable interest in this area, and an increasing number of experimental studies have examined its use together with chemotherapy, targeted therapy, or immunotherapy.

3.1.1. Lung cancer

Several studies in non-small cell lung cancer have suggested that TCM may enhance anti-tumor immunity through regulation of tumor-associated macrophages (TAMs). Hu et al. reported that artesunate promoted M1 polarization through activation of the STAT1/IRF1 signaling pathway, resulting in increased T-cell infiltration and improved responses to anti-PD-1 therapy in Lewis lung cancer models [13]. In another study, Zhan et al. showed that crude polysaccharides isolated from Danggui Buxue Decoction (DBDP) reduced deoxycytidine secretion by M2 macrophages and decreased cytidine deaminase (CDA) expression by promoting the transition from M2 to M1 macrophages, thereby alleviating TAM-associated resistance to gemcitabine [14]. Bufei Decoction (BFD) has also been reported to interfere with the TAM–IL-10–PD-L1 signaling axis, suppressing the malignant behavior of lung cancer cells and suggesting a possible role for combination treatment with immune checkpoint inhibitors [15].

3.1.2. Liver cancer

In hepatocellular carcinoma, Polygonatum sibiricum polysaccharide (PSP) has been shown to activate the TLR4/MyD88/NF-κB pathway, promoting macrophage polarization toward the M1 phenotype and suppressing tumor growth [16]. Lu Linzhu and colleagues further reported that Aconitum polysaccharide (FPS), when combined with lenvatinib, enhanced the anti-tumor activity of lenvatinib by increasing M1 macrophage polarization, indicating that TCM polysaccharides may improve the efficacy of targeted therapy [17].

3.1.3. Intrahepatic cholangiocarcinoma

Yang et al. investigated the interaction between tumor metabolism and immune regulation in intrahepatic cholangiocarcinoma. Their study showed that celastrol reduced glycolysis in tumor cells through inhibition of the AKT/mTOR pathway, leading to lower lactate production. As lactate is an important driver of M2 polarization, this metabolic change was accompanied by reduced M2 polarization and inhibition of tumor progression [18].

3.1.4. Breast cancer

Different mechanisms have also been reported in breast cancer models. Using TAM membrane-coated magnetic nanoparticles together with LC-MS analysis, Yang et al. identified liquiritin as one of the major active components of Aidikang Formula (ADQ). Liquiritin increased cathepsin K (CTSK) expression, promoted lysosomal degradation of CXCL1 in TAMs, and reduced endothelial tube formation and tumor angiogenesis [19]. Jin et al. found that total glucosides of paeony (TGP) suppressed TAM recruitment through inhibition of the NF-κB/CCL2 pathway while increasing memory T-cell populations, suggesting an improvement in anti-tumor immune responses [20]. In another study, dandelion extract regulated the IL-10/STAT3/PD-L1 pathway and promoted the transition of TAMs from the M2 phenotype to the M1 phenotype [21].

3.1.5. Esophageal cancer

Recent work has also examined the interaction between tumor metabolism and macrophage polarization in esophageal squamous cell carcinoma. Wang et al. reported that IL-4 released by tumor cells activated

the JAK2/STAT6 pathway in macrophages, promoting M2 polarization. These macrophages subsequently enhanced glycolysis in tumor cells, as reflected by increased expression of HK2, GLUT1, and LDHA together with elevated glucose uptake and lactate production. *Zuogui Yin* did not directly suppress glycolysis in tumor cells, but inhibited M2 polarization by targeting JAK2 in macrophages and blocking IL-4/JAK2/STAT6 signaling. This indirect effect was associated with reduced glycolytic activity in tumor cells. Mass spectrometry combined with molecular dynamics analysis further identified isoferulic acid and dehydrocorydaline as two active compounds capable of binding stably to JAK2 [22].

3.2. Clinical research applications of TCM characteristic treatment technologies

In clinical practice, several Traditional Chinese Medicine (TCM) formulas have been evaluated as adjunctive treatments for different types of cancer. *Jianpi Yangzheng Xiaozheng* Decoction (JPYZXZ), which was developed according to the principle of "invigorating the spleen, supporting healthy *qi*, resolving stasis, and dissipating masses," has been used for many years in patients with gastric cancer. Clinical studies suggest that it may improve quality of life, prolong survival, reduce chemotherapy-related adverse effects, and enhance immune function, including macrophage activity [23]. Following multicenter clinical evaluation, the formula has been included in the Guidelines for Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Gastric Cancer.

Fuzheng Jiedu Xiaoji Formula has been reported in the treatment of hepatocellular carcinoma (HCC). Some clinical data suggest that it may help relieve symptoms in patients and also slow down disease progression to a certain extent. In studies where it was used together with PD-1/PD-L1 inhibitors, an improvement in median survival has been observed. This effect is often discussed in relation to changes in the tumor immune microenvironment, especially the balance between M1 and M2 macrophages [24].

Fuzheng Yiliu Formula (FZYL) has also been used in prostate cancer, mainly as an adjunct therapy. Clinical observations are still relatively limited, but there are reports suggesting that it may delay progression and improve symptom control. These effects are thought to be related to regulation of tumor-associated macrophages as well as chemokine-related signaling [25]. In a similar way, *Gehua Jiecheng* Decoction (GHJCD) has been applied in lung cancer patients to relieve clinical symptoms. Both experimental and clinical findings point to possible involvement of immune regulation, reduction of inflammatory activity, and suppression of angiogenesis, although the mechanisms are not fully consistent across studies [26].

At the same time, it should be noted that clinical evidence for many of these interventions is still not strong enough. Most studies are either small-scale or not well-controlled, and large prospective trials combining TCM with immune checkpoint inhibitors are still rare. External therapies used in TCM practice, such as topical herbal applications combined with paraffin-based treatment, have been reported in some cases, but overall supporting data is quite limited.

Table 1 gives an overview of recent studies on TCM in anti-tumor applications. From preclinical research, it is generally suggested that TCM may affect tumor progression through several different routes, including regulation of TAM polarization, interference with immunosuppressive signaling, and metabolic-immune interactions. Some clinical reports also mention potential benefits from formulas such as *Jianpi Yangzheng Xiaozhong* Decoction and *Aidikang* Formula. However, how to translate these findings into standard clinical use is still not very clear. More work is needed, especially on how to combine TCM with chemotherapy or immunotherapy in a more rational way, and also on identifying which patient groups may

actually respond better.

Table 1. Research progress of TCM in anti-tumor therapy

TCM / Active Ingredient	Tumor Type	Regulatory Effect on TAMs	Core Molecular Mechanism	Reference
Bufei Decoction (BFD)	Non-small cell lung cancer	Inhibits IL-10 secretion by TAMs, downregulates PD-L1 expression	Regulation via IL-10/PD-L1 axis, inhibits immune escape	[15]
Jianpi Yangzheng Xiaozheng Decoction (JPYZXZ) and its decomposed formulas	Gastric cancer	Promotes TAMs M2→M1 polarization; inhibits EMT	JPYZ regulates polarization; XZSJ inhibits EMT	[23]
Gehua Jiecheng Decoction (GHJCD)	Liver cancer (DEN-induced)	Regulates immune cells and inflammatory factors	Inhibits NF-κB/ WNT signaling pathway	[26]
Fuzheng Jiedu Xiaoji Formula (FZJDXJ)	Liver cancer	Inhibits tumor cell proliferation and migration	Regulates AKT/ CyclinD1/p21/p27 pathway	[24]but its curative effect still requires extensive clinical research and mechanistic analysis.\nPURPOSE: To explore the effectiveness of FZJDXJ in HCC patients and investigate its biological function and mechanism underlying anticancer therapy.\ nMETHODS: This randomized controlled clinical trial enrolled 291 HCC patients receiving transcatheter arterial chemoembolization (TACE
Dandelion extract	Triple-negative breast cancer	Promotes M1 polarization, inhibits M2 polarization	Inhibits IL-10/ STAT3/PD-L1 pathway	[21]
Total glucosides of paeony (TGP)	Breast cancer	Inhibits TAMs recruitment, increases T cell memory subsets	Inhibits NF-κB/ CCL2 signaling axis	[20]
Crude polysaccharides of Danggui Buxue Decoction (DBDP)	Lung cancer	Reshapes TAMs (M2→M1); reverses chemoresistance	Inhibits dC secretion and CDA expression, combined with gemcitabine	[14]
Fuzheng Yiliu Formula (FZYL)	Prostate cancer	Inhibits TAMs/ CCL5 pathway; inhibits cancer stem cell self-renewal	Inhibits cancer stem cell renewal, EMT and metastasis	[25]
Polygonatum sibiricum polysaccharide (PSP)	Liver cancer	Induces TAMs M2→M1 polarization	Activates TLR4-MyD88-NF-κB pathway	[16]
Aconitum polysaccharide (FPS) + Lenvatinib	Hepatocellular carcinoma	Promotes TAMs M1 polarization	Upregulates iNOS/IL-12b, downregulates Arg-1/IL-10; combined targeted therapy	[17]

TCM / Active Ingredient	Tumor Type	Regulatory Effect on TAMs	Core Molecular Mechanism	Reference
Celastrol	Intrahepatic cholangiocarcinoma	Inhibits tumor glycolysis; reverses lactate-driven M2 polarization	Inhibits AKT/mTOR pathway, reduces lactate production	[18]
Artesunate (AS) + anti-PD-1 antibody	Non-small cell lung cancer	Reprograms TAMs (M2→M1); enhances T cell activation	Mediated by STAT1/IRF1, synergistic with immunotherapy	[13]
Aidikang Formula (ADQ) / Liquiritin	Breast cancer	Promotes lysosomal degradation of CXCL1 in TAMs; inhibits angiogenesis	Mediates CXCL1 degradation via CTSK	[19]
Zuogui Yin (ZGY)	Esophageal squamous cell carcinoma	Blocks M2 polarization; indirectly inhibits tumor glycolysis	Inhibits IL-4/JAK2/STAT6 pathway	[22]

4. Limitations of current research and future directions

Although considerable progress has been made in recent years, several issues continue to limit the clinical application of TAM-targeted Traditional Chinese Medicine (TCM) therapies.

4.1. Technical challenges related to the bioavailability of TCM components

One of the main problems with many active components in Traditional Chinese Medicine (TCM) is that their bioavailability is not very high. This includes monomers, polyphenols, and polysaccharides. In most cases, this is related to poor water solubility, fast metabolism in vivo, and also limited accumulation in tumor tissues [27]. Because of these factors, the actual amount of drug reaching the target site can be quite low, which may in turn reduce therapeutic effect.

To address this issue, a number of drug delivery approaches have been explored. Nanotechnology-based systems, for example, liposomes and polymeric nanoparticles, are often mentioned. These systems are mainly designed to improve stability and also control drug release. Some pH-responsive nanocarriers are reported to release drugs more efficiently in acidic tumor environments, which may slightly improve local targeting [28]. Apart from this, there are also other experimental platforms such as exosome-based delivery systems and metal-organic frameworks, but most of them are still in early-stage research and not yet close to clinical use.

4.2. Standardization of integrated TCM-Western medicine therapy

In recent years, combining TCM with chemotherapy or immune checkpoint inhibitors has shown some promising results in clinical studies. Some reports mention improved survival outcomes and also changes in immune-related indicators within the tumor microenvironment [29]. However, it is also clear that the overall clinical evidence is still not strong enough at this stage.

One major issue is that treatment protocols are not consistent across studies. Different research groups use different dosages, schedules, and even different ways to evaluate efficacy. Because of this, it is very difficult to compare results directly. For example, there is still no clear agreement on how to choose doses or how to set treatment timing when TCM formulas are used together with immune checkpoint inhibitors.

Management of adverse reactions is also not standardized.

At present, most of these combination strategies are still at the exploratory stage. More clinical data, especially from multicenter studies, will probably help clarify which patient groups may benefit more and how these therapies should be used more consistently.

5. Conclusion

Current evidence suggests that tumor-associated macrophages (TAMs) have an important role in the tumor microenvironment, and changes in macrophage polarization are closely related to tumor growth, immune escape, and metastasis. A number of signaling pathways, including PI3K/Akt/mTOR, STAT6, NF-κB, and IL-10/PD-L1, participate in these processes and have therefore become potential targets for anti-tumor therapy.

There are quite a few studies suggesting that Traditional Chinese Medicine (TCM) can influence tumor-associated macrophages (TAMs), but the way it works does not seem to be limited to one single pathway. Compounds like artesunate, matrine, and celastrol have all been mentioned in the literature, although each of them seems to act through different and sometimes overlapping mechanisms. The same kind of pattern is also reported in several formulas such as *Bufei* Decoction, *Danggui Buxue* Decoction, and *Aidikang* Formula.

In addition to effects on macrophage polarization itself, some studies also point out that TCM may affect how macrophages interact with other cells in the tumor microenvironment. This includes tumor cells, T cells, and endothelial cells, but the exact degree of each interaction is still not very clear.

There are also experimental and some clinical findings suggesting that TCM might enhance the effects of chemotherapy, targeted therapy, or immunotherapy when they are used together. A few formulas, for example *Jianpi Yangzheng Xiaozhong* Decoction, *Fuzheng Jiedu Xiaoji* Formula, and *Fuzheng Yiliu* Formula, have shown relatively positive results in clinical reports. But it has to be said that most of these studies are still small, and many come from single hospitals or limited datasets, so the evidence is not really strong yet.

At the same time, there are still many things that remain unclear. For example, pathways like STAT1/IRF1, TLR4-MyD88, and CTSK are often mentioned in experimental work, but how important they really are in actual human patients is still uncertain. It is also not very clear whether TCM works mainly by reshaping the tumor immune microenvironment or whether it just adds to the effect of existing treatments in a more general way. In addition, problems such as poor bioavailability of some compounds and the lack of unified treatment standards are still there and continue to limit clinical use.

Moving forward, progress will likely depend on how well experimental work and clinical studies can be linked together. It would be important to identify which components in effective formulas are actually responsible for the observed effects, and how they act at the molecular level. Drug delivery systems, including nanocarriers or exosome-based approaches, may help improve this, but most of these are still in early stages. On the clinical side, larger and better-designed multicenter studies are still needed to really understand how TCM should be combined with chemotherapy, targeted therapy, or immunotherapy. For now, the role of TCM in regulating the tumor immune environment is still being explored rather than clearly defined.

Disclosure statement

The authors declare no conflict of interest.

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