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Review

Research Progress of Cytokines and Their Receptors in Ovarian Cancer

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Abstract

Ovarian cancer is characterized by its high occurrence rate, poor prognosis, high recurrence rate, and increasing incidence rate year by year. The cause of the disease is not clear, probably related to heredity, hormones, lifestyle, and environment. Many studies have shown that cytokines such as interleukins not only play a key role in the abnormal proliferation, differentiation, apoptosis, carcinogenesis, metastasis, and multidrug resistance (MDR) of ovarian cancer cells, but also play an important role in the diagnosis, prevention and prognosis of ovarian cancer. In this review, we expound the influence and therapeutic effects of cytokines on ovarian cancer by referring the relevant research studies. This will help us understand the expression levels of cytokines in ovarian cancer and provide evidences for immunologic diagnosis and prognosis as well as new therapeutic targets for cancer immunotherapy.

Keywords: Ovarian cancer, cytokines, the dual role of cytokines, therapeutic target

INTRODUCTION

Often known as the silent killer, ovarian cancer is frequently not diagnosed until it is at an advanced stage because of its generally vague symptoms, making it hard to treat on a curative basis.[1] Thus, ovarian cancer is the deadliest gynecological cancer with Case Fatality Ratio (CFR) of nearly three times that of breast cancer, which is ranked fifth within the main causes of cancer deaths in women.[2,3] According to the statistics released by the International Cancer Research Center (IARC) in 2020, there are 310,000 new cases and 210,000 deaths due to ovarian cancer around the world.[3] Specially, epithelial ovarian cancer, the most common among ovarian malignant tumors, account for about 50% to 70% of ovarian tumors. The second most common is malignant germ cell tumor, including immature teratoma, endodermal sinus tumor, dysgerminoma, mixed type, embryonal carcinoma and polyembryoma.[4] The last type of ovarian cancer is a specialized stromal cell tumor. High-grade serous ovarian carcinoma (HGSOC) is the most common subtype of ovarian cancer. Besides, the 5-year survival rate of ovarian cancer is less than 40% due to extremely poor prognosis.[5,6] Also, the mortality rate is highest in all kinds of gynecological tumors, which poses a serious threat to the lives of women.

Cytokine is a class of small-molecular soluble polypeptides secreted by immune cells and tissue cells with mutual regulation. They play an important role in the development and differentiation of immune cells, immune response, and immune regulation by binding to corresponding receptors to regulate the activities of themselves or other cells. As targeted biological agents, cytokines have certain clinical value in the treatment of tumors, autoimmune diseases, immunodeficiency, infection and so on. This review focuses on recent research developments on common cytokines and

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ovarian cancer due to their critical involvement in the onset and progression of the disease.

CYTOKINES

INTERLEUKIN (IL)

Interleukin is a group of soluble proteins secreted by leukocytes and can regulate the function of other leukocytes and histiocytes. They are participants in the activation and regulation of immune cells as well as proliferation, differentiation of T and B cells, and inflammation.

Interleukin-6

Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory cytokine, a core participant in chronic inflammatory diseases including cancer, as well as one of the main immunomodulatory cytokines in tumor micro-environment. Studies have shown that IL-6 regulates tumor progression including anti-apoptosis, inducing proliferation, promoting metabolism, enhancing tissue invasiveness, metastasis, etc.[7] It has been found that the over-expression and dysfunction of IL-6 are related to ovarian cancer, multiple myeloma, and breast cancer.[8-10] For example, high levels of IL-6 promoted the progression of malignant ascites in ovarian cancer,[11] and also promoted the enrichment of ovarian cancer stem cells after platinum-based chemotherapeutic treatment.[12] In addition, leukemia inhibitory factor (LIF) in parallel with IL-6 promote the progression of ovarian cancer, hence simultaneous blocking of both can improve survival.[13] The STAT3 signaling pathway is highly regulated and instantaneous in normal cells, while it is constantly activated by IL-6 in cancer cells, which is related to the invasion and poor prognosis of ovarian cancer.[14,15] In fact, activated STAT3 is more common in epithelial ovarian cancer diagnosed at a late stage. The activation of JAK/STAT signaling pathway correlated with aggressiveness of ovarian cancer, survival and proliferation of cells, which suggest that STAT3 is necessary for cell migration in ovarian cancer.[16]

Interleukin-8

Interleukin-8 (IL-8), also named as CXCL8, is a pro-inflammatory chemokine secreted by multiple cell types, such as monocytes, mesothelial cells, endothelial cells, tumor cells etc. It has been confirmed that the elevated levels of IL-8 in ovarian cyst fluid, ascites, serum and tumor tissues of patients with ovarian cancer are associated with poor prognosis and survival.[17] IL-8 may cause the malignant behavior such as excessive proliferation of cancer cells by inducing relevant molecular signaling pathways in cells. Specifically, cell proliferation stimulated by IL-8 and increased cell cycle-regulated Cyclin D1 and B1 promote the activation of PI3K/Akt and Raf/MEK/ERK.[18] Meanwhile, the invasiveness of epithelial ovarian cancer cells enhanced by IL-8 is closely related to the expression of MMP-2 and MMP-9.[18] IL-8 can also promote human ovarian cancer cell mobility by inducing epithelial-mesenchymal transformation (EMT) *in-vitro*.[19] In addition, neurobehavioral stress leads to the increase of *FosB* drive in IL8, which plays a role in promoting the growth and metastasis of ovarian cancer.[20] In epithelial ovarian cancer cells, histone deacetylase (DHAC) inhibitors may induce IL-8/CXCL8 expression in a dependent manner through IκB kinase (IKK). IKK inhibitors may work synergistically with DHAC inhibitors when treating solid tumor-ovarian cancer and other cancers characterized by increased expression of IL-8/CXCL8.[21] Current studies have described that osteopontin, macrophage migration inhibitory factor and anti-IL-8 antibody can be used as markers for early detection of ovarian cancer as well as in combination with CA125.[22]

Others

Natural killer (NK) cells belong to the first group of innate lymphocytes, which have the ability to kill malignant cells and inhibit the metastasis and spread of cancer.[23] NK cells with high spontaneous cytotoxicity are associated with a reduction in the incidence of human cancer.[24] Cytokines bind to receptor complexes in cell membrane and activate intracellular signaling pathways based on phosphorylation of signal transducing and transcription-activating protein kinases. For example, IL-10 and other cytokines present in the tumor environment affected the JAK/STAT5 pathway by reducing the phosphorylation status of STAT5 protein, and enhanced the expression of VEGF in NK cells at the same time.[25] IL-15 can significantly enhance NK cell's Anti-tumor response.[26, 27]

Most of the cell types in the ascites of ovarian cancer patients are lymphocytes (37%) and macrophages (32%), which contribute to the progression and metastasis of ovarian cancer.[28] Interleukin 20 receptor subunit alpha (IL20RA), as a key receptor in regulating the polarization of peritoneal macrophages, is silenced in disseminated ovarian cancer cells for the accumulation of M2-subtype macrophages in the peritoneal cavity for a successful metastatic growth.[29] However, the administration of recombinant IL-18 significantly suppresses the metastasis of IL20RA-deficient ovarian cancer cells. When ovarian cancer cells spread to the abdominal cavity, it greatly induces the expression of IL-20 and IL-24 in peritoneal mesothelial cells, activating the downstream signal of IL20RA in ovarian cancer cells to produce mature IL-18, ultimately leading to the polarization

of macrophages to M1-like subtype to eliminate cancer cells.[29]

COLONY-STIMULATING FACTOR (CSF)

Colony-stimulating factor (CSF) is a group of glycoproteins, including granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF) and multi-potential colony-stimulating factor (Multi-CSF), which regulate the proliferation and differentiation of granulocytes, mononuclear macrophages and some correlative hematopoietic stem and progenitor cells.

M-CSF is a homodimer formed by hydrolysis of precursor protein, also known as colony stimulating factor 1 (CSF-1). It plays an important role in regulating the proliferation and differentiation of mononuclear macrophages.[30] Secreting large amounts of CSF-1 is a distinctive feature of many human epithelial ovarian cancers.[31] In epithelial ovarian cancer, the overexpression of CSF-1R and CSF-1/CSF-1R activated by CSF-1 enhances invasiveness and promotes metastasis, and is thus associated with poor prognosis.[32,33] CSF-1 not only play a role in converting macrophages into M2 phenotype,[34] but also increases the ascites of patients, which indicates that the CSF-1/CSF1R axis may directly promote carcinogenic effects on tumor cells.[31] Previous research has found that CSF-1R is up-regulated in cisplatin-resistant cells in which inhibiting the expression of CSF-1R is able to reduce the polarization of M2 macrophages, therefore delay the growth of tumor cells. It suggests that the expression of genes and proteins related to M-CSF can be used as novel therapeutic targets for ovarian cancer.[35] Another research detected the expression G-CSFR in advanced serous ovarian epithelial cancers and some ovarian cancer cell lines. Mediated by signaling via the downstream JAK2/STAT3 pathway, stimulation of G-CSFR-expressing ovarian epithelial cancer cells with G-CSF led to increased migration and survival against chemotherapy-induced apoptosis in these cells.[36] Experimental results in mice have shown that targeting the GM-CSF contributes to overcoming the anti-VEGF therapy resistance in ovarian cancers, because both anti-VEGF therapy and recruiting and suppressing tumor immunity were inducing tumor hypoxia and the expression of GM-CSF.[37]

INTERFERON (IFN)

Interferon is the first cytokine discovered. According to its origin and physicochemical properties, interferon can be divided into type I (IFN- α, IFN- β), type II (IFN- γ) and type III (IFN- λ) interferon. IL-28/IL29 reported recently is classified into type III.[38] Type I interferon is mainly produced by virally infected cells, while IFN-γ is a glycoprotein primarily secreted by activated Th1 cells, CTLs and NK cells. Many studies have investigated the characteristics and biological activities of type II interferon (IFN- γ), suggesting that it has similar features to type I IFN, such as anti-proliferation, anti-virus, immunomodulatory, anti-tumor effects and so on.[39]

The view that IFN-γ has anti-tumor effects on cancer patients is widely recognized. However, Zaidi *et al.*[40] believed that IFN-γ has both immune-activation/immunoregulatory and antitumor/tumor-promoting effects and that the inhibition of FN-γ/IFN-γ receptor pathway might be a feasible new therapeutic target for some malignant tumors. Because of the difference in the cancer microenvironment, IFN-γ secreted by CD8-positive lymphocytes upregulates Programmed death-ligand 1 (PD-L1) on ovarian cancer cells and promotes tumor growth.[41] A previous study has shown that interferon signal transduction in tumor-associated macrophages (TAMs) in ascites of patients with ovarian cancer is closely related to the good clinical prognosis of the patient subgroup.[42] The increase in tumor-infiltrating lymphocytes (TIL) infiltration is associated with the increase in cytokine IFN- γ levels, which is a prognostic factor for prolonging survival as observed in clinical trials for the treatment of ovarian cancer.[43] Cytokine immunotherapy with IFN-α and IFN-γ is mainly used in the intraperitoneal treatment of ovarian cancer. Previously, studies suggested that autologous monocytes injected into the peritoneum have anti-tumor properties. Recent research studies have shown that combination of monocyte and cytokine immunotherapy is more effective than monotherapy in treating cancer.[44,45] In addition, bone marrow monocytes derived from pluripotent stem cells can produce IFN-β. IFN-β reduces the patient's ascites retention by reducing the production of VEGF and maintaining vascular integrity, thereby controlling severe malignant ascites, which can be used as a new therapeutic strategy for advanced ovarian cancer.[46] New polyethylene glycol IFN-β, as a strong inhibitor of malignant ascites in human peritoneal metastasis model, has the potential to maintain vascular integrity.[47] Some studies have also shown that recombinant IFN-γ gene expressed and reorganized in mammalian cells increases the death of drug-resistant SKOV3 cells. Fas-associating protein with a novel death domain (FADD) may inhibit apoptosis through the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Therefore, FADD in SKOV3 can be used as a new therapeutic target.[48] At the same time, interferon regulators are also used to overcome the drug resistance of human ovarian cancer to VSV-GP oncolytic virus therapy.[49]

TUMOR NECROSIS FACTOR (TNF)

Tumor Necrosis Factor (TNF) was originally identified because of its antitumoral activity *in vivo* and its selective cytotoxic/cytostatic activity on some transformed cell lines in 1975.[50] It is a soluble multifunctional cytokine mainly synthesized by activated macrophages. It can participate in inflammation and cellular immune responses and play a critical role in the pathology of many diseases, such as rheumatoid arthritis, crohn's disease and so on.[51,52] TNF gene family includes TNF-α and lymphotoxin (LT).

It is well known that TNF-α is a key cytokine in inflammation and was initially considered to be anti-tumor. However, recent studies have emphasized the role of TNF-α in immunosuppression and its ability to enhance tumor growth.[53] TNF-α released from TAM stimulated the expression of PD-L1 on the surface of the cancer cells.[54] In ovarian cancer, the expression of TNF-α is related to different histologic subtype.[55] TNF-α self-expression in ovarian tumor cells can increase the synthesis of MCP-1, SDF-1, IL-6, MIF and VEGF which enhance angiogenesis and peritoneal diffusion of tumor.[56] Besides, the production of TNF-α also enhances the synthesis of IL-17, which can cause recruitment of myeloid cells and eventually lead to the progression of ovarian tumor.[57] In advanced epithelial ovarian cancer, TNF-α in ascites interacts with IL-6, driving tumor progression and chemotherapy resistance and increase the potential of these cytokines as prognostic biomarkers to treat ascites leves.[58] Previous studies have shown that overexpression of tumor necrosis factor receptor-associated protein 1 (TRAP1) is associated with poor prognosis of epithelial ovarian cancer.[59] A recent research has found that spermatogenesis associated 2 (SPATA2) is identified as TNF receptor modulator, which is necessary for TNF-induced inflammation and apoptosis. The expression of SPATA2 regulated by TNF-α and IL-1β has been found to independently affect the clinical outcome of patients with ovarian cancer.[60] In addition, the decreased expression of tumor necrosis factor-alpha-induced protein 8 (TNFAIP8) is a predictive biomarker for neoadjuvant chemotherapy drug-resistance. TNFAIP8 may be involved in chemoresistance induced by cisplatin through interaction with autophagy-related proteins in which it is expected to become an important target for ovarian cancer therapy.[61]

GROWTH FACTORS

Vascular endothelial growth factor

Vascular endothelial growth factor (VEGF) is a cytokine that promotes angiogenesis and can be synthesized by a variety of cells, such as endothelial cells, macrophages, tumor cells, etc. VEGF, especially VEGF-A, is a key angiogenic factor, which plays an important role in inducing neovascularization, progression, and metastasis of many human cancers.[62] It is up-regulated by oncogene expression, a variety of growth factors and also hypoxia.[63] The production of VEGF and other growth factors by the tumor results in the 'angiogenic switch', where new vasculature is formed in and around the tumor, allowing it to grow exponentially.[64] This core role makes it a reasonable target for anti-cancer treatment. For example, during ovarian tumor progression, the imprinted tumor suppressor NOEY2 dramatically downregulated VEGF and hypoxia-inducible factor-1α (HIF-1α) via direct binding to vascular endothelial growth factor receptor-2 (VEGFR-2).[65] F-box and WD repeat domain containing 7 (FBXW7) inhibited invasion, migration and angiogenesis of ovarian cancer cells by suppressing VEGF expression through inactivation of β-catenin signaling.[66] Compared to women with benign tumors or healthy ovaries, the distribution of VEGF genotypes in patients with epithelial ovarian cancer is different, which indicated that CGTCT and CGTGT haplotypes have a poorer prognosis.[67] VEGF genotype may predict prognosis in patients with epithelial ovarian cancer. High levels of VEGF were found in primary ovarian cancer tumors and ascites, which was related to poor survival. Therefore, Bevacizumab, a monoclonal antibody that targets VEGF, has been approved for treatment of advanced and recurrent ovarian cancer which is shown to prolong the non-progressive survival period.[68] Studies have shown that the expression of VEGF in ovarian cancer suppresses tumor immunity by inducing myeloid-derived suppressor cells.[69] VEGF also promotes the metastasis of ovarian cancer by promoting angiogenesis and vascular permeability by acting on the peritoneum. The inhibition of VEGF completely suppressed the formation of ascites, with partial inhibition of the ovarian tumor growth in peritoneum. It is suggested that the pathology of tumor aggressiveness in advanced ovarian cancer may be related to ascites caused by early vascular permeability disorder.[70] In addition, studies have shown that the combined use of anti-VEGF, anti-IL-8 and anti-IGFR antibodies can inhibit tumor growth and improve the survival of preclinical models.[71] Not only that, with the growth of tumor, the concentration of VEGF-A becomes more localized so that a decrease in concentration of VEGF-A in serum can be easily observed.[72] Thus, serum VEGF-A can be used as a strong diagnostic biomarker in the early stages of ovarian cancer and has inverse relation in terms of concentration with the advancement of the disease.[73]

Transforming growth factor-β

Transforming growth factor-β (TGF-β) can act as a tumor suppressor and tumor promoter. Signal transduction of TGF-β plays an important role in occurrence, development and metastasis of tumor. As with most aspects of tumor progression, there are multiple potential mechanisms for this switch, including both cell autonomous (i.e. EMT) and non-cell autonomous (i.e. angiogenesis and immune system) mechanisms.[74] Studies have shown that the dysregulation of TGF-β signal conduction may contribute to occurrence of ovarian cancer. TGF-β can promote migration of ovarian cancer cells, which may be associated with up-regulation of junction protein 43 through Smad2/3 signal pathway.[75] On one hand, TGF-β is an effective cell growth inhibitor, and on the other hand a malfunction of its pathway in tumor microenvironment leads to uncontrolled cell growth and proliferation, which can progress to the occurrence and development of tumor.[76] Tumor progression occurs when cancer cells can escape the inhibitory effects of TGF-β and instead begin to overexpress TGF-β thus promoteing EMT, resulting in increased cell proliferation, invasiveness and enhanced metastatic potential. This will generate a more aggressive tumor phenotype.[77] Recent studies have shown that LY2157299 monohydrate, a TGF-β R1 inhibitor, can suppress tumor growth and the development of ascites in ovarian cancer.[78]

Epidermal growth factor (EGF)

Epidermal growth factor (EGF) is reported to be associated with a variety of cancers, especially ovarian cancer. EGF can stimulate the ovarian cancer cell line Caov-3 to enter EMT and then participate in cell cycle regulation.[79] In recurrent ovarian cancer, activity of spleen tyrosine kinase (SYK) positively regulates the EGF receptor (EGFR) pathway, providing a biological basis for the co-targeting of SYK and EGFR.[80] Increased expression of EGFR on ovarian cancer cells is associated with poor prognosis. Not only that, the activation of EGFR can activate the IL-6/STAT3 pathway, increasing the migration of epithelial ovarian cancer cells. Therefore, high EGFR and IL-6/STAT3 expression predicts poor survival in patients with ovarian cancer, which indicates that the high expression of EGFR/IL-6/STAT3 pathway components may be positively correlated with the progression of ovarian cancer.[81] Phase III clinical studies have also shown that an increase in EGFR gene copy number is associated with the deterioration in overall survival and progression-free survival (PFS) of patients with ovarian cancer.[82] EGFR has become a new therapeutic target for ovarian cancer.[83,84]

In more than 30% of ovarian cancer cases, human epidermal growth factor receptor 2 (HER2) is overexpressed and plays an important role in tumorigenesis and metastasis.[85] However, the treatment results of clinical trials using HER2 antibody targeted therapy have shown poor to modest therapeutic responses.[86,87]

Peritoneal metastatic tumors cannot be completely removed through Debulking Surgery and have developed chemoresistance, which are the main clinical challenges for the treatment of ovarian cancer. Further study has found that in the ovarian cancer xenograft model in nude mice, the systemic delivery of HER2-targeted magnetic iron oxide nanoparticles carrying cisplatin significantly inhibited the growth of primary tumor and peritoneal and lung metastases.[88] This targeted cancer therapy has the potential to effectively treat metastatic ovarian cancer.

In serous ovarian cancer, the expression of fibroblast growth factor 18 (FGF18) is significantly correlated with micro-vessel density and tumor-associated macrophage infiltration. Signal of FGF18 regulates the aggressiveness and microenvironment of ovarian tumors, thereby promoting tumor progression. It increases the production of carcinogenic factors and chemokines by activating NF-κB to control the migration, invasion and tumorigenicity of ovarian cancer cells. This leads to a tumor microenvironment characterized by enhanced angiogenesis and augmented tumor-associated macrophage infiltration and M2 polarization.[89]

CHEMOKINES

Chemokines, a superfamily of inducible, secreted, heparin-binding proteins, are structurally homologous and are involved in tumor growth and metastasis.[90] Besides, chemokines were first studied as mediators of inflammation.[91] They have the following functions and characteristics: binding with chemokine receptors to induce chemotaxis of cells, inducing Chemotactic migration of target cells, rebuilding the cytoskeleton, enhancing the adhesion of target cells and endothelial cells etc. Besides, they have a variety of physiological functions, such as widely participating in cell growth, development, differentiation and apoptosis. Not only can they chemotactically direct inflammatory cells, but also play an important role in growth and metastasis of tumor.[92]

CC-chemokine ligand 18 (CCL18) is mainly produced by TAM. The level of CCL18 in ascites is positively correlated with the ability of ascites in promoting cell migration. The CCL18 blocking antibody significantly reduces cancer cell metastasis induced by ascites. Ascites and CCL18 stimulate

the phosphorylation of proline-rich tyrosine kinase 2 (PYK2) in human ovarian cell line. However, the expression of phosphorylated Pyk2 in serous ovarian cancer tumors is associated with short PFS.[93] CCL18 levels in serum have been used as a potential biomarker to distinguish ovarian cancer with gynecological benign diseases in patients.[94] Infiltration of $CD8^+$ T lymphocyte is an indicator of good prognosis for ovarian cancer. The homeodomain transcription factor MEIS1 triggers the expression of chemokines CCL18, CCL4, CXCL7, CCL5, CXCL1 and IL8, and participates in infiltration of $CD8^+$ T lymphocyte in early ovarian cancer.[95] Studies have shown that CXCR7 plays a key role in the invasion of ovarian cancer cells. Under the control of the estrogen receptor α (ERα), the activation of the CXCR7/CXCL11 axis may promote a feedforward mechanism to induce remodel of ECM, EMT, and metastasis of ovarian cancer cells.[96] In addition, in ovarian cancer cells, the overexpression of scaffold protein Gab2 promotes tumor growth and angiogenesis by up regulating the expression of some chemokines depended by IKKβ, such as CXCL1, CXCL2, and CXCL8. Co-targeting IKKβ and PI3K pathways, the downstream of Gab2, may be a promising therapeutic strategy to treat the ovarian cancer that overexpress Gab2.[97]

In addition, chemokines such as CXCL8, CXCL1 and CCL2 bind to CXCR1 and CXCR2 expressed by endothelial cells as well as lead to the proliferation, migration of endothelial cells and blood vessel formation.[98] For example, under hypoxic conditions, the interaction of CXCL12 produced by cancer cells and CXCR4 expressed by endothelial cells may enhance angiogenesis in ovarian cancer. Regulating the immune system via the CCR4/CCL22 axis and CCL2/CCR2 axis, they respectively determine the degree of T cell and macrophage infiltration in ovarian cancer. In addition, the CX3CL1/CX3CR1 axis supports the adhesion and proliferation of ovarian cancer cells, and plays a potentially key role in the occurrence and progression of ovarian cancer metastasis. Therefore, according to the actual patient's condition and the different effects of chemokine receptor axes, chemotherapy combined with immunotherapy is used to pursue the greatest anti-tumor effects.

CONCLUSION

Cytokines are mutually promoted or restricted in the body. They form a particularly complex network system. Thus, cytokines play a double-edged role in the occurrence and development of ovarian cancer. On one hand, certain cytokines have anti-tumor effects, such as IFN. On the other hand, certain cytokines promote occurrence and development of tumor, such as IL-6, IL-8, and VEGF. However, some cytokines play a dual role, such as TNF-α, GM-CSF, and TGF-β. The mechanisms and applications of cytokines to tumor therapeutics remain unclear. Therefore, understanding the expression levels of cytokines in ovarian cancer tissues may provide a basis for the immunological diagnosis and prognosis assessment of tumors, at the same time, provide new therapeutic targets for tumor immunotherapy.

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Conflicts of interest

There are no conflicts of interest.

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