

# An Exploration of the Development of Melanoma ICI Resistance and Prevention and Treatment Strategies Based on the “Zheng-Xie” Theory

Zicheng Zhang<sup>1</sup>, Liwen Wang<sup>1</sup>, Danlei Tong<sup>2,\*</sup>

<sup>1</sup>Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

<sup>2</sup>Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

\*Correspondence Author

**Abstract:** Immune checkpoint inhibitors (ICIs) are currently the primary treatment for melanoma, and resistance to ICIs is a major factor leading to treatment failure, recurrence, and metastasis in melanoma. The development of melanoma is closely related to the Traditional Chinese Medicine (TCM) theory of “Zheng and Xie”: deficiency of Zheng Qi is the foundation of melanoma onset; the accumulation of Xie is a trigger for its progression; and the combination of Zheng deficiency and Xie accumulation promotes the progression of melanoma. The pathological state of “deficiency of Zheng Qi and accumulation of Xie” creates conditions for the development of ICI resistance. The prevention and treatment of ICI resistance in melanoma using Traditional Chinese Medicine (TCM) should focus on two aspects: strengthening Zheng Qi and consolidating the foundation to address the “deficiency state,” and expelling Xie and clearing the source to address the “Xie state.” By restoring the balance between Zheng and Xie and implementing comprehensive, full-process treatment management, this approach provides new insights for the prevention and treatment of ICI resistance in melanoma using TCM.

**Keywords:** Melanoma, Deficiency of the body’s vital energy and accumulation of pathogenic factors, ICI resistance, Prevention and treatment.

## 1. Introduction

Immune checkpoint inhibitors (ICIs) are currently the primary clinical treatment for melanoma; however, during treatment, some patients exhibit resistance as early as the initial phase, and 20%-30% of those who initially respond to treatment eventually experience recurrence or progression. Only a handful of patients achieve long-term benefit [1]. Traditional Chinese medicine (TCM) offers distinct advantages in regulating the body’s internal environment, enhancing immune function, alleviating adverse reactions to ICIs, improving cancer patients’ tolerance to therapeutic drugs, prolonging survival, and enhancing quality of life [2]. There is ample clinical evidence supporting the synergistic and toxicity-reducing effects of TCM on ICIs in the treatment of melanoma [3].

The theory of “Zheng and Xie” originates from the “Huangdi Neijing” and is one of the core theories of Traditional Chinese Medicine for understanding, diagnosing, and treating diseases. According to Traditional Chinese Medicine, “Zheng” (正) refers to Zhengqi, which denotes the body’s ability to resist pathogenic factors, self-regulate, and repair itself; “Xie” (邪) refers to Xieqi, which denotes various pathogenic factors that can damage the body’s Zhengqi, leading to the onset and progression of disease. The struggle between Zheng and Xie is the fundamental pathogenesis of disease and runs throughout the entire course of the illness. In the treatment of melanoma with ICIs, “Zheng Qi” can be analogized to the body’s antitumor immune response (including the activity of immune cells such as T cells and NK cells), while “Xie Qi” refers to tumor cells and their immunosuppressive microenvironment [4]. The body is constantly engaged in a struggle between antitumor and pro-tumor forces, and the outcome of this struggle determines whether ICI resistance develops.

From the perspective of the “Zheng-Xie” theory, the essence of tumor immunotherapy is to suppress “Xie Qi” by enhancing “Zheng Qi.” ICIs work by lifting the suppression exerted by tumor cells on the immune system and enhancing the antitumor activity of immune cells, which is equivalent to bolstering “Zheng Qi” to counteract “Xie Qi.” When the body’s “Zheng Qi” is deficient, ICIs cannot fully activate immune cells, resulting in an inability to effectively recognize and eliminate tumor cells, which leads to the development of ICI resistance [5]; as pathogenic factors accumulate, the tumor microenvironment becomes saturated with immunosuppressive cells and factors, enabling tumor cells to evade the immune system through various mechanisms [6] (such as genetic mutations, antigen loss, and upregulation of immunosuppressive molecules), thereby leading to ICI resistance. Therefore, the development of ICI resistance in melanoma can be viewed as the result of “deficiency of the body’s vital energy and accumulation of pathogenic factors.” This article combines modern medical research to explore the relationship between “deficiency of the body’s defensive energy and accumulation of pathogenic factors” and ICI resistance, and proposes prevention and treatment strategies.

## 2. Deficiency of Zheng Qi and Accumulation of Pathogenic Factors Underlie the Formation and Development of Melanoma

The onset of melanoma can be viewed as a weakening of the body’s vital energy, which reduces the body’s ability to resist external invasions and creates conditions for pathogenic factors to enter the body; the progression of melanoma causes the body to consume large amounts of energy and nutrients, thereby depleting the body’s vital energy [7]. Modern research indicates that malignant tumor cells can interfere with immune surveillance through multiple pathways,

allowing tumors to evade recognition and elimination by the immune system over the long term [8]. In summary, deficiency of Zheng Qi is the root cause, while the accumulation of pathogenic factors is the manifestation; the two are mutually reinforcing and together constitute the important pathological basis for the formation and development of melanoma.

## 2.1 Deficiency of Zheng Qi as the Foundation of Melanoma Onset

As stated in the “Huangdi Neijing” (The Yellow Emperor’s Classic of Internal Medicine), if “vital energy resides within,” the body remains in a “steady state”: the five zang organs are robust, the muscles function smoothly, the blood vessels are harmonious, and qi and blood are abundant—in such a state, “pathogenic factors cannot invade.” If vital energy is deficient, however, “pathogenic factors take hold,” leading to the formation of accumulations. Zhang Yuan-su’s “Essentials of the Living Methods” states: “Healthy individuals have no accumulations, while deficient individuals do... all can lead to accumulations.” This reveals that the weakness of vital energy is the fundamental condition for the development of melanoma. When vital energy is abundant, qi, blood, and essence nourish the skin, and the skin’s various physiological functions remain normal; conversely, when vital energy is deficient, the skin’s protective, reparative, and barrier functions are impaired, leaving it unable to resist or expel external pathogens, thereby creating conditions conducive to the development of melanoma.

According to Traditional Chinese Medicine, “deficiency of the Zheng Qi” primarily manifests in two aspects: deficiency of qi, blood, yin, and yang, and insufficiency of organ function. The causes are often attributed to congenital insufficiency, improper postnatal care, emotional distress, or invasion by external pathogens, which damage the zang-fu organs and disrupt the balance of qi, blood, and yin-yang. This leads to the intermingling of phlegm, blood stasis, and toxins, ultimately resulting in melanoma. “Vital energy” (zhengqi) originates from congenital essence (kidney qi) and acquired essence (the essence of food and drink transformed by the spleen and stomach); therefore, deficiency of vital energy is often attributed to the spleen and kidney. The spleen and stomach transform and transport the essence of food and drink, serving as the foundation of acquired vitality, and perform defensive functions through defensive qi (wei qi) [10]. Spleen deficiency, leading to abnormal transformation and transportation of qi and blood, can result in impaired immune function; the defensive qi is then unable to fortify the exterior, allowing external pathogens to invade and trigger melanoma. Decline of kidney yang, resulting in a failure to provide warmth and nourishment, leads to the generation of internal cold; the circulation of qi and blood becomes stagnant due to the cold, thereby producing pathological products such as blood stasis and cold phlegm that induce melanoma. “Treatise on the Origins and Symptoms of Various Diseases: Symptoms of Black Moles” states: “Those with black moles... When a person’s blood and qi are abundant, the skin is moist and radiant, and no blemishes or masses arise. If there is deficiency or depletion, black moles will develop.” “The Authentic Treatise on Surgery: Black Moles” states: “Black moles are a type of nevus. Turbid qi from the skin and kidneys

clouds the yang; as yang qi contracts, it condenses into black moles that are firm and do not dissipate.” The above discussions reflect that “deficiency of the Zheng Qi”—caused by the deficiency of the zang-fu organs and imbalances in qi, blood, yin, and yang—is the foundation for the onset and progression of melanoma. [9]. Due to factors such as congenital insufficiency, inadequate postnatal nourishment, emotional disturbances, and invasion by external pathogens, patients experience deficiency of the zang-fu organs and imbalances in qi, blood, yin, and yang, which in turn lead to the accumulation of phlegm, stasis, and toxins, ultimately progressing to melanoma. “Vital energy” (zhengqi) originates from congenital essence (kidney qi) and acquired essence (the essence of food and drink transformed by the spleen and stomach); therefore, deficiency of vital energy is often attributed to the spleen and kidney. The spleen and stomach transform and transport the essence of food and drink, serving as the foundation of acquired vitality, and perform defensive functions through defensive qi (wei qi) [10]. Spleen deficiency, leading to abnormal transformation and transportation of qi and blood, can result in impaired immune function. When Wei Qi fails to fortify the exterior, external pathogens invade, inducing melanoma. Decline of Kidney Yang, causing dysfunction in its warming and nourishing functions, leads to the internal generation of yin-cold. The circulation of qi and blood becomes stagnant due to the cold, producing pathological products such as blood stasis and cold phlegm, which in turn induce melanoma. The “Treatise on the Origins and Symptoms of Various Diseases: Symptoms of Black Moles” states: “Those with black moles... When a person’s blood and qi are abundant, the skin is moist and radiant, and no blemishes or masses arise. If there is deficiency or debility, black moles may develop.” The “Authentic Treatise on Surgery: Black Moles” states: “A black mole is a type of nevus. Turbid qi from the skin and kidneys obscures the yang; as yang qi contracts, it coalesces into a black mole that is firm and does not dissipate.” The above discussions reflect that “deficiency of the Zheng Qi”—resulting from the deficiency of the zang-fu organs and imbalances in qi, blood, yin, and yang—constitutes the foundation for the onset and progression of melanoma.

## 2.2 The Accumulation of Pathogenic Factors Is a Trigger for the Development of Melanoma

According to Traditional Chinese Medicine, the accumulation of pathogenic factors in melanoma results from “deeply latent toxic pathogens and the mutual entanglement of phlegm and blood stasis.” Its etiology and pathogenesis involve both external pathogenic invasions and internally generated pathogenic factors arising from internal injury; these interact causally with the deficiency of Zheng Qi, jointly driving the onset and progression of melanoma.

In cases of congenital deficiency and inherent insufficiency of qi and blood, when compounded by emotional distress and organ dysfunction, and further exposed to toxic pathogens, the pathogenic toxins penetrate inward. This leads to stagnation in the Wei layer, where heat toxins clash with blood and qi, causing obstruction in the meridians, blood stasis, and qi stagnation, which then accumulate at the skin surface. Over time, qi stagnation forms masses; water and dampness condense into phlegm-turbidity; and impaired blood

circulation leads to blood stasis. Pathogenic factors such as phlegm, blood stasis, qi, and dampness intertwine, gradually laying the foundation for melanoma. As stated in “A Clear Illumination of the Origins and Course of Miscellaneous Diseases”: “When pathogenic factors prevail, the body’s vital energy cannot contain them, and they thus coalesce into a mass.” Subsequently, phlegm and stasis become tightly bound, obstructing the collateral vessels; the tumor gradually swells. Pathogenic toxins rupture the vessels and escape, circulating with the qi and blood; they accumulate internally in the viscera and bones, and externally erode the skin, causing the ulcerated surface to turn black and become eroded. Stagnant heat transforms into pus, which infiltrates and spreads, ultimately leading to malignant transformation. Therefore, the accumulation of pathogenic factors is the fundamental cause of the onset and progression of this disease.

### **2.3 Deficiency of the Righteous Qi and Accumulation of Pathogenic Factors Promote the Development of Melanoma**

The chapter on “Accumulations” in “Essential Readings on Medicine” points out that the formation and progression of tumors are dynamic processes resulting from the struggle between the healthy body’s vital energy and pathogenic factors; melanoma is no exception.

Spleen deficiency leads to an insufficiency in the source of qi and blood, resulting in the accumulation of phlegm and dampness within the body; kidney deficiency results in an insufficiency of original qi, causing a failure to regulate warmth, and leading to the concurrent development of cold stagnation and blood stasis. Qi deficiency causes sluggish blood circulation, resulting in stasis; yang deficiency causes body fluids to congeal into phlegm; and yin deficiency causes fire to scorch and transform phlegm into heat. Therefore, deficiency of the righteous qi serves as the foundation for the accumulation of pathogenic factors. Melanoma depletes qi, blood, and body fluids, causing the body to gradually waste away; heat-toxin scorches the lungs, damp-toxin impairs the spleen, and the zang-fu organs further decline. Pathogenic factors accumulate and obstruct the collaterals; phlegm, stasis, and toxins coalesce, hindering the distribution of qi and blood, causing the deficient to become even more deficient. Deficiency of the Zheng invites pathogenic factors, and the accumulation of pathogenic factors damages the Zheng—a mutual cause-and-effect relationship forming a vicious cycle. Therefore, deficiency of the Zheng is the root cause of the disease, while the accumulation of pathogenic factors is the pivotal point of its progression; strengthening the Zheng and consolidating the root, while expelling pathogenic factors and resolving toxins, must be maintained throughout the entire treatment process.

### **3. Deficiency of the Righteous Qi and Accumulation of Pathogenic Factors Are Interdependent Causes of ICI Resistance in Melanoma**

In recent years, immune checkpoint inhibitors (ICIs) have achieved significant progress in the treatment of melanoma. However, among patients with malignant melanoma treated

with programmed cell death receptor 1 (PD-1) inhibitors, up to 60% show no response [11], and the underlying mechanisms of action and factors contributing to resistance remain incompletely understood. According to Traditional Chinese Medicine (TCM), the onset and progression of melanoma are closely related to “deficiency of Zheng Qi and accumulation of pathogenic factors.” Therefore, this paper elucidates the relationship between “deficiency of Zheng Qi and accumulation of pathogenic factors” and ICIs resistance in melanoma from two perspectives: first, that ICIs damage Zheng Qi and promote the accumulation of pathogenic factors; and second, that the pathological state of “deficiency of Zheng Qi and accumulation of pathogenic factors” creates conditions for ICIs resistance.

#### **3.1 ICIs Damage Zheng Qi and Promote the Accumulation of Pathogenic Factors**

ICIs are potent and aggressive agents, often used to treat intractable and chronic diseases. Patients typically present with complex pathological mechanisms and protracted, difficult-to-treat conditions; their qi and blood are already deficient, leaving them unable to tolerate such potent and aggressive treatments. At the same time, the harsh nature of these drugs can further damage the body’s Zheng Qi. Once Zheng Qi is depleted, qi loses its ability to transport toxins, and blood loses its capacity to transform toxins, thereby intensifying the toxicity. Furthermore, even toxic herbs intended to attack pathogenic factors can, if administered at the wrong time or in excessive doses, cause the medicinal energy to wane. As a result, the intense toxicity intensifies and turns inward to attack the body. In such cases, not only is the body unable to expel the pathogenic factors, but the vital energy suffers further harm; indeed, pathogenic toxins cannot be resolved without sufficient vital energy. [12]. Therefore, prolonged or improper use of ICIs can damage the body’s vital energy, leading to various symptoms of deficiency.

The lung-wei system plays a vital role in protecting the body from external pathogenic factors and fighting infections. The aggressive nature of ICIs can weaken the protective function of the lung-wei system and deplete lung qi, making the body more susceptible to viral and bacterial attacks and increasing the risk of infection. This may result in symptoms such as coughing and sputum production, and in severe cases, may even lead to abnormal lung function. Most ICIs are cytotoxic drugs that can easily damage immune organs, and the spleen—as one of the body’s key immune organs—is particularly vulnerable. ICIs can damage the spleen; when the spleen and stomach are impaired, the normal ascending and descending movements of qi are disrupted, leading to spleen qi deficiency, insufficiency of spleen ying, and liver-spleen disharmony. Clinically, this may manifest as poor appetite, diarrhea, nausea, vomiting, constipation, and hepatitis [14], among other symptoms. The diseases treated with ICIs in clinical practice are often chronic and intractable conditions. The pathogenesis of such diseases is complex, and patients often already have deficient vital energy (zhengqi). The use of immunosuppressants will inevitably exacerbate the patient’s qi deficiency syndrome. Since the kidneys are the root of qi and the foundation of yin and yang in the body, damage to any organ or viscera can affect the kidneys, thereby causing kidney dysfunction [15]. As mentioned earlier, the use of ICIs

can impair the lungs, affect the spleen, and damage the kidneys, leading to deficiency of qi and blood, disharmony among the zang-fu organs, and the accumulation of pathogenic factors.

### 3.2 Deficiency of Zheng Qi and Accumulation of Pathogenic Factors Create Conditions for Melanoma Resistance to ICIs

#### 3.2.1 Insufficiency of the Body's Defensive Qi Is the Root Cause of Drug Resistance

ICIs exert their therapeutic effects by activating T-cell-mediated antitumor immunity; however, treatment failure in melanoma is often due to drug resistance. Insufficiency of the body's vital energy (deficiency of the spleen and kidneys, and disharmony of qi, blood, and yin-yang) essentially results in a decline in the body's immune surveillance and response functions, rendering it unable to effectively mobilize T cells to kill tumors, while simultaneously creating an immunosuppressive tumor microenvironment (TME).

The spleen is the source of the generation of qi and blood; spleen deficiency leads to impaired energy metabolism in T cells and NK cells, manifesting as T-cell exhaustion (high PD-1 expression) and diminished anti-tumor persistence [16]. The kidneys store essence and govern the bones; kidney deficiency suppresses bone marrow hematopoiesis, reduces the production of CD8<sup>+</sup> T cells, and causes abnormal DNA methylation, leading to a loss of immune memory and a failure of the immune response [17]. Qi deficiency results in insufficient T-cell infiltration into the tumor microenvironment (TME), leading to sparse distribution of immune cells [18]; blood stasis obstructs the meridians, causing abnormal proliferation of tumor blood vessels and hindering the penetration of T cells and drugs [19]. Yin deficiency with excessive fire, where deficient fire scorches body fluids, leads to the excessive release of inflammatory factors such as IL-6 and TNF- $\alpha$  within the TME, inducing the expansion of MDSCs and Tregs; Yang deficiency with cold stagnation results in hypoxia and acidification of the TME, where HIF-1 $\alpha$  activation upregulates PD-L1 expression, thereby enhancing immune suppression [21]. In summary, deficiency of the body's vital energy not only weakens immune surveillance and effector functions but also shapes a suppressive TME, which is the fundamental cause of melanoma resistance to ICIs.

#### 3.2.2 Accumulation of Pathogenic Factors and Widespread Toxicity: The Driving Force Behind Resistance

Resistance to ICIs in melanoma is actually caused by the persistent retention and widespread dissemination of phlegm, stasis, and toxic pathogens throughout the body. This leads to the remodeling of the tumor microenvironment (TME) and the spread of cancer toxins, creating a vicious cycle in which the two phenomena are mutually reinforcing. This mechanism not only inhibits T-cell chemotaxis and activation but also drives tumor heterogeneity and immune evasion, constituting the core mechanism of ICI resistance.

Deficiency in the central earth element leaves the body's vital

energy unable to overcome pathogenic factors; qi stagnation and blood stasis allow dampness and heat pathogens to pervade and accumulate in the skin, eventually transforming into toxins. The accumulation of pathogenic factors and the proliferation of toxins form the tumor microenvironment (TME), creating conditions for immune evasion [22]. "Toxic proliferation" represents the final stage of carcinogenesis. Among these, heat-toxin-induced inflammation creates a pro-inflammatory microenvironment saturated with inflammatory mediators, promoting melanoma progression; stasis-toxin, resulting from stagnant blood flow, creates a hypoxic-like microenvironment characterized by abnormal neovascularization and oxygen-deprived blood supply [23]. Phlegm-toxin is viscous and turbid, creating an acid-like microenvironment where acidic metabolic byproducts accumulate, aiding cancer cell escape and metastasis [24]. Studies indicate that qi stagnation and blood stasis can lead to abnormal vascular proliferation, reduce T-cell migration and infiltration, and weaken the efficacy of ICIs [25]; whereas the accumulation of phlegm-dampness increases immunosuppressive factors, inhibiting T-cell activation [20]. In summary, the TME resulting from the accumulation of pathogenic factors and the spread of toxins—with impaired T-cell infiltration, tumor heterogeneity, and immune evasion as key mechanisms—is the core driver of melanoma resistance to ICIs.

## 4. Prevention and Treatment Strategies for Melanoma ICI Resistance Guided by the Theory of Zheng and Xie

### 4.1 Nourishing the "Zheng Qi" and Regulating "Deficiency States"

Deficiency of "Zheng Qi" is a fundamental condition for the development of melanoma. Consequently, invigorating "Zheng Qi" and strengthening immune function are the primary principles of treatment. Therefore, enhancing immune cells and their effector factors that exert positive immune regulation, strengthening innate and adaptive immune responses, and improving the cytotoxic efficacy against tumor cells—thereby effectively inhibiting their proliferation, growth, and metastasis—is precisely the concrete manifestation of "Zheng Qi" at the immune level.

Traditional Chinese medicines and their active compounds in the "tonifying the body's vital energy and consolidating the foundation" category can enhance the innate immune response and modulate the adaptive immune response by increasing the cytotoxic capacity of NK cells, promoting antigen presentation by dendritic cells (DCs), enhancing the phagocytic capacity of M1 macrophages to tumor cells, and regulating T-lymphocyte subsets, thereby improving the body's "deficient state" [26]. Research has found that astragaloside, the primary component of *Astragalus membranaceus*—a representative herb for tonifying the spleen and boosting qi—can further stimulate NK cells and T cells, enhance the role of T cells in the tumor microenvironment, and strengthen antitumor immunity [27]. Ginsenoside Rg3, the main component of ginseng, induces apoptosis and inhibits tumor proliferation and metastasis by suppressing the NF- $\kappa$ B, AP-1, VEGF, and PI3K/Akt pathways [28]. In addition, qi-tonifying agents can suppress

inhibitory immune cells and cytokines, thereby reversing immunosuppression and enhancing the body's antitumor capacity—that is, eliminating pathogenic factors by strengthening the body's vital energy. The combination of Rucanqi Qi-Tonifying Injection with PD-L1 antibodies produces a synergistic effect; the mechanism may be related to promoting dendritic cell (DC) infiltration and T-cell activation, and immunohistochemical analysis also suggests that it improves the microenvironment [29]. Jinshui Liuju Decoction exerts its anticancer effects by downregulating p-P38, p-JNK, and P62, while upregulating Beclin1 and the LC3 II/I ratio. This blocks the P38 and JNK signaling pathways, inhibits B16 cell proliferation, and simultaneously promotes apoptosis and activates autophagy [30].

#### 4.2 Eliminating Pathogenic Factors, Clearing the Source, and Regulating “Pathogenic States”

The accumulation of pathogenic factors serves as a trigger for the development of melanoma; therefore, eliminating these pathogenic factors is the cornerstone of its treatment. Specifically, eliminating pathogenic factors focuses on clearing negative immune responses that promote tumor growth and weaken antitumor activity, as well as abnormal factors that disrupt the homeostasis of the immune microenvironment, encompassing tumor cells, immunosuppressive cells, and microenvironmental imbalances.

The active compounds in traditional Chinese medicine modulate immunosuppressive states through mechanisms that include reversing the polarization of TAMs toward the M2 phenotype, regulating MDSCs, and inhibiting the proliferation and activation of Tregs. Simultaneously, they block the transformation of “positive energy” into “pathogenic factors,” improve the “pathogenic state,” and thereby suppress melanoma. Studies have found that Polysaccharides from *Coptis chinensis* activate the TLR4/TRIF/STAT1 pathway in RAW264.7 cells, enhancing immune activity and inhibiting the proliferation and metastasis of B16F10 cells [31]; Andrographolide arrests human melanoma C8161 and A375 cells in the G2/M phase, induces apoptosis, and increases CD4<sup>+</sup> and CD8<sup>+</sup> T-cell infiltration [32]; Safflower polysaccharides can induce macrophage polarization toward the M1 phenotype by activating the Notch1 signaling pathway within macrophages, thereby inhibiting the invasion and migration of melanoma cells [33]. The combination of *Salvia miltiorrhiza* and *Panax ginseng* can inhibit the secretion of stimulatory factors such as S100A8/9, IL-6, CXCL1/2, and GM-CSF by tumor tissues, reduce the infiltration of MDSCs in the tumor microenvironment, remodel the tumor immunosuppressive microenvironment, and restore the activity of immune cells such as CD8<sup>+</sup> T cells, thereby achieving the goal of inhibiting melanoma metastasis [34].

#### 5. Summary

There is substantial clinical and experimental evidence supporting the use of TCM interventions for melanoma ICI resistance and multidrug resistance. From the perspective of the “Zheng-Xie” theory, ICI resistance is essentially a pathological imbalance caused by “deficiency of Zheng and

excess of Xie, with accumulated toxins that fail to dissipate”: Insufficiency of Zheng Qi (deficiency of the spleen and kidneys, and imbalance of Qi, blood, Yin, and Yang) weakens immune surveillance, constituting the root cause of resistance; the accumulation of pathogenic factors and the spread of toxins (coagulation of phlegm and blood stasis, and the flow of cancerous toxins) reshape the microenvironment, serving as the driving force behind resistance. The two factors are mutually causative; as the “Righteous Qi” becomes more deficient, the “Pathogenic Factors” become more rampant, creating a vicious cycle. Therefore, in the prevention and treatment of melanoma resistance, we should focus on strengthening the “Righteous Qi” and consolidating the foundation to address the “deficient state,” while expelling the “Pathogenic Factors” and clearing the source to address the “pathogenic state.” This approach restores the balance between the “Righteous Qi” and “Pathogenic Factors,” improves the internal environment, enhances the body's immune function, and prevents drug resistance. Traditional Chinese medicine (TCM) treatment offers distinct advantages in regulating the internal environment, enhancing immune function, alleviating adverse reactions to ICIs, improving patients' tolerance to therapeutic drugs, prolonging survival, and enhancing quality of life; its multi-target approach is conducive to overcoming the bottleneck of drug resistance. Future research should further focus on developing a quantitative evaluation system for the “dynamic balance between the body's vital energy and pathogenic factors” (e.g., the association between biomarkers and TCM syndrome patterns) and establishing precision treatment regimens that integrate TCM and Western medicine (e.g., combining ICIs with TCM), thereby offering advanced melanoma patients the potential to transition from “living with the tumor” to “eliminating pathogenic factors and restoring the body's equilibrium.”

#### References

- [1] OTT PA, BANGYJ, PIHA-PAUL SA, et al. T-cell-inflamed gene expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028 [J]. *J Clin Oncol*, 2019, 37(4): 318-327.
- [2] ZHANG Zhipeng, CHEN Ziqi, TIAN Jianhui. The attenuating and potentiating effects of traditional Chinese medicine in immune checkpoint therapy [J]. *Chinese Journal of Clinical Pharmacology and Therapeutics*, 2024, 29(03): 339-347.
- [3] XU Xiangning, WANG Yindi, LYU Zhen, ZHENG Guisen, WU Jianjun. Research Progress on Combined Traditional Chinese and Western Medicine Anti-tumor Treatment Based on the PD-1/PD-L1 Immune Checkpoint Pathway [J]. *Journal of Basic Chinese Medicine*, 2024, 30(07): 1258-1264.
- [4] LING Changquan. Cancerous Toxin Is the Key Pathogenic Factor of Malignant Tumors [J]. *Journal of Chinese Integrative Medicine*, 2008, 6 (2): 111-114.
- [5] TANG Zhenhao, LAN Congying, LIN Lizhu. On “Deficient Vital Qi and Excess Pathogenic Qi” in Cancer and Its Treatment Based on the Cancer Immunoediting Hypothesis [J]. *Journal of Traditional Chinese Medicine*, 2019, 60(13): 1113-1117.

- [6] XIE Yingying, LI Dongdong, ZHANG Xiaoqing, MA Chunzheng, HU Yiyang, ZHAO Ningning, ZHANG Juan. Research Progress on Non-coding RNA Regulating Tumor Immune Escape [J/OL]. Chinese Journal of Immunology, 2026, 42(3): 729-735741.
- [7] LU Xinyi, LUO Bin, QUE Zujun, JIANG Lei, TIAN Jianhui. Discussion on the inflammatory-cancer transformation of pulmonary nodules and traditional Chinese medicine prevention and treatment strategies based on the theory of latent toxicity due to vital qi deficiency [J]. Shanghai Journal of Traditional Chinese Medicine, 2023, 57(4): 8-12.
- [8] MEYER M A, BAER J M, KNOLHOFF B L, et al. Breast and pancreatic cancer disrupt IRF8-dependent dendritic cell development to overcome immune surveillance [J]. Nat Commun, 2018, 9(1):1250.
- [9] GUO Tianhao, LI Liu, CHENG Haibo. Review of Research on the Tumor Pathogenesis of Traditional Chinese Medicine [J]. JOURNAL OF BASIC CHINESE MEDICINE, 2024, 30(08): 1415-1418.
- [10] ZHAI Yarong, WU Yao, QIU Xueying, ZHENG Haolong, SUI Guoyuan, SONG Nan, JIA Lianqun. Traditional Chinese Medicine Regulates the Immune System to Affect Tumors: Based on "The Spleen Acts as the Guardian of the Five Zang Organs and Six Fu Organs" [J]. World Chinese Medicine, 2022, 17(8): 1105-1109.
- [11] Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 Pathway Blockade for Cancer Therapy: Mechanisms, Response Biomarkers, and Combinations [J]. Sci Trans. Med, 2016, 8(328): 328rv4.
- [12] LI Chang-qing, ZHOU Xue-ping. Discussion on the Essence of the Method of Combining Traditional Chinese Medicine Formulas with Body-Strengthening and Detoxification [J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2021, 36(12): 7093-7095.
- [13] ZHAO Bofeng, ZHANG Yamin, CHEN Ping, FENG Wei, LIU Jinpeng, NAN Kejun, CHEN Baoying. CT Imaging Characteristics of Severe (Grade 3-4) Immune Checkpoint Inhibitor-Related Pneumonitis in Lung Cancer [J]. Chinese Journal of Medical Imaging, 2024, 32(09): 903-907.
- [14] KENNEDY L B, SALAMA A K S. A review of cancer immunotherapy toxicity [J]. CA Cancer J Clin, 2020, 70(2): 86-104.
- [15] ZHAO Xiao-hong, YAN Ci-lin, PAN Chen, GUO Ming-xing, CUI Xiang-li. Data Mining of Adverse Events Related to Immune Checkpoint Inhibitors in Acute Kidney Injury Based on FAERS [J]. Chinese Journal of New Drugs, 2023, 32(23): 2434-2440.
- [16] CHEN Ling, YANG Jinzu, LI Xin, LU Yanlin, TAO Li, LI Zhiming. Exploration of the Correlation Between the Pathogenesis of Spleen Deficiency in Cancer and the Reprogramming of Energy Metabolism [J]. Chinese Journal of Information on Traditional Chinese Medicine, 2025, 32(03): 29-33.
- [17] CAO Ji-gang, REN Mei-rong, ZHAO Min. On the Relationship Between Congenital Kidney Deficiency and Immunity and Its TCM Countermeasures [J]. JOURNAL OF LI-SHIZHEN TRADITIONAL CHINESE MEDICINE, 2021, 32(01): 143-145.
- [18] KUANG Ziyu, YAN Ningzhe, LIU Kexin, LI Jie. Discussion on the Pathogenesis of the "Deficiency-Toxicity" Interaction in Malignant Tumors and Differentiation and Treatment from the Perspective of Immunoediting [J]. China Journal of Traditional Chinese Medicine and Pharmacy, 2024, 39(12): 6404-6408.
- [19] JIANG Jia-wang, LI Zhi-ming, HUANG Lin. Meta-analysis of the Efficacy of "Activating Blood to Resolve Stasis" Therapy on Tumor Angiogenesis and the Tumor Hypoxia Microenvironment [J]. Journal of Oncology in Chinese Medicine, 2022, 4(1): 69.
- [20] HUANG Wenbo, PAN Li, HUANG Ya, JIANG Yifang, YAN Ran, ZHU Jie, YOU Fengming. "On Yin Fire and Tumor Genesis in Traditional Chinese Medicine Based on Energy Metabolism Reprogramming" [J]. Journal of Traditional Chinese Medicine, 2022, 63(10): 905-909.
- [21] DAI Yining, LI Huijie, LI Xiurong. Discussion on the Formation and Intervention of the Tumor Microenvironment Based on the Theory of "Where There Is Mass Hardness, There Must Be Latent Yang" [J]. Journal of Traditional Chinese Medicine, 2023, 64(22): 2275-2281.
- [22] LU Taicheng, XU Bowen, WU Jinyang, LI Jie, Ni Baoyi, YU Jingwen, ZHAO Weizhe. Biological Basis of the Five-Phase Evolution of Malignant Tumors from the Perspective of "Immune Editing" [J]. Chinese Journal of Experimental Traditional Medical Formulae, 2023, 29(21): 172-179.
- [23] PATEL A, SANT S. Hypoxic Tumor Microenvironment: Opportunities to Develop Targeted Therapies [J]. Biotechnol Adv, 2016, 34(5): 803-812.
- [24] YIN Chang, SHI Yin, LIU Ran, ZHANG Yiwen, XU Ying, ZHENG Bingyuan, LI Jing, HAN Tao. Research on Traditional Chinese Medicine Targeting the Hepatocellular Carcinoma Microenvironment Based on the "Strengthening the Body and Eliminating the Pathogen" Theory [J]. Journal of Liaoning University of Traditional Chinese Medicine, 2026, 28(6): 120-128.
- [25] Xu Yan, Ying Guo, Donglin Sun, Nan Wu, Yan Jin. Mechanisms of drug resistance to anti-angiogenesis therapy in tumors [J]. Hereditas (Beijing), 2024, 46(11): 911-919.
- [26] LIU Ying, Cao Hongfu, Zhao Hui, Shen Li. Study on the Method of: Invigorating and Detoxifying in the Treatment of Tumors [J]. JOURNAL OF BASIC CHINESE MEDICINE, 2023, 29(01): 164-168.
- [27] WANG Jieru, WANG Jinying, ZHANG Tingting, CHENG Xiaodong. Regulatory Effect of Astragalus Polysaccharide on the Expression of PD-1/PD-L1 Molecules in Melanoma Mice [J]. Academic Journal of Shanghai University of Traditional Chinese Medicine, 2014, 28(5): 74-79.
- [28] Meng L, Ji R, Dong X, et al. Antitumor activity of ginsenoside Rg3 in melanoma through downregulation of the ERK and Akt pathways [J]. Int J Oncol, 2019, 54:2069-2079.
- [29] ZHOU Zhihua, CHANG Jingwen, YAN Yuanyuan, QI Yanan, HAN Jingjing, ZHU Xinyi, YU Chen, WU Hongyan, FAN Fangtian. Enhancement of the Antitumor Effect of the Immune Checkpoint Inhibitor Anti-PD-L1 by Shenqifuzheng Injection and a Study of the Mechanism [J]. Chinese Journal of Clinical Pharmacology and Therapeutics, 2024, 29(07):792-799.

- [30] HONG Xuemin, PENG Yuan, ZHANG Chong, YANG Li, CHEN Juanping. Network pharmacology combined with in vitro experiments to explore the molecular mechanism of Jinshui Liuju Decoction in adjuvant radiotherapy for malignant melanoma [J]. Journal of Shenyang Pharmaceutical University, 2024, 41(03): 330-342.
- [31] YANG Biping, ZHU Lijun. Exploring the Effect of Cordyceps cicadae polysaccharide on Enhancing Immunity and Suppressing Melanoma Cells via the TLR4/TRIF/STAT1 Pathway [J]. Mycosystema, 2024, 43(08): 129-139.
- [32] Liu G, Chu H. Andrographolide inhibits proliferation and induces cell cycle arrest and apoptosis in human melanoma cells [J]. Oncol Lett, 2018, 15:5301-5305.
- [33] ZHANG Yunchao, MA Jinyun, CHENG Xiaodong. Safflower polysaccharide inhibits the invasion and migration of melanoma cells by inducing M1-type polarization of macrophages [J]. Immunological Journal, 2021, 37(05): 380-389.
- [34] YANG Ge-jun, ZOU Jue-yao, ZHAO Han, CHEN Qiong, HE Yong, LU Yin, CHEN Wen-xing. Combination of Danshen and Renshen Regulates MDSCs to Remodel the Immune Microenvironment of Melanoma [J]. Journal of Nanjing University of Traditional Chinese Medicine, 2022, 38(08):717-726.