Drug resistance and tumor immune microenvironment: An overview of current understandings (Review)

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Abstract. The use of antitumor drugs represents a reliable strategy for cancer therapy. Unfortunately, drug resistance has become increasingly common and contributes to tumor metastasis and local recurrence. The tumor immune microenvironment (TME) consists of immune cells, cytokines and immunomodulators, and collectively they influence the response to treatment. Epigenetic changes including DNA methylation and histone modification, as well as increased drug exportation have been reported to contribute to the development of drug resistance in cancers. In the past few years, the majority of studies on tumors have only focused on the development and progression of a tumor from a mechanistic standpoint; few studies have examined whether the changes in the TME can also affect tumor growth and drug resistance. Recently, emerging evidence have raised more concerns regarding the role of TME in the development of drug resistance. In the present review, it was discussed how the suppressive TME adapts to drug resistance characterized by the cooperation of immune cells, cytokines, immunomodulators, stromal cells and extracellular matrix. Furthermore, it was reviewed how these immunological or metabolic changes alter immuno-surveillance and thus facilitate tumor drug resistance. In addition, potential targets present in the TME for developing novel therapeutic strategies to improve individualized therapy for cancer treatment were revealed.

Contents

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1. Introduction

In recent years, developments in the medical space have resulted in the establishment of several tumor treatment methods. However, drug therapy remains to be a primary strategy in the treatment for various types of cancers (1). Unfortunately, drug resistance has become a huge obstacle for cancer therapy, often leading to relapse and metastasis. Drug resistance refers to a state in which tumor cells become insensitive to antitumor drugs, a significant factor contributing to the failure of therapy and a pressing challenge in cancer treatment (2). Tumor cells can develop resistance to chemotherapeutic drugs through either natural or acquired mechanisms. Natural drug resistance refers to the natural resistance of tumor cells to chemotherapeutic drugs, either because the drug within the cell does not reach the concentration required to inactivate the target or because the tumor cells fail to respond to the induction of apoptotic mechanisms (3). Acquired drug resistance develops gradually during the course of drug therapy: Typically, drug resistance is acquired by tumor cells following long-term treatment with small doses of cytotoxic drugs (4). While continuous chemotherapy can inhibit tumor growth and extend patient survival, cancer cells adapt to effects of drugs over time through mutations. This adaptation reduces drug efficacy and may lead to the treatment becoming ineffective, resulting in the development of drug resistance (5).

The tumor immune microenvironment (TME) is a complex network of cells, molecules and physiological factors present at the tumor, which together with tumor cells constitute the tumor tissue ecosystem. Although the specific components of each TME are differentiated and dependent on the type of tumor, the TME often has common characteristics, such as the tumor cells themselves, the surrounding blood vessels and cytokines, immune cells, stromal cells and extracellular matrix (ECM) (6). The TME significantly influences tumor initiation and progression, exhibiting substantial differences from the

microenvironment of normal tissues. Within the TME, tumor cells interact with surrounding cells, altering their function through interactions with the tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs) and stromal cells. These interactions facilitate tumor growth, invasion and metastasis (7).

In addition, the TME significantly decreases the efficacy of immunotherapy, and immune cells in the TME may be altered by tumor cells, losing their immune monitoring effect on the tumor, and even being transformed into suppressive cells by tumor cells, thus creating an environment that favors tumor escape. The immunosuppressive TME includes the immunosuppressive factors and cells, and physical and mechanical barriers, where impaired tumor antigen presentation process as well as metabolic alterations can be considered as the main site of drug resistance. The typical composition of the TME is demonstrated in Fig. 1.

Currently, the relationship between the TME and tumor drug resistance is not fully understood. The present review primarily discussed the relationship between the TME and tumor drug resistance based on existing research, highlighting the challenges and directions for future research. It also described the mechanisms by which the TME interacts with the tumor and the occurrence of tumor drug resistance, to showcase potential novel treatment strategies and drug targets. New strategies for overcoming tumor drug resistance and improving the effects of cancer treatment are also highlighted.

2. Impaired tumor antigen presentation process

Downregulation of major histocompatibility complex (MHC) expression. Tumor antigens bind to MHC-I molecules and are presented on the surface of tumor cells. This renders them recognizable by immune effector cells. Therefore, tumor cells with dysregulated presentation of antigens bound to MHC-I for presentation are more likely to avoid detection by the immune system (8). In general, tumor cells can downregulate the antigen presentation by MHC-I via either deletion of the MHC-Igene or inhibition of MHC-Igene transcription. The human MHC genes encodes various molecules expressed on white blood cells called human leucocyte antigen (HLA). The expression of HLA-I antigen is downregulated in most malignant tumors, such as melanoma, gastric cancer (GC), breast cancer and ovarian cancer. Moreover, the degree of this downregulation is positively correlated with the degree of malignancy and metastasis of tumors.

Aberrant expression of tumor antigens. The elimination of tumor cells by the immune system relies on the reaction of immune effector cells to antigens present on the surface of tumor cells. However, tumor cells often exhibit reduced or absent expression of tumor antigens, inhibiting the activation of T cells by dendritic cells (DCs) and evading recognition and destruction by cytotoxic T lymphocytes (CTLs). It has been reported that tumor cells will undergo antigen mutation when co-cultured with monoclonal and polyclonal transgenic CTLs, which specifically recognize the tumor antigen P1A, and thus, P1A is not readily recognized by CTLs (9). In addition to generating antigenic mutations, tumor cells can also evade recognition by the immune system by shedding the antigens expressed on their surface. For example, carcinoembryonic antigen can be shed from the surface of tumor cells, which renders tumor cells unrecognizable by immune effector cells. Similar to the loss of tumor antigens, tumor cells can also evade recognition and attack by NK cells following the release of natural killer cell group 2-member D (NKG2D) ligands (10).

Lack of co-stimulatory signals. Activation of T cells requires the induction of the first signal produced by the binding of T cell receptors to antigen peptide-MHC complexes, and also the second signal provided by the binding of costimulatory molecules (CMs) on antigen-presenting cells or tumor cells to CM receptors on T cells. Tumor cells that only express MHC-I antigens, but lack CMs participate in the antigen presentation process, but cannot activate T cells and elicit strong immune responses. Such tumor cells can lead to the emergence of immune tolerance (11). The B7 family of molecules and their receptors are the most important CM pairs participating in the activation of T cells. The binding of each molecule to its receptors promotes activation and proliferation of T cells. Studies found that tumor cells downregulated the expression of B7-1 and B7-2 molecules, meaning there is insufficient induction of T cell activation signals such that T cells do not proliferate, whereas the expression of B7-H1 and B7-H4 molecules is upregulated. Once they bind to the receptors, these inhibitory CMs generate inhibitory signals, induce the apoptosis of T cells, and inhibit the antitumor immune response of the body (12,13).

3. Immunosuppression in the tumor

Secretion of immunosuppressive factors. The TME contains numerous immunosuppressive cytokines, including TGF-β, IL-6 and IL-10, which impede antitumor immune responses through direct or indirect mechanisms. TGF-β, for example, hinders the proliferation of immune effector cells, suppresses DC maturation, reduces CTL and NK cell activation, reduces the levels of antitumor immune cytokines such as IFN-γ and TNF-α, and inhibits MHC-II antigen expression induced by IFN-γ in melanoma cells (14). IL-10 can reduce the expression of CMs on DCs, inhibit tumor antigen presentation, alter their phenotypes, inhibit the activity of T cells, and block T cell-mediated attacks on tumor cells. It has been shown that TNF can induce hemorrhagic necrosis of certain tumor blood vessels, specifically eliminate tumor cells, and modulate the immune functions of cells, while tumors can express soluble TNF binding protein, which prevents the eliminating effect of TNF (15). Additionally, vascular endothelial growth factor (VEGF) has been implicated in the development of tumor immune escape mechanisms. As a specific endothelial cell stimulating factor, VEGF can accelerate tumor neovascularization, increase the permeability of blood vessels, and promote the infiltration and metastasis of tumor cells. It can also suppress the maturation of DCs, affecting antigen presentation function, and induce the programmed death ligand 1 (PD-L1) expression in mature DCs, eventually stimulating the T cells and the formation of CTLs (16,17).

ECM: A key player in tumor progression and drug resistance. The ECM in the TME supports the proliferation and metastasis

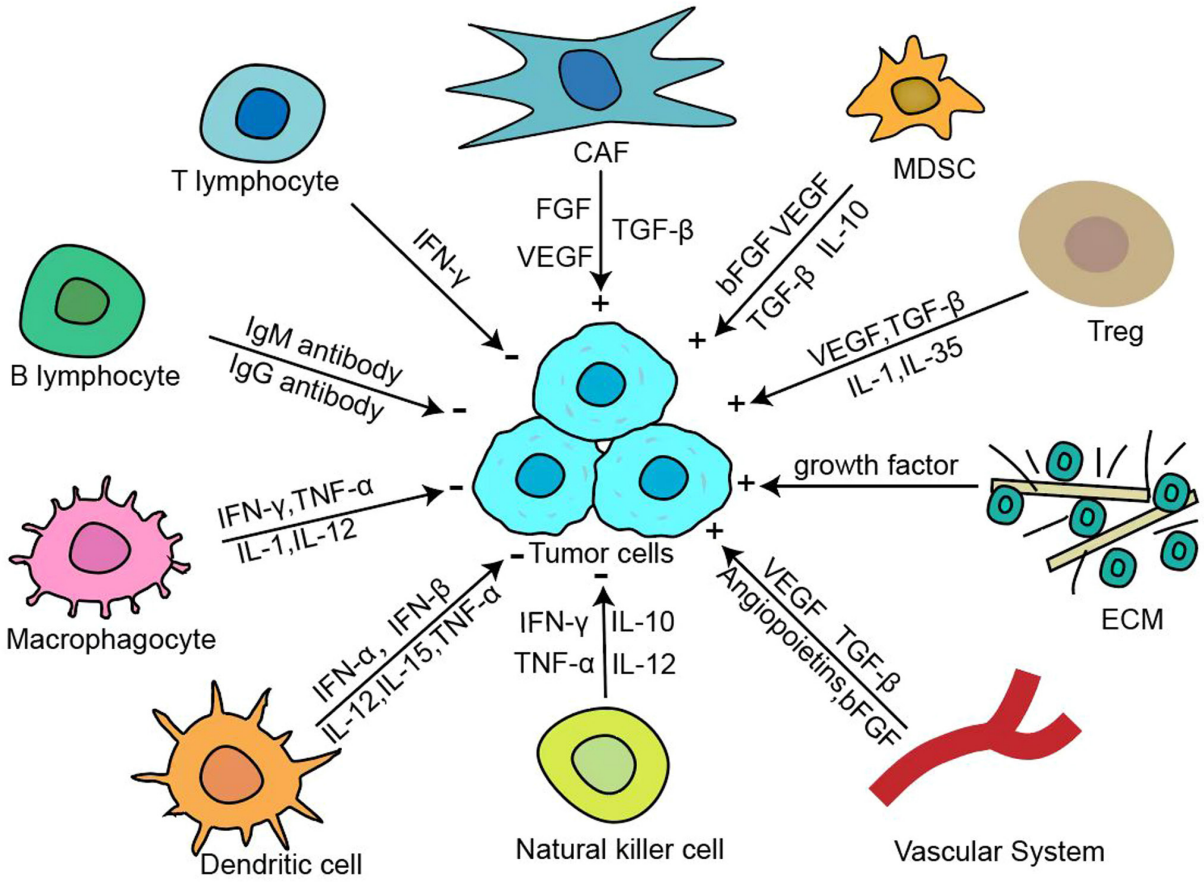

Figure 1. Components of the TME. +, immunosuppression; -, immunostimulatory; INF-γ, interferon γ; INF-α, interferon α; INF-β, interferon β; TNF-α, tumor necrosis factor α; IL, interleukin; VEGF, vascular endothelial growth factor; bFGF, basic fibroblast growth factor; TGF-β, transforming growth factor β.

of tumor cells. The ECM is also an important component of a hypoxic TME is composed of CAFs, TAMs, mesenchymal stem cells (MSCs), inflammatory cells and endothelial cells (18). The ECM is an important non-cellular component of the TME and plays a key role in maintaining tissue structure and function. As a physical barrier of the tumor, the ECM can dissolve drugs or delay drug delivery (19). Fibronectin (FN), hyaluronic acid, collagen (Col) and laminin are the main components of the ECM, and can form ECM fibers. Specific enzymes, such as lysyl oxidase cross-link these fibers, regulating tumor hardness and promoting fibrosis (20). Laminin has been revealed to be highly expressed in multidrug-resistant cells (21,22). Alterations in the ECM can facilitate tumor cell invasion and metastasis, influence the penetration and distribution of chemotherapeutic drugs, and diminish their effectiveness.

Di Martino *et al* (23) found that type III Col induced tumor cell dormancy *in vivo* and *in vitro* experiments, and demonstrated that changes in ECM Col orientation represented the transition from dormancy to reactivation (23). Puttock *et al* (24) identified that the TAM population associated with cancer immunotherapy and ECM composition and found that tumor ECM can directly educate TAMs found in ovarian cancer tissues that are associated with a poor prognosis, and that targeting ECM can improve immune invasion and immunotherapy sensitivity. Wang *et al* (25) developed an ECM deprivation system based on FN-targeted self-assembly peptide as a chemotherapy sensitizer, which can significantly inhibit the tumor-promoting effect of ECM, and may become a novel method to inhibit ECM and enhance the sensitivity of chemotherapeutic drugs (25).

Enrichment of immunosuppressive cells. During tumor growth, immunosuppressive cells undergo differentiation, proliferation and aggregation at the tumor site, including TAMs, regulatory T cells (Tregs), tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs) and tumor-associated DCs (TADCs) (26). Several immunomodulatory factors have been reported to date. In the present review, the main components of the TME and their mechanisms of action were introduced.

TAMs. TAMs are a special class of macrophages derived from monocytes in the peripheral blood and migrate to tumor tissues. They are an important part of the TME, contributing to the occurrence and progression of tumors by creating an immunosuppressive microenvironment (27). TAMs typically differentiate into one of two activation states: M1 macrophages, which have a tumor-suppressive function, and M2 macrophages, which have a tumor-promoting function (28). M1 macrophages exert proinflammatory effects, eliminate tumor cells and inhibit tumor growth. By contrast, M2 macrophages inhibit inflammatory processes and modulate the immune cells thereby promoting tumor growth, invasion, metastasis and angiogenesis (29). M1 macrophages eliminate cancer cells through antibody-dependent cell-mediated cytotoxicity such as TNF, immune killer molecules and inflammatory cytokines (30). In comparison, activated M2 macrophages

have been reported to accelerate the proliferation, invasion and metastasis of tumor cells by enhancing angiogenesis and inhibiting the antitumor function of immune cells (31). VEGF, IL-1, TNF-α, prostaglandin E2, adrenomedullin and brain signaling protein 4D contribute to angiogenesis (32).

By interacting with other cells, TAMs regulate the composition and function of the TME and affect the behavior and characteristics of tumor cells. Indeed, targeting TAMs is being considered as a strategy for cancer treatment. M2 macrophages are also closely associated with tumor angiogenesis and lymphangiogenesis, known to directly modulate tumor proliferation and metastasis, induce tumor drug resistance, and secrete cytokines such as IL-10 and TGF-β, which inhibit immune responses (33). The secretion of PD-L1, cytotoxic T lymphocyte-associat-edantigen-4 (CTLA-4) and other molecules may enhance CTL apoptosis and inhibit CTL activation (34), resulting in immunosuppression.

Chen *et al* (35) found that Jumonji domain containing 6 (JMJD6) can reduce the growth of Lewis lung carcinoma tumors and B16F10 melanomas by inducing M2 polarization through STAT3/IL-10 signaling, and make tumors sensitive to immune checkpoint blockades (ICBs), which can enhance the treatment potential of ICBs. Tang *et al* (36) used a transgenic mouse model to effectively combat hepatocellular carcinoma (HCC) by targeting xCT-mediated ferroptosis; it was found that pro-tumoral polarization of macrophages is effective against HCC and enhances the efficacy of the anti-PD-1/L1 response (36). Li *et al* (37) found that a membrane spanning four domains A4A promotes M2 polarization of macrophages by activating the PI3K/AKT and JAK/STAT6 pathways, which can improve the efficacy of immune checkpoint inhibitor and is a novel avenue for anticancer immunotherapy.

Tregs. Tregs constitute a subset of immune cells primarily responsible for maintaining immune homeostasis and suppressing the immune response against cancer (38). They achieve this by restraining the activity of other immune cells, thereby preventing excessive immune reactions and the development of autoimmune diseases. Tregs are categorized into two primary types: Natural Tregs (nTregs), which originate in the thymus, and induced Tregs (iTregs), which differentiate in peripheral tissues (39,40). nTregs, also known as thymus-derived Tregs, primarily control the inflammatory response following infection and maintain normal immune tolerance. iTregs, also known as peripherally-induced Tregs (41), can generate immune factors and thereby decrease the activity of immune cells or directly bind to immune cells to inhibit their activity. Tregs are a double-edged sword. They can regulate the strength and duration of the immune response by inhibiting the activity and function of other immune cells to ensure the normal response of the immune system to external antigens and prevent the occurrence of autoimmune diseases. Within the TME, hyperactive Tregs cells can inhibit immune cell assault on tumors, consequently allowing tumor evasion and proliferation (42).

Tregs participate in immune regulation, autoimmune diseases and tumor immune escape among other processes. Further studies into the function and regulatory mechanism of Tregs are required to improve our understanding of the immune balance, occurrence and development of immune-related diseases. This is essential for developing new immunoregulatory therapies. Tregs have been reported to inhibit DCs by expressing IL-10, TGF-β and IL-35, and secrete granzyme and perforin to eliminate effector cells directly, and inhibit the proliferation of effector cells. In addition, Tregs highly express CD39 and CD73 molecules, which increase adenosine production, and bind to adenosine receptors on the surface of effector cells to exert inhibitory effects (43).

Zhang *et al* (44) proposed that YTHDF2 is essential for Tregs in the TME by regulating transcription of M^6A-modified NF-κB negative regulators and may serve as a potential drug target for cancer immunotherapy. Wen *et al* (45) found that salidroside (SAL) can inhibit the function of Tregs and inhibit the proliferation of lung cancer cells by regulating the Hsp70/stub1/Foxp3 pathway in Tregs, which is a new mechanism for the use of SAL in tumor therapy. Shiri *et al* (46) found that Treg-derived IL-10 upregulates PD-L1 expression in monocytes, which in turn reduces $CD8^+$T cell infiltration and associated antitumor immunity in colorectal cancer (CRC)-derived liver metastases. These findings provide the basis for future monitoring and targeting of IL-10 in CRC-derived liver metastases (46).

TANs. TANs are a class of neutrophils that are present in the TME. As an important type of cell of the immune system, TANs participate in tumor development and progression. They are functionally divided into tumor-suppressive N1 cells and tumor-promoting N2 cells (47). TGF-β induces N1 to N2 polarization of TANs (48). N1 TANs can activate the effector T cells to prevent tumor development, promote tumor cell apoptosis via tumor necrosis factor-associated apoptosis-inducing ligand, and promote the release of matrix metalloproteinase 8 (MMP8) to degrade the ECM, which favors tumor metastasis (49). Conversely, N2 TANs enhance angiogenesis by stimulating VEGF, facilitate tumor advancement and metastasis through cathepsin G and reactive oxygen species (ROS) (50), and affect tumor aggressiveness and prognosis via various mechanisms. TANs form a complex network alongside tumor cells and other immune cells. They regulate the inflammatory milieu, modulate immune responses, and mediate cell-to-cell interactions within the TME, thereby influencing tumor progression. Investigating the functions and mechanisms of TANs is instrumental in identifying novel therapeutic targets and devising innovative strategies for cancer treatment.

Hu *et al* (51) performed a single-cell transcriptomic analysis of 81 patients with non-small cell lung cancer (NSCLC) and identified a TAN-promoting cluster with High mobility group box 1 (HMGB1) upregulation that was predicted to suppress tumor immunity and mediate immune escape via the GATA2/HMGB1/TIM-3 axis. Sheng *et al* (52) found that TAN-derived relaxin-2 (RLN2) promoted the migratory capacity of MCF7 cells via a PIK3-AKT-MMP-9 axis. The analysis of surgical samples from 20 patients with breast cancer found that the presence of TANs in breast cancer supported the invasion and migration of malignant cells (52). Chan *et al* (53) demonstrated *in vivo* and *in vitro* that pancreatic melatonin enhanced antitumor immunity in pancreatic cancer and neuroendocrine tumors by regulating TANs infiltration.

MDSCs. MDSCs, as one of the most important types of stromal cells of the TME, are multifunctional cells derived

from the bone marrow, and they exhibit immunosuppressive effects in pathological conditions to protect tumor cells from attack by the host's immune system via the production of ROS to inhibit T cell function (54,55). Their morphology is very similar to that of granulocytes or monocytes. Therefore, the two major populations of MDSCs are called polymorphonuclear neutrophil MDSCs (PMN-MDSCs) and monocyte MDSCs (M-MDSCs). Both types can inhibit the activity of the TME, in which M-MDSC shows significant plasticity and differentiation direction regulated by the TME (56). M-MDSCs may exhibit non-specific inhibition via various mechanisms and secrete various immunosuppressive factors, such as nitrous oxide, granulocyte-macrophage colony-stimulating factor, IL-10 and IL-6, among other factors, which can directly or indirectly inhibit the activity of T cells (57). By contrast, PMN-MDSCs exhibit antigen-specific T cell tolerance and function as non-specific suppressor cells capable of producing cytokines that promote tumor angiogenesis. MDSCs are important regulatory cells in the TME, and their immunosuppressive function influences tumor growth and response to treatment. In-depth studies on MDSCs are required to determine the mechanisms of tumor immune escape and provide new ideas and strategies for individualized and precise treatment. Aggregation of MDSCs can directly stimulate tumor angiogenesis by releasing various pro-angiogenic factors. Moreover, MDSCs can enhance the expression of immunosuppressive factors, including arginase 1, ROS and inducible nitric oxide synthase to induce apoptosis of activated T cells (58-60).

Zhang *et al* (61) found that C-C motif chemokine ligand 20 (CCL20) can regulate the TME to promote cancer development, especially the interaction between PMN-MDSCs and breast cancer stem cell in breast cancer, and this is hypothesized to underlie novel strategies for cancer treatment. Mei *et al* (62) found that 1L-37 can inhibit the development of tumors by inhibiting the immunosuppression of MDSCs in the TME through metabolic reprogramming, highlighting it as a novel avenue for cancer immunotherapy.

There is strong evidence indicating that tumors can interfere with the differentiation of monocytes into normal DCs and induce their differentiation into other types of monocytes of the same lineage, thus acting as immunosuppressive cells in the TME. Such cells are called TADCs. The expression of the surface antigen presentation related molecules MHC-I, MHC-II and activation molecules CD80 and CD86, are decreased on TADCs. This decreases its antigen processing and presentation ability. Moreover, TADCs exhibit upregulated expression of signal transducers and activators of transcription protein3 (STAT3), IL-12 transcription, suppression of DC maturation and the activation of T cells (63,64). Bregs, a special subtype of B lymphocytes, can secrete IL-10, TGF-β and IL-35, and promote Treg generation, which also exerts immunosuppressive effects (65).

Expression of immunosuppressive molecules in tumor cells. Factor-associated suicide (Fas) is a crucial death receptor known to trigger apoptosis. Under physiological conditions, T cells can induce apoptosis in Fas-positive target cells via Fas/Fas ligand (FasL)-mediated pathways. However, tumor cells possess mechanisms to evade T cell attacks; They can downregulate Fas expression or harbor Fas mutations, rendering themselves resistant to T cell-mediated apoptosis. Moreover, tumor cells often exhibit upregulated expression of FasL, which binds to Fas receptors on T cells, leading to T cell apoptosis (66). In addition to aberrant expression of Fas/FasL molecules and the development of resistance to apoptosis, tumor cells also exhibit upregulated expression of certain other immunosuppressive molecules and induce apoptosis of immune effector cells. For example, indoleamine2, 3-dioxygenase (IDO), which is upregulated in tumor cells, promotes tryptophan degradation. On the one hand, tryptophan deficiency can result in the arrest of T cells in the G1 phase of the cell cycle and suppress the proliferation of T cells. On the other hand, tryptophan degradation generates metabolites with cytotoxic and pro-apoptotic effects, which inhibit apoptosis-inducing effects on both T cells and NK cells (67). In addition, upregulation of B7-H1 molecule (also known as PD-L1), which is present on the surface of tumor cells, when combined with the T-cell inhibitory receptor PD-1, can induce T cell tolerance. Furthermore, it stimulates the secretion of IL-10 and induces apoptosis of T cells (68,69).

Metabolic alterations

Immune cells and the inflammatory response. A large quantity of immune cells is present in the TME, such as TAMs, MDSCs and Tregs (70), which regulate tumor growth and drug response by secreting cytokines, chemokines and growth factors. For example, TAMs can suppress the antitumor immune response by secreting immunosuppressive factors such as IL-10 and TGF-β, thereby reducing the effectiveness of immunotherapy (71).

Hypoxic microenvironment and drug tolerance. Hypoxia occurs in tumor tissues due to rapid growth which is not matched by an increase in blood and oxygen supply, and a hypoxic environment induces activation of various pro-survival signaling pathways, such as hypoxia inducible factor-1α (HIF-1α) pathway (72). HIF-1α promotes tumor cell survival and adaptation by regulating the expression of multiple genes, such as VEGF and glucose transporter (GLUT) 1, thereby improving tumor cell tolerance to chemotherapeutic drugs (73). Hypoxia also enhances the stability of HIF-1α which in turn modulates the hypoxia-induced gene expression and metabolism (74), including genes related to angiogenesis, erythropoiesis, glucose uptake and anaerobic metabolism (75) and multiple drug resistance genes including multi-drug resistance gene (MDR1) and the alkalized ECM protein (76). Studies have demonstrated that its upregulation increases the aggressiveness of tumor cells and emergence of drug-resistant phenotypes in high-grade gliomas (77). For example, in treating glioblastoma (GBM), hypoxia is a common feature of rapidly growing tumors such as GBM because they quickly outpace the vascular system and the nutrient supply (78). Mitochondria are initiators of oxidative phosphorylation channels which support hypoxic utilization. This suggests that inhibiting mitochondrial oxidative phosphorylation channels and blocking the TME feeding cycle may be an effective therapeutic strategy to improve tumor drug resistance (79).

Metabolic reprogramming. Tumor cells adapt to changes in the TME through metabolic reprogramming, such as by enhancing the use of the glycolytic pathway through the Warburg effect, which not only supports the rapid proliferation

of tumor cells but also affects the metabolism and effects of drugs (80). Metabolic changes in tumor cells can lead to a reduction in the active form of drugs within the cell, or affect drug uptake and efflux by altering the permeability of the cell membranes (81). Shigeta *et al* (82) found that gemcitabine-resistant urothelial cancer cells have metabolic reprogramming, which promotes pyrimidine biosynthesis by increasing the metabolic stimulation of aerobic glycolysis and pentose phosphate pathways, thereby reducing the therapeutic effect of gemcitabine. Li *et al* (83) revealed that the downregulation of retinoic acid receptor responder 2 promotes breast cancer brain metastasis (BCBrM) through lipid metabolic reprogramming, which can be used as a potential target for BCBrM treatment (83).

Tumor tissues often create an acidic microenvironment by generating acidic metabolites. This acidity can reduce the effectiveness of chemotherapy drugs by lowering their concentrations both inside and outside the cells (84). High lactate levels in the TME contribute to immunosuppression by inhibiting the function of immune cells such as T cells and natural killer (NK) cells (85). Lactate promotes tumor progression by stabilizing HIF-1α, enhancing angiogenesis, and altering the behavior of CAFs (86). For example, in GBM treatment, byproducts of cell fermentation such as lactic acid, glutamic acid and carbon dioxide contribute to the acidification of the microenvironment, promoting drug resistance, increased invasiveness and higher rates of tumor recurrence (87). Li *et al* (88) found that lactate accumulates in the tumor environment of metastatic CRC and acts as a substrate for histone acidification, which is further induced by enhanced cellular glycolysis under hypoxia (88). Wang *et al* (89) found that Proprotein convertase subtilisin/kexin type 9 (PCSK9) mediated by macrophage migration inhibitory factor and lactate levels play an important role in macrophage phenotypes polarization, targeting PCSK9 expression or activity can be used to effectively control colon cancer (89).

Upregulation of drug efflux pump. Cytokines and growth factors in the TME can induce tumor cells to upregulate MDR proteins such as P-glycoprotein (P-gp) and MDR-associated protein, which are able to actively pump drugs out of tumor cells, thereby reducing the intracellular accumulation of drugs and leading to resistance (90).

Physical and mechanical barriers

The barrier role of the ECM. The ECM acts as structural support in the TME while also forming a physical barrier to drug penetration. The components of the ECM include Col, elastin and glycosaminoglycans, which limit the spread of drugs within tumor tissues (91). In addition, the high-density fiber web in the ECM may trap and sequester a drug, reducing its effective concentration in tumor cells (92).

The TME not only affects tumor cells through biochemical signals, but also affects drug delivery and efficacy through physical and mechanical barriers. Tumor cells often exhibit different mechanical properties compared with normal cells, such as higher rigidity and the ability to deform (93). These mechanical properties enable tumor cells to survive and move through the high-density ECM, thus promoting tumor invasion and metastasis (94). Abnormal accumulation and recombination of the ECM in tumor tissues can lead to the increased density and rigidity of the matrix, thus forming a physical barrier that limits the spread and penetration of drugs in tumor tissues (95). This dense and rigid ECM prevents the passage of drug molecules, making it difficult for drugs to reach deep inside the tumor, thus reducing the effectiveness of treatment (96). Tumor blood vessels often exhibit abnormal structures, such as irregularity, distortion and increased permeability, which can lead to inefficient drug delivery. On the one hand, increased vascular permeability leads to the rapid delivery of drugs into the tumor stroma (97). On the other hand, the abnormal structure of blood vessels can lead to uneven drug distribution, such that certain tumor areas do not receive sufficient quantities of a drug, thus affecting the overall therapeutic effect of said drug (98). Rapid tumor growth can lead to increased interstitial pressure, which is primarily caused by tumor cell proliferation, ECM accumulation and abnormal function of new blood vessels. High interstitial pressure compresses the blood vessels inside the tumor, further reducing the ability of the drug to enter the tumor tissue through the blood vessels (99).

Tumor architecture. Cytoskeletal proteins have long been recognized as structural proteins that provide the necessary mechanical structure for cell development and tissue balance. As the cancer genome project completed, scientists are surprised to find that a large number of mutations was annotated as cytoskeleton or related proteins (100). Cells respond to environmental conditions, both chemical stimuli and physical stimuli such as mechanical stress. For example, cells can sense the hardness of the surrounding material through transmembrane proteins such as integrin, and further trigger the structural changes of cytoskeletal proteins such as actin and myosin, and the shape of the cell will change accordingly (101). It was found that the actin cytoskeleton can form a chelate with tripartite motif (TRIM)-containing protein (TRIM21), in cells under the condition of high tension; consequently, TRIM21 loses the 'freedom'. Thus, the phosphofructokinase activity was maintained and glycolysis was promoted (102). The mechanisms underlying tumor suppression by immune cells are shown in Fig. 2.

4. TAMs and tumor drug resistance

The role of TAMs in tumor resistance via modulation of the immune microenvironment. Administration of chemotherapeutic drugs such as paclitaxel promotes the secretion of CSF1 and IL-34 from breast cancer cells, thereby attracting macrophages to infiltrate the TME. Subsequently, this inhibits the activation and proliferation of CTLs, thereby diminishing their antitumor immune capacity. It also inhibits the antitumor effect of cytotoxic drugs (103). Conversely, neutralizing antibodies targeting CSF1 can inhibit TAM infiltration in breast cancer, thereby enhancing the antitumor immune response of CTLs to a certain extent and improving the efficacy of chemotherapy. In lung cancer, the cytotoxic drug doxorubicin (DOX) induces the production of IL-34 from tumor cells through the activation of the NF-κB pathway. IL-34, regulated by EBPβ, augments the immunosuppressive and tumor-promoting functions of TAMs. This prevents CTL responses and promotes regulatory T lymphocyte responses, thereby facilitating tumor immune evasion, maintaining TME homeostasis during chemotherapy, and reducing chemotherapeutic efficacy (104).

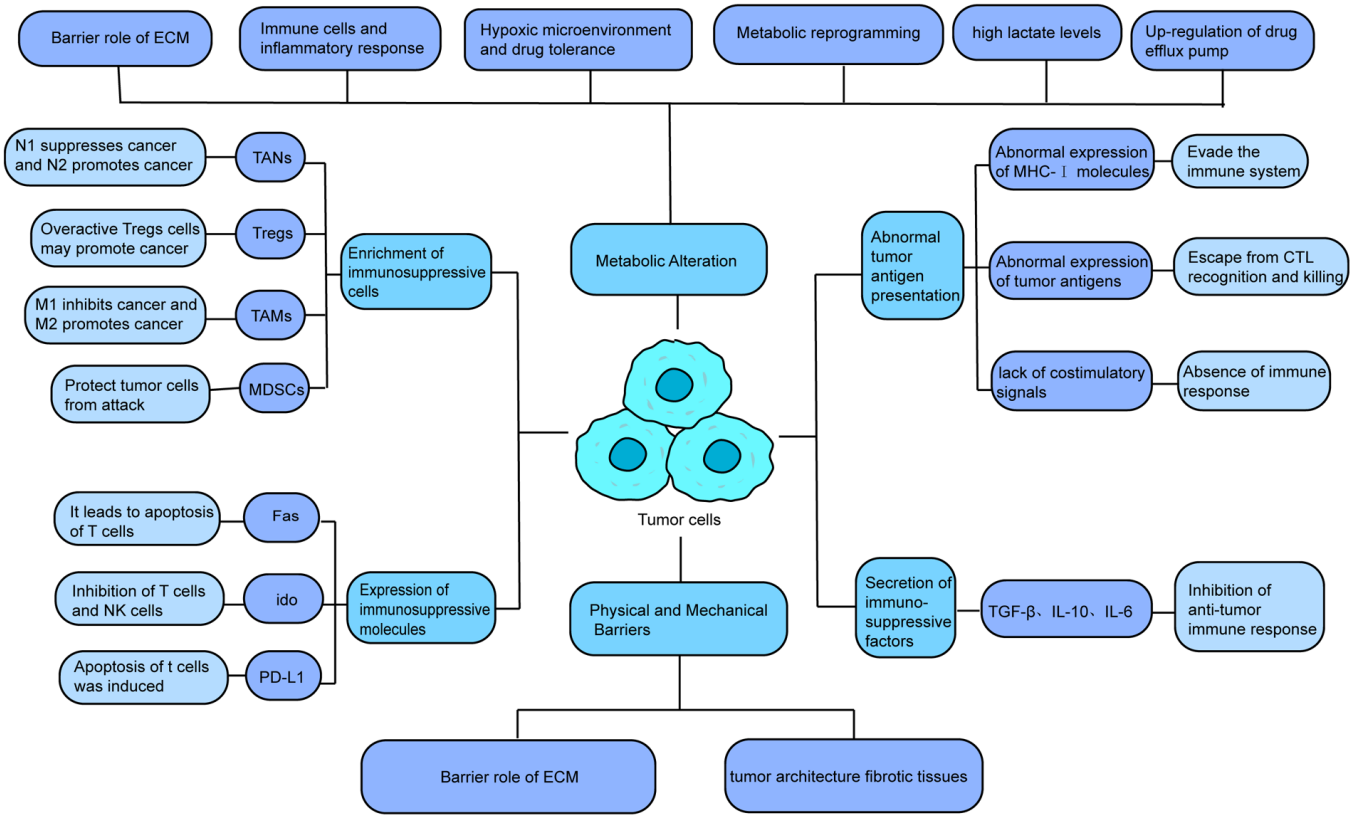

Figure 2. Causes of tumor immunosuppressive microenvironment. This illustrates the mechanisms leading to tumor immunosuppressive microenvironment. There are four main parts, each of which lists what cytokines or pathways ultimately cause immunosuppression. TAMs, tumor-associated macrophages; ECM, extracellular matrix; PD-L1, programmed death-ligand 1; MDSCs, myeloid-derived suppressor cells; Tregs, regulatory T cells; TANs, tumor-associated neutrophils; CTLs, cytotoxic T lymphocytes.

Tumor treatments act by improving the CTL response and achieving immune checkpoint blockade; however, certain patients do not respond to programmed death-1/ligand-1 (PD-1/-L1) antibody treatment. TAMs express PD-L1 and CTLA-4 ligands. By binding to PD-1 and CTLA-4 on T cells, they inhibit the immune response of T lymphocytes directly and decrease the efficacy of immunotherapy (105).

TAMs involvement in tumor resistance through cytokines. IL-6, secreted by TAMs can decrease the levels of the tumor suppressor miR-204-5p by activating STAT3, thereby enhancing the anti-apoptotic ability of CRC cells and the development of resistance to 5-fluorouracil (5-FU) and oxaliplatin (OXA) (106). It has been demonstrated that M2-type TAMs in breast cancer tissues and tumor cells promote the development of tumor resistance to DOX via the paracrine circuit of IL-6 (107). IL-10 is primarily activated and released by M2-type TAMs, which stimulates STAT3 to upregulate the expression of the protooncogene Bcl-2, thereby reducing the apoptotic effect of paclitaxel on breast cancer (108). CCL22, secreted by M2-type TAMs in colorectal tumors can promote epithelial-mesenchymal transition (EMT) of tumor cells and inhibit caspase-mediated cell apoptosis. It can also promote resistance of tumor cells to 5-FU (109).

The hypoxic conditions within GC lesions activate the HIF-1α, thereby increasing the expression of HMGB1. This elevation in HMGB1 levels can facilitate the migration of macrophages to a tumor and stimulate the production of growth differentiation factor 15. Consequently, this process accelerates the oxidation of fatty acid β in GC cells, ultimately promoting tumor resistance (110). It has been revealed that M2-type TAMs induce gemcitabine resistance in pancreatic ductal adenocarcinoma (PDAC) via the insulin-like growth factor (IGF) (111). Cathepsins, a type of cysteine proteinase, participate in the development of cancer drug resistance. Upon activation by IL-4, cathepsins B and S within TAMs are implicated in drug resistance in lung, colon and breast cancer. This mechanism may involve the degradation of drug target proteins by cathepsins.

TAMs modulate signaling pathways in tumor resistance. Macrophages in breast cancer tissues inhibit tumor cell apoptosis and induce autophagy by activating PI3K/AKT/survivin signaling pathway, leading to a reduction in sensitivity of breast cancer cells to DOX (112). TAMs can enhance the anti-apoptotic ability of breast adenocarcinoma cells via the CCL2/PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathway. This further leads to the development of resistance to tamoxifen (113). In GC, conventional chemotherapeutic drugs such as 5-FU induces GLUT3-dependent glycolysis in M2-type TAMs, which activates the CCL8/Janus kinase1 (JAK1)/STAT3 signaling pathway. It also enhances the tolerance of tumor cells to 5-FU (114). In addition, studies it has been indicated that TAMs in GC can promote drug resistance in tumor cells by activating the HIF1α/leukemia inhibitory factor/STAT3 signaling pathway (115).

TAMs regulate angiogenesis to promote tumor resistance. It has been indicated that TAMs in malignant tumors contribute to ECM degradation and remodeling by producing MMPs. In addition, TAMs regulate the synthesis and release of pro-angiogenic factors, thereby facilitating tumor blood vessel formation. Stockmann *et al* (116) found that VEGF derived from TAMs induces tumor resistance to cyclophosphamide by promoting the formation of an abnormal tumor vascular network characterized by low vascular density, low tortuosity and low adventitia cell coverage. In line with this, TAMs induce the formation of abnormal blood vessels with low perfusion by secreting VEGF, limiting the entry of chemotherapeutic drugs into the tumor to exert antitumor effects, and significantly reducing the effect of chemotherapy (117). In lung adenocarcinoma, M2-type TAMs can upregulate VEGF-C expression and its receptor VEGFR3, promoting tumor growth and downregulation of the tumor suppressor genes p53 and PTEN, thereby inhibiting tumor cell apoptosis and reducing their sensitivity to chemotherapeutic drugs (118). In ovarian cancer treatment with anti-VEGF drugs, the expression of VEGFR1 and VEGFR3 in TAMs may decrease. Despite this reduction, TAMs retain their capacity to facilitate tumor cell tolerance to anti-VEGF drugs by activating alternative angiogenic pathways (119).

The interactions between TAMs and cancer stem cells (CSCs). CSCs, a subset of cancer cells, are multipotent cells with self-renewal and tumor initiation properties. These features contribute to the occurrence, development and drug resistance of tumors. It has been found that the M2-type TAMs can induce tumor cells to acquire stem cell characteristics, thereby promoting the malignant progression of tumors (120). IL-17 in ovarian cancer tissues is primarily derived from TAMs and $CD4^+$ T lymphocytes, which bind to the IL-17 receptor expressed on tumor cells with a stem cell phenotype. It can activate the NF-κB/p38 mitogen activated protein kinase (MAPK) signaling pathway, and hence the stem cell characteristics of tumor cells and the promotion of tumor progression and drug resistance (121). Milk fat globulin epidermal growth factor8 and IL-6 secreted by M2 TAMs synergistically activate the transcription factor STAT3 which enhances the stem cell properties of pancreatic cancer cells. They inhibit a CTL immune response, thereby promoting tumor drug resistance, while reducing the infiltration of TAMs and the stem cell characteristics of tumor cells (122). Similarly, TAM-derived IL-10 can also significantly enhance the stem cell characteristics of small cell lung cancer cells by activating the JAK1/STAT1/NF-κB/Notch1 signaling pathway (123).

Influence of TAMs on drug metabolism. TAMs can regulate the expression of drug metabolism enzymes intra and extracellularly and alter the metabolic processes mediated by drugs in tumor cells. For example, cytokines secreted by TAMs, such as IL-10 and TGF-β, can upregulate the CYP450 enzyme system in tumor cells, thereby altering the metabolic rate of chemotherapeutic drugs and affecting the activity and half-life of drugs (124). TAMs inhibit the activity of effector T cells and NK cells, thereby weakening the immune system's attack on the tumor. Through these immunomodulatory effects, TAMs indirectly affect the efficacy of antitumor drugs, increasing the likelihood of tumor cell survival and proliferation (125). TAMs promote the degradation and remodeling of ECM by secreting a variety of stroma-degrading enzymes, change the physical and chemical characteristics of the TME, and affect the distribution and metabolism of drugs in tumor tissues (126).

Modulation of tumor repair mechanisms. TAMs can promote the repair of DNA damage in tumor cells induced by chemotherapy, promote the proliferation of endothelial cells by secreting certain cytokines such as VEGF and 1L-1, promote angiogenesis, and provide nutrients and oxygen for tissue repair (127). TAMs degrade and reshape the ECM by secreting matrix remodeling enzymes such as MMPs to provide spatial and structural support for the growth and migration of new tissues (128). This promotes cell survival and tissue repair by activating multiple signaling pathways. For example, TAMs can promote the proliferation and survival of tumor cells by secreting epidermal growth factor (EGF) and activating the EGF receptor signaling pathway (129). After chemotherapy, TAMs promote tissue repair by secreting anti-inflammatory factors and immunosuppressive factors that regulate the local immune environment and reduce inflammatory response and immune attack. For example, TAMs reduce inflammatory damage by secreting IL-10 and TGF-β, inhibiting the activity of effector T cells and NK cells (130). Several studies have shown that TAMs can support the survival and proliferation of CSCs by secreting specific cytokines, such as IL-6 and CSF-1. These cytokines can activate key signaling pathways in CSCs, such as JAK/STAT3 and PI3K/AKT, and enhance drug resistance and repair ability of CSCs (131).

Interestingly, Lurbinectedin (PM01183) enhanced the antitumor of gemcitabine in PDAC by exhibiting a specific depletion of TAMs that downregulated cytidine deaminase expression and increased gemcitabine-mediated DNA damage (132). Radioresistance of tumor cells could potentially be one of the causes for local recurrence post treatment. HMGB1 was shown to play a role in bladder cancer radioresistance through its intracellular functions in promoting DNA damage repair and autophagy. Moreover, combining radiation and HMGB1 inhibition significantly impaired tumor infiltrating MDSCs and TAMs-but not Tregs- and shifted the overall tumor immune balance towards antitumor response (133). Hong *et al* (134) experimentally verified that TAMs enhanced WTAP-mediated N6-methyladenosine RNA methylation through a CXCL16/CXCR6 axis and promoted cisplatin resistance in ovarian cancer cells.

Therefore, TAMs promote tumor drug resistance by modulating the immune microenvironment, cytokines, signaling pathways, angiogenesis and CSCs (Fig. 3).

5. CAFs and tumor drug resistance

CAFs are generated by various cellular sources. Currently, researchers have identified that CAFs are primarily activated by fibroblasts in normal tissues. Various cytokines secreted by tumor cells participate in this process, including TGF-β, EGF, platelet-derived growth factor (PDGF) and fibroblast growth factor 2 (135,136). In addition to fibroblasts, CAFs can also be produced by the transformation of MSCs, endothelial cells and epithelial cells. Furthermore, the transformation of adipocytes

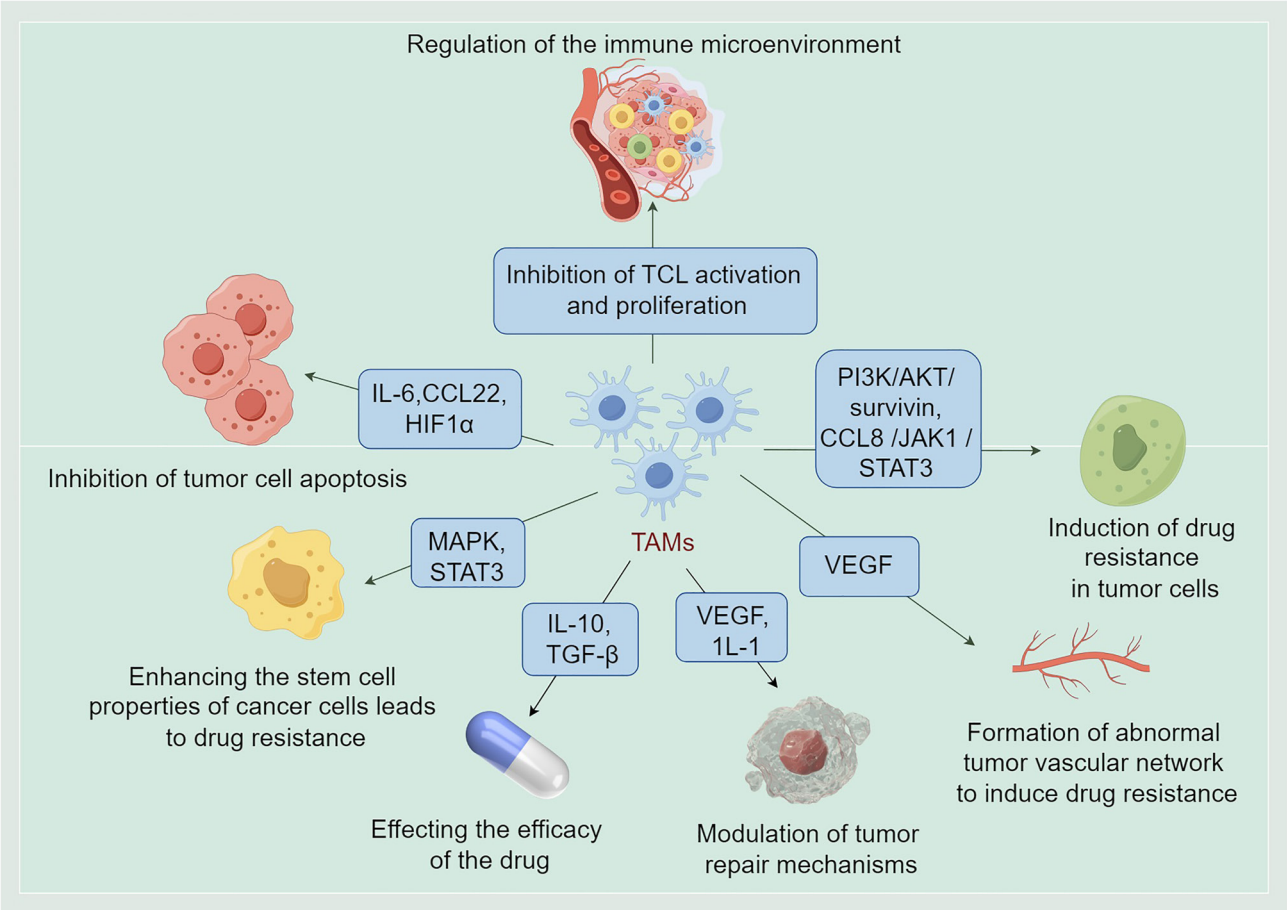

Figure 3. Drug resistance mechanism of tumor immune microenvironment factors. Wnt, Wingless/Int; Wnt/β-catenin, Wingless/Int classical pathway; NF-κB, The κ-light chain of B cells activated by nuclear factor is enhanced; IL-11/IL-11R/gp130/JAK/STAT3, Anti-apoptotic signaling pathway; Smad2/3, Mothers against decapentaplegic homolog 2; STAT3, The gene on chromosome 17; PI3K/AKT/mTOR, classic pathways that respond to insulin signals; STAT3/NF-κB, dual signal antitumor; WWOX, REDOX enzyme gene containing WW domain; CSF1, macrophage colony stimulating factor; IL, interleukin; PD-1, immunosuppressive molecule; CTLA-4, cytotoxic T lymphocyte-associated protein 4; CCL22, antibody to eosinophil chemotactic protein 22; HIF1α, hypoxia-inducible factor; GDF15, growth differentiation factor 15; IGF, insulin-like growth factor; PI3K/AKT/survivin, phosphatidylinositol 3-kinase/protein kinase B/survivin signaling pathway; CCL8, CC chemokine ligand 8; JAK1, non-receptor tyrosine kinase; VEGF-C, vascular endothelial growth factor C; VEGFR3, VEGF receptor 3; MAPK, mitogen-activated protein kinase.

or pericytes into CAFs through trans-differentiation is also a mechanism of CAF generation (137).

Maintaining the characteristics of CSCs by CAFs. In CRC, CAFs enhance the secretion of lncRNA H19 by activating the Wnt/β-catenin pathway. This enhances the stemness of CSCs, promoting resistance to OXA in CRC cells (138). Moreover, CAFs induce the expression of Wnt signaling-related genes in CRC cells, such as T lymphoma invasion and metastasis inducing protein-1, mediating resistance to 5-FU (139). In addition, activation of the NF-κB pathway can regulate the self-renewal of CSCs, also contributing to drug resistance (140). In GC, CAFs activate the NF-κB pathway by secreting the neuroregulatory factor 1, and this process is closely related to GC drug resistance and prognosis (141). In addition, CAFs may activate the IL-11/IL-11R/gp130/JAK/STAT3 anti-apoptotic signaling pathway in GC cells by secreting IL-11, to promote the maintenance of chemotherapeutic resistance of CSCs (142). There is evidence that CAFs can secrete TGF-β1 through the Smad2/3 pathway and upregulate the expression of STAT4 in PDAC tumor cells, thereby maintaining the characteristics of CSCs and promoting the resistance of tumor cells to gemcitabine (143).

CAF-mediated promotion of the EMT. EMT, regulated by transcription factors such as ZEB and Snail, is a key process that modulates cancer progression. In CRC, the expression of Snail1 in the tumor stroma enhances chemoresistance in tumor cells. As a result, CAFs facilitate the emergence of resistance in CRC to drugs such as 5-FU and paclitaxel by increasing Snail1 expression (144). In addition, CAFs induce EMT of tumor cells by upregulating the expression of cyclooxygenase-2 and prostaglandin E2 synthesis in CRC cells, thereby reducing the sensitivity of CRC cells to OXA (145). In esophageal squamous cell carcinoma (ESCC), IL6, secreted by CAFs, upregulates the expression of CXCR7 in tumor cells and promotes the process of EMT via the STAT3/NF-κB pathway. This suggests that CAFs may affect cisplatin resistance by secreting IL-6 (146).

Secretion of exosomes from CAFs. Exosomes secreted by CAFs promote the occurrence and development of

gastrointestinal tumors and chemotherapeutic resistance. The mechanism by which CAFs promote chemotherapeutic resistance is as follows: i) They can deliver molecules that may induce drug resistance: CAF-derived exosomes carry microRNAs (miRNAs or miRs), which can alter the gene expression profile of tumor cells and promote drug resistance by downregulating tumor suppressor genes or upregulating drug-resistance-related genes (147). Proteins contained in exosomes (such as MMPs and TGF-β) can activate signaling pathways within tumor cells, enhancing their viability and drug resistance (148). ii) Regulation of the TME: CAF-derived exosomes create a microenvironment conducive to tumor growth and drug resistance by regulating immune cells, such as inhibiting T cell activity and promoting the accumulation of immunosuppressive cells (149). Factors in exosomes can promote the formation of new blood vessels, provide more nutrients and oxygen to tumor cells, and also affect the distribution and effectiveness of chemotherapeutic drugs by altering the permeability of blood vessels (150). iii) Enhance autophagy of tumor cells: MiRNAs and proteins in exosomes can activate autophagy-related signaling pathways (such as MTOR and AMPK), enhance the survival capacity of tumor cells under chemotherapeutic pressure, and reduce the cytotoxicity of chemotherapy drugs (151).

Zhang *et al* (152) found that CAF-derived exosome NT-AS1 can regulate HIF-1 expression, enhance the proliferation and metastasis of PDAC cells, and reprogram glucose metabolism. Wang *et al* (153) used (PDGF-BB) to induce human oral mucosal fibroblasts to transform into CAFs and extract exosomes, and found that CAF-Exo had a stronger ability to promote oral squamous cell carcinoma (OSCC) proliferation. These results suggest that CAF-Exo may possess the ability to immunomodulate and promote OSCC proliferation (153). Miaomiao *et al* (154) found that miR-21 could transform normal fibroblasts into CAFs, and miR-21 was upregulated in various tumors. Exosomes from CAFs promote angiogenesis by introducing miR-21 into multiple myeloma endothelial cells. Therefore, CAF-derived extracellular miR-21 may serve as a novel diagnostic biomarker and therapeutic target (154).

It has been revealed that cricN4BP2L2 in exosomes secreted by CAFs activates the PI3K/AKT/mTOR pathway by binding to EIF4A3, which then promotes the stemness and OXA resistance of CRC cells (155). In addition, miR-625-3p in exosomes secreted by CAFs may enhance the invasive capacity of CRC cells and promote chemotherapeutic resistance of CRC cells by inhibiting the CELF2/WWOX pathway (156). In PDAC, once taken up by adjacent tumor cells, miR-106b in exosomes secreted by CAFs directly targets tumor protein 53 and induces nucleoprotein 1 to promote tumor cell survival and GEM resistance (157). In addition, in ESCC, IL-6 secreted by CAFs and miR-21 packaged in exosomes upregulates STAT3 expression in tumor cells, promotes the generation of MDSCs of monocytes, and finally enhances the resistance of ESCC cells to cisplatin (158). In HCC, CAF-derived exosomes deliver circ-ZFR to tumor cells and promote cisplatin resistance of tumor cells by inhibiting the STAT3/NF-κB pathway (159).

Forming therapeutic barriers to the development of chemotherapeutic resistance. Emerging evidence indicates that CAFs participate in ECM remodeling through a several pathways, which increases the density and stiffness of tumor tissues compared with normal tissues. The remodeled ECM prevents the entry of chemotherapeutic agents into tumor cells, limiting their therapeutic efficacy. In CRC, CAFs are particularly active in synthesizing ECM, which substantially impedes the penetration of the majority of antitumor drugs into solid tumors (160). In addition, increased adhesion between tumor cells and the ECM can arrest the cell cycle induced by the quiescent state, which promotes the development of drug resistance. Taken together, these findings suggest that the influence of ECM and CAFs on the response to chemotherapy is multifaceted, not only forming a protective barrier to block drug diffusion, but also enhancing anti-apoptotic effects through the integrin and focal adhesion kinase (FAK) signaling pathways, as well as forming a hypoxic environment and increased metabolic stress promoting tumor growth, acquisition of a CSC phenotype and treatment resistance (161).

CAF-mediated resistance to immunotherapy

CAF-mediated recruitment of TAMs and induction of a pro-tumor phenotype. CAFs induce the recruitment and differentiation of monocytes into tumor-promoting macrophage subsets through the secretion of abundant soluble mediators. This process inhibits T cell proliferation and enhances immunosuppression. For example, in triple-negative breast cancer, CAFs regulate the CXCL12-CXCR4 axis to redirect monocytes into immunosuppressive lipid-associated macrophages (LAMs), thereby inhibiting T cell activation and proliferation. Depletion of genes in this subset of LAMs prevents tumor growth (162). This finding suggests a potential targeting strategy for reducing immune suppression in breast cancer. For example, IGFBP7 secreted by CAFs promotes the polarization of macrophages towards an M2/TAM phenotype by regulating the FGF2/FGFR1/PI3K/AKT axis. IGFBP7 is upregulated in various tumors, and its complex biological role and molecular mechanism in tumorigenesis remains the focus of current attention. Similarly, M2/TAMs can influence the activation of CAFs (163). Activated CAFs further enhances TAM activity, which reinforces the cycle of immunosuppression.

Involvement in the recruitment and differentiation of TANs by CAFs. It has been demonstrated that CAF-derived CLCF1 promotes the secretion of CXCL6 and TGF-β in tumor cells, enhancing TAN infiltration and polarization in a paracrine manner in HCC. Conversely, CXCL6 and TGF-β secreted by tumor cells activate the ERK1/2 signaling pathway in CAFs to promote the production of CLCF1, thereby forming a positive feedback loop to accelerate the induction of liver cancer cell stemness and TANs 'N2' polarization. This suggests that CLCF1 holds promise as a prognostic biomarker for HCC. Moreover, it has been proposed that targeted inhibition of CLCF1 or ERK1/2 signaling may represent a viable therapeutic strategy for patients with HCC (164). In another study on HCC, peripheral blood neutrophils were recruited by CAFs to HCC via the SDF1a/CXCR4 pathway, and IL6 were released by CAF-induced TANs to differentiate into $PDL1^{+}$TANs via the JAK-STAT3 signaling pathway, thereby inhibiting the activity of T cells (165). Therefore, CAF-mediated activation of TANs provides a novel mechanism for tumor immunotherapy.

Stimulating $CD4^{+}$ T cell differentiation into Tregs and Th2 cells by CAFs. Previous evidence has demonstrated

that IL-1/NF-κB and TGF-β signaling pathways modulate the differentiation of normal mesothelial cells into antigen-presenting CAFs (apCAFs), which in turn promotes the differentiation of $CD4^+$T cells into FoxP3 Tregs (166). It was also identified that mesothelial cells are the origin of apCAFs. Therefore, further research is required to expand our understanding of the transformation process of mesothelial cells into apCAFs and the function of apCAFs may provide a novel direction for designing novel immunotherapies. CAFs can promote the transformation of Th cells into Th2 cells, exert immunosuppressive effects, and mediate tumor immune escape. In pancreatic cancer, tumor cells promote the secretion of IL-1β by releasing inflammasome adaptor proteins, leading to the activation of CAFs. The activated CAFs secrete thymic stromal lymphopoietin, produce chemokines that attract Th2, promote Th2 polarization, and promote tumor growth (167). Chen *et al* (168) constructed salvianolic acid B pegylated liposomes and found that they interfered with the activation of CAFs by inhibiting TGF-β1/Smad signaling. Moreover, it was observed that the levels of Th2 cytokines and the chemokine CXCL13 were decreased in tumor tissues, and this was correlated with the inactivation of CAFs. Thus, it has been suggested that inactivating CAFs and inhibiting the differentiation of Th2 cells may be an effective approach to immunotherapy.

CAF-mediated infiltration and induction of MDSCs. CAFs facilitate the migration and induction of MDSCs through the secretion of a variety of cytokines and chemokines, thereby exerting inhibitory effects on both adaptive and innate immunity. It has been suggested that CAFs derived from lung squamous cell carcinoma promote the migration of $CD14^+CCR2^+$ monocytes to the local TME by releasing CCL2. Subsequently, these monocytes are reprogrammed into MDSCs. MDSCs, in turn, enhance the production of ROS by upregulating the expression of NOX2 and IDO1. Moreover, it was found that the proliferation of $CD8^+$T cells was decreased, causing immune tolerance (169). This also suggests that efficient removal of excess ROS may improve T cell responses. A recent study in ESCC demonstrated that IL-6 and exosomal miR-21 secreted by CAFs induced the production of M-MDSCs by activating the STAT3 signaling pathway, while abrogating the differentiation towards DCs and macrophages. It cannot effectively activate antitumor immunity and promote drug resistance of tumor cells (139). These data suggest that targeting the IL-6/miR-21-STAT3 axis may be a potential approach for reversing drug resistance.

Production of excess metabolites and enhancing tumor immune escape by CAFs. CAFs produce excess metabolites through aerobic glycolysis thereby enhancing the anabolic demand of adjacent cancer cells, and this is termed the 'reverse Warburg effect' (170). In a study on prostate cancer, lactate released by CAF glycolysis reduced Th1 through sirtuin 1 (SIRT1)-mediated deacetylation of T-bet, and activated NF-κB to upregulate the expression of FoxP3, thereby stimulating the polarization of $CD4^+$T cells to Tregs (171). CAFs also induce immune tolerance by increasing IDO and arginase 2 (ARG2) activity. IDO1-induced tryptophan degradation can inhibit the proliferation of T cells and promote the differentiation of Tregs. Tryptophan metabolites, including kynurenine and 3-hydroxykynurenine, can induce apoptosis of activated T cells and NK cells. ARG2 inhibits cancer immune responses by depleting arginine, thereby inducing T cell anergy and promoting TAM reprogramming to an immunosuppressive phenotype (172). Therefore, CAFs regulate immune cells via metabolites generated by metabolic reprogramming to achieve antitumor immunosuppression. These findings suggest that excessive production of metabolites by CAFs is involved in the process of immunosuppression.

CAF-mediated inhibition of the antitumor immune effects. CAFs inhibit the T-cell priming process. DCs are the most important antigen-presenting cells involved in the activation of T lymphocytes. CAFs inhibit the differentiation and maturation of DCs by secreting TGF-β and downregulating the expression of MHC-II molecules and the CMs, CD40, CD80 and CD86 expressed on the surface of DCs (173). CAFs suppress the infiltration of CTLs into the tumor. In a previous study employing paired syngeneic mouse models of breast cancer featuring varying levels of CAFs, it was observed that an increased abundance of CAFs was associated with lower levels of CTLs. Models rich in CAFs displayed a phenotype characterized by CTL exclusion. Targeting a specific subset of CAFs by genetically knocking out the myofibroblastic-restricted receptor Endo180 (Mrc2) in mice increased the infiltration of CTLs and responsiveness to immune checkpoint inhibitors (174).

CAFs can also directly or indirectly inhibit the antitumor immunity of NK cells via several mechanisms. One such mechanism is that CAFs reduce NK cell activity and function by downregulating the expression of their activating receptors/receptor-associated ligands. The poliovirus receptor (PVR/CD155), is a ligand that activates the NK receptor DNAM-1, and CAFs can suppress PVR expression on the cell surface, thereby inhibiting the eliminating activity of NK cells (175). Second, CAFs inhibit NK cell-mediated antitumor elimination by secreting inhibitory factors that bind to inhibitory receptors on the surface of NK cells. In PDAC, $NetG1^+$CAFs were reported to induce immunosuppression, and its deletion reprograms them to an antitumor phenotype that allows NK cells to eliminate cancer cells. The mechanism involved depends, in part, on its ability to limit the secretion of immunosuppressive cytokines and increase the expression of IL-15 (176). Notably, it has been found that TGF-β is a key factor that links CAFs to NK cells. TGF-β secreted by CAFs can significantly inhibit the activation and cytotoxic activity of NK cells by suppressing the activation of receptors of NK cells, reducing the production of interferon-γ, and blocking the metabolic signal transduction downstream of stimulatory cytokines (177). Although some progress has been made in understanding the mechanism by which CAFs inhibit NK cells, the detailed mechanisms by which CAFs function are complex and require further study.

In CRC, CAFs upregulate the expression levels of immune checkpoint molecules TIM3, LAG3 and CD39 and downregulate that of CD137 through cathepsin S-dependent tumor antigen cross-presentation, which decreases T cell toxicity (178). Conversely, CAFs can also alter T cell immunity by upregulating the expression of immune checkpoint ligands. α-SMA^+CAFs upregulate PD-L1 expression in lung adenocarcinoma cells by secreting CXCL2, and the interaction between PD-L1 and PD-1 contributes to the immune escape of tumor cells (179).

Interaction between CAF and the immune system. The interaction between CAFs and the immune system plays a crucial role in the TME. CAFs affect the function of immune cells through multiple mechanisms, thereby promoting tumor growth and immune escape. In the present review, a few key aspects of the interaction between CAFs and the immune system were described: i) Establishment of an immunosuppressive environment: CAFs inhibit antitumor immune responses by secreting a variety of immunosuppressive factors, such as TGF-β, IL-6 and IL-10. These factors can inhibit effector T cells and NK cells, reducing their capacity to eliminate cells (180). ii) Promoting immune escape: CAFs downregulate the expression of MHC-I and reduce the possibility of tumor cells being recognized by immune cells and thus reduce the likelihood of being cleared. Secretion of CXCL12 can direct immune cells away from the tumor area, thereby reducing immune cell-mediated attacks on the tumor cells (181). iii) Influencing the infiltration of antitumor immune cells: CAFs promote angiogenesis by secreting angiogenic factors (such as VEGF), but the new blood vessels are typically structurally abnormal, making it difficult for immune cells to pass through (182). CAFs change the structure and composition of the ECM by secreting MMPs and other matrix remodeling enzymes, thus limiting the migration of immune cells (183). iv) Directly interacting with immune cells: CAFs interact with DCs to inhibit their maturation and antigen-presenting function, reducing the effectiveness of the antitumor immune response. Interactions with macrophages promote their maturation towards an M2 phenotype, which has a pro-tumor and immunosuppressive function (184).

Role of autophagy related to CAFs. Promotion of autophagy in tumor cells: Autophagy allows tumor cells to survive stresses induced by chemotherapy, and CAFs can influence this process through direct cell-cell interactions or paracrine signaling. CAFs promote autophagy in tumor cells by secreting autophagy-related factors, such as TGF-β, IL-6 and CXCL12. These factors enhance the autophagic activity of tumor cells by activating downstream signaling pathways such as the PI3K/AKT, AMPK and mTOR pathways (185). Metabolic interactions between CAFs and tumor cells, such as the exchange of lactic acid, amino acids and lipids, can regulate the autophagic activity of tumor cells (186).

As a support cell for autophagy: CAFs participate in ECM remodeling by secreting matrix degrading enzymes such as MMPs. This process may indirectly affect the autophagic activity of tumor cells by regulating the composition and structure of the ECM (187). CAFs can enhance the resistance of tumor cells to chemotherapeutic drugs by promoting autophagy in tumor cells. The specific mechanism may involve autophagy-mediated cell survival signaling and anti-apoptotic effects (188). It has been shown that CAFs in breast cancer enhance the autophagy activity of breast cancer cells by secreting IL-6 and TGF-β, thus promoting the survival of tumor cells and chemotherapeutic resistance (189). In pancreatic cancer, CAFs facilitate tumor cell survival in nutrient deficient and hypoxic environments by promoting autophagy (190). As the most abundant stromal cells in the TME, CAFs influence the emergence of tumor resistance (Fig. 4).

Taken together, cellular and molecular factors in the TME can influence the occurrence of drug resistance of tumor cells, including through immune escape mechanisms, creating a hypoxic environment, acidic microenvironment and regulating extracellular mechanism among other means, which may affect the sensitivity of tumor cells by regulating the environment and metabolic state of tumor cells (Fig. 5).

6. Therapeutic potential of targeting the TME

The development of drug resistance related to the TME is a major factor that reduces the effectiveness of several treatments, which decreases patient survival as well as the quality of life of patients. Thus, therapeutic potential of targeting TME especially the TAMs and CAFs, cannot be underestimated for the treatment of a wide range of cancer. A more thorough investigation of pharmacological blockade for drug-resistant cancer therapy has been augmented with the scientific rigor and depth of the content.

Therapeutic potential of targeting TAMs. Considering the therapeutic effects of TAMs, they are not being investigated for potential alleviation/prevention of tumor drug resistance and malignant progression. The combination of TAMs with commonly used chemotherapeutic drugs, targeted therapeutic drugs, or immunotherapeutic drugs can reduce tumor drug resistance and enhance antitumor efficacy. Current antitumor strategies targeting TAMs include: i) Inhibition of macrophage recruitment in the TME; ii) removal of M2 TAMs from the TME; iii) repolarization of M2 TAMs into M1 TAMs; and iv) delivery of antitumor drugs.

Chemokine-chemokine receptor signaling pathways, such as CCL2-CCR2 and CCL5-CCR5, act as the primary mechanisms for recruiting macrophages into the TME. Interventions aimed at blocking this signaling to impede macrophage infiltration into the TME have been investigated in both preclinical models and clinical trials. CCR2 antagonists such as PF-04136309 and MLN1202 have demonstrated efficacy in reducing macrophage infiltration in the TME in preclinical animal studies. Moreover, combining CCR2 antagonists with the chemotherapeutic regimen FOLFIRINOX has been shown to augment CTL immune responses in pancreatic tumors, thereby enhancing the efficacy of chemotherapy and inhibiting tumor progression (191). It has been demonstrated that inhibition of CCL5-CCR5 signaling can enhance the therapeutic effect of tumors such as breast cancer, GC, CRC and pancreatic cancer, and CCR5 antagonists can reduce the tumor burden of GC and inhibit its peritoneal metastasis, ultimately prolonging the survival of patients (192-195). *In vitro* cell experiments have indicated that CCR5 antagonists can suppress the proliferation of pancreatic cancer cells and cell apoptosis. Moreover, animal transplantation tumor models have also revealed that CCR5 antagonists can alleviate liver metastasis of pancreatic cancer (196). Therefore, CCR2 and CCR5 antagonists combined with conventional chemotherapeutic drugs are promising treatments for cancer.

Targeted depletion of M2 TAMs can promote antitumor immune responses and inhibit tumor growth. Lee *et al* (197) found that the hybrid peptide MEL-dKLA could target

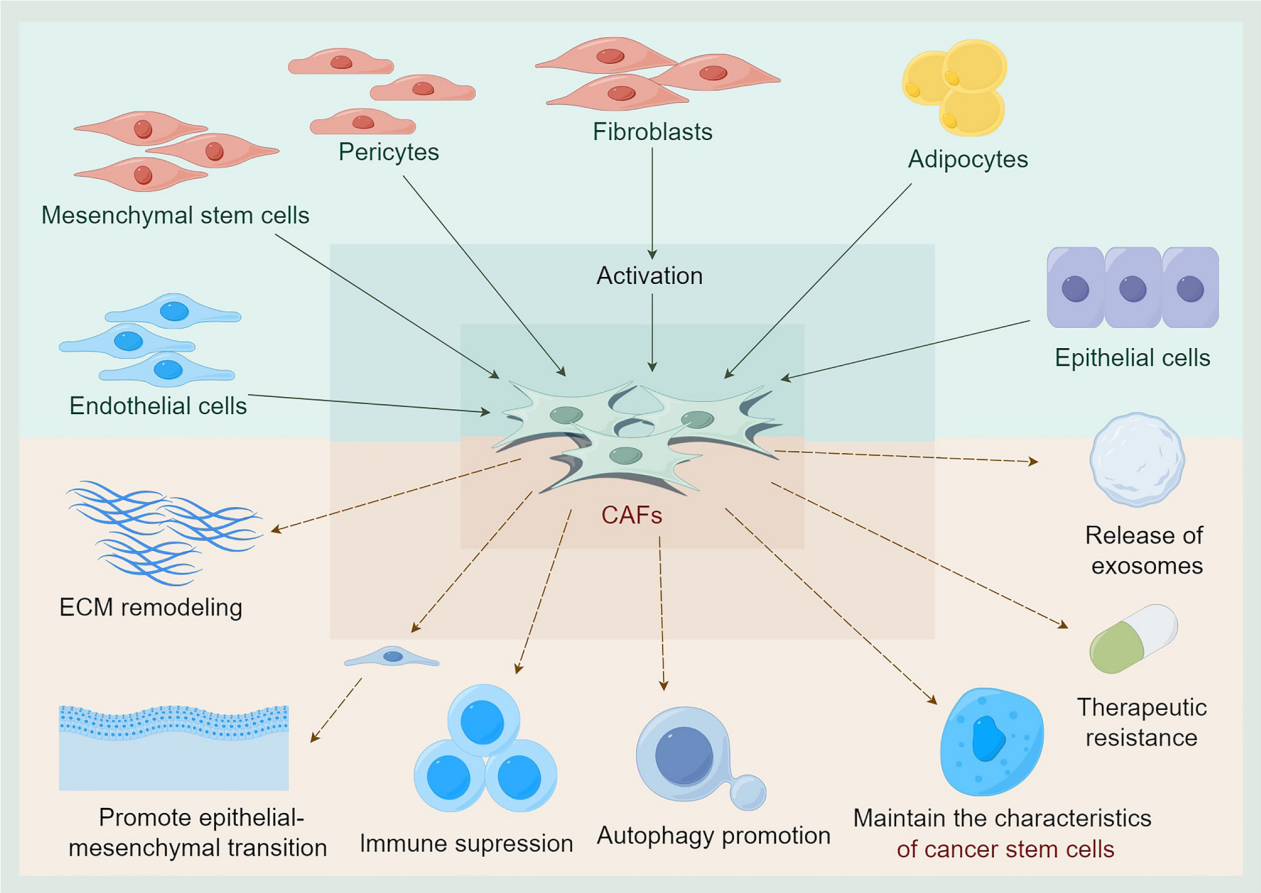

Figure 4. Relevant mechanism of tumor-associated macrophages. IL-6, interleukin 6; CCL22, antibody to eosinophil chemotactic protein 22; HIF1α, hypoxia-inducible factor; MAPK, mitogen-activated protein kinase; STAT3, the gene on chromosome 17; VEGF, vascular endothelial growth factor; PI3K/AKT/survivin, phosphatidylinositol 3-kinase/protein kinase B/survivin signaling pathway; JAK1, Janus kinase 1; STAT3, signal transducer and activator of transcription 3.

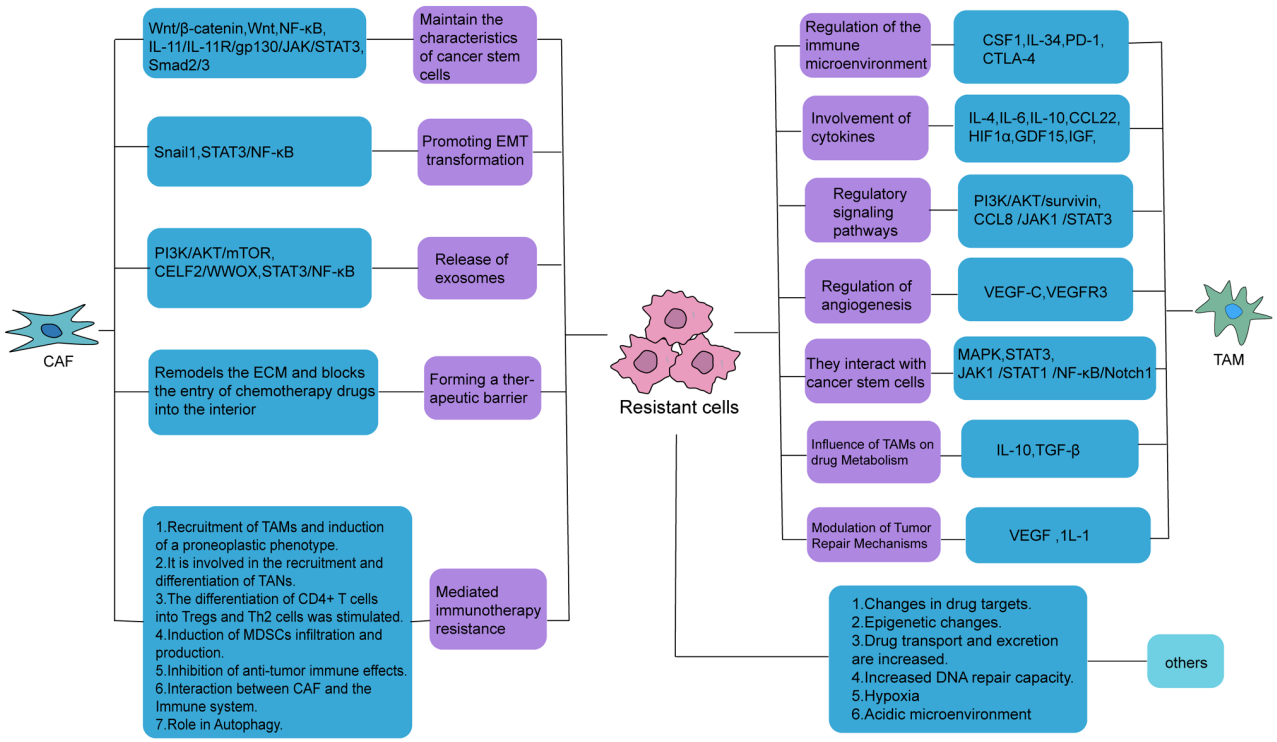

Figure 5. The mechanism associated with CAFs. This figure presents a simple description of the composition of CAFs and resistance mechanism. CAFs, cancer-associated fibroblasts.

M2 TAMs and induce mitochondrial apoptosis, and had a low affinity for M1 TAMs, T lymphocytes, DCs and other immune cells. Moreover, *in vivo* experiments have validated its capacity to suppress tumor angiogenesis and decrease tumor burden. CSF-1 plays a pivotal role in the polarization of M2 TAMs. Anti-CSF-1 receptor antibodies AFS98 and M279 have demonstrated efficacy in eliminating M2 TAMs in breast adenocarcinoma by intercepting CSF-1 signal transduction. This intervention not only inhibits tumor cell proliferation but also extends the survival of animal models (198).

Corosolic acid (CA) can inhibit the transcription factor STAT3. Liposome-packaged CA combined with anti-CD163 antibody can target TAMs, downregulate the expression of IL-10 and upregulate the expression of TNF-α, as well as promote the transformation of TAMs into M1 (40). Rodell *et al* (199) reported that Toll-like receptor 7/8 (TLR7/8) antagonist R848 induced the transformation of macrophages into M1. R848 carried by nanoparticles can repolarize M2 TAMs into M1 TAMs in a variety of tumor animal models, and its combination with anti-PD-1 antibody can significantly improve its antitumor immune ability. Immune-response gene 1 (IRG1) is expressed as TAMs in both human and mouse tumors. It has been demonstrated that deletion of IRG1 in mice can inhibit the growth of multiple tumor types, and IRG1-deficient macrophages represent an effective cell-based therapeutic strategy for cancer treatment (200). N-methyl-D-aspartate receptor (NMDAR) is an ion channel expressed on macrophages, and it was found that blocking the TAM phenotype of NMDAR functional and metabolic changes can improve promotion of antitumor immunity mediated by T cells and NK cells (201).

Due to the strong phagocytic ability of macrophages, their efficient migration to tumor lesions following stimulation by chemokines, TAM-mediated antitumor drug delivery has become an important research focus. In previous studies, macrophages were incubated in the peritoneal cavity containing antitumor drugs in the form of nanoparticles or liposome (LPO), and then injected back into animal models. This caused a significant prolongation of the circulating half-life of drugs, enhanced their antitumor efficacy, and reduced drug toxicity (202). In an animal model of lung cancer transplantation tumor, LPO-DOX delivered by TAMs exhibited higher antitumor efficacy with the advantage of low toxicity (203).

Therapeutic potential of targeting CAFs. A study of two distinct cohorts comprising over 160 PDAC samples showed that FAK activity was increased in CAFs within PDAC compared with fibroblasts from healthy pancreatic tissue. Moreover, elevated FAK activity in PDAC-associated fibroblasts emerged as an independent prognostic indicator for both disease-free and overall survival in multivariate analysis. This highlights the FAK activity in fibroblasts as a pivotal regulator of PDAC advancement and an independent prognostic marker for PDAC progression (204). In a transcriptomic analysis of OSCC xenografts, four genetic indices including FN1, TGFB2, TGFBR2 and TGFBI were detected as CAF indices and were reported to be strong predictors of survival in binary analysis of different subtypes of patients. Moreover, the CAF index is more powerful than the EMT score in predicting survival outcomes (205). In addition, using independent CAF-related prognostic genes, a model for predicting the prognosis of HCC was established. Furthermore, the immune infiltration characteristics, chemosensitivity and immunotherapeutic response of TME were analyzed. The prognostic value the of CAF-related genes was also determined (206). CAFs can resist the immunosuppressive effects and related mechanisms of PD-1/PD-L1 immunotherapy. Researchers have identified several key molecules, such as TGF-β, Ln-γ2, Wnt2 and exosomes. Therapeutic strategies targeting CAF biomarkers are currently in clinical trials with the aim of improving patient survival (207). LncRNA Disheveled binding antagonist of beta catenin3 antisense1 (DACT3-AS1), a CAF derivative, targets miR-181a-5p/SIRT1. OXA resistance-induced downregulation of DACT3-AS1 in CAFs-derived exosomes enhanced OXA resistance through miR-181a-5p/SIRT1 signaling pathway in GC (208).

Other clinical findings. Tumor response to drug exposure is largely affected by TME, which can reduce the efficiency of chemotherapy drugs and limit the efficacy of immunotherapy. Some clinical findings have shown that targeting TME can enhance the efficacy of chemotherapeutic drugs and immunotherapy. Emerging evidence demonstrated that targeting CAFs can improve cancer chemotherapy by increasing intratumoral drug uptake. Loeffler, a kind of fibroblast activation protein of the oral DNA vaccine, can reduce the expression of type 1 Col, increasing the absorption of the tumor cells to chemotherapy drugs by 70%. Compared with the control group, the life span of the vaccinated mice was 3-fold longer, and the tumor growth was significantly inhibited (209). A pooled analysis of 3,771 patients treated with neoadjuvant therapy found that the pathological complete response (PCR) of breast cancer was 31%, and lymphocyte infiltration of the PCR was only 2% of breast cancer. The presence of CD3 or CD20 lymphocyte infiltration and a low proportion of $CD146^{+}$CAFs indicate higher chemotherapy sensitivity (210).

Among 1,201 patients with NSCLC treated with PD-(L)1 blockade, acquired resistance is common, occurring in >60% of initial responders. Memon *et al* (211) found that the relapse of tumor can be raised by IFN-γ reaction gene or stable expression to separate. Persistent inflammation of the acquired resistant TME, rather than elimination or abandonment, may provide a new strategy for reversing drug resistance (211).

Ferroptosis is an iron-dependent mode of programmed cell death characterized by the accumulation of lipid ROS to manipulate cancer cell mutation and drug resistance through the lipid metabolic pathway that aggregates on phospholipid glutathione peroxidase. Zhu *et al* (212) found that ferroptosis achieves lethal levels by accumulating ROS and LPO products in the TME, and ferroptosis-driven nanotherapeutics can reverse drug resistance, showing superior efficacy over traditional methods. Preparation of paclitaxel-loaded ginsenoside Rg3 liposomes has been shown to inhibit the 1L-/STAT3/p-STAT3 pathway for tumor cells and the double effect of TME remodeling, realizing the high tumor inhibition rate of 90.3% (213).

7. Conclusion and future prospects

Numerous studies have demonstrated that the TME influences the formation of tumor drug resistance. The infiltration and activation of immune cells affect the efficacy of tumor treatment, but may also be utilized by tumor cells to escape immune attack. Tumor cells can increase resistance to treatment via various mechanisms. Although current immunotherapeutic strategies have been successful, there are several limitations, such as individual differences in patients, immune escape and drug resistance, among others, which need to be further investigated and accounted for. Future studies should focus on the complexity of the TME, including the interaction of different immune cell subsets and the communication between immune cells and tumor cells. Scientists should explore novel therapeutic strategies, such as the combined application of immune checkpoint inhibitors and the development of personalized immunotherapeutic strategies, to address the challenges of tumor resistance. Future investigations should aim to enhance the synergy between basic bench research and clinical applications, facilitating the translation of laboratory discoveries into practical treatments. Moreover, efforts should be directed towards refining current therapeutic strategies. In summary, investigating the TME and drug resistance holds theoretical and clinical importance. It is anticipated that future studies will uncover novel breakthroughs for cancer treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YL, JL, YZ and QG made substantial contributions to this paper, both in terms of conception and design analysis. All authors participated in the drafting and revision of the article, finalized the version to be published and agreed to take responsibility for all aspects of the work. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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