Review Article

The mechanism of cytokine regulation of cancer occurrence and development in the tumor microenvironment and its application in cancer treatment: a narrative review

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Background and Objective: The occurrence and development of tumors in human tissues widely depend on their surrounding environment, known as the tumor microenvironment (TME), which comprises various cells, molecules, and blood vessels. Through modifications, organization, and integration, these elements serve as potential therapeutic targets in anti-cancer therapy, supporting and promoting the proliferation, invasion, and metabolism of tumor cells. Cytokines within TME are responsible for immune cell activation, proliferation, and differentiation, thereby influencing the tumor's behavior. This article reviews the use of cytokines in tumor immunotherapy and combs the network signals that cytokines mediate in the development of malignancies.

Methods: A literature search of international sources was carried out on the PubMed and Web of Science databases, using main keywords such as "tumor immunotherapy", "cytokines", "chemokines", "tumor microenvironment", "recombinant cytokine engineering", and "tumor necrosis factor superfamily".

Key Content and Findings: The review provides a thorough summary of the functions of tumor necrosis factor superfamilies, chemokines, and interleukins within the TME as well as their therapeutic uses. Their potential as novel targets for tumor treatment is also evaluated. Furthermore, this paper focuses on various feasible strategies for recombinant cytokines reported in recent years, especially the cytokine engineering methods for targeting tumors. Ultimately, this paper contributes to an enhanced understanding among researchers of the mechanisms underlying the impact of the TME on disease development, thereby laying a solid foundation for the future development of new tumor therapies based on cytokines within the TME.

Conclusions: Cytokine immunotherapy holds promise on antitumor therapy. It is anticipated that the effectiveness of tumor treatment and the quality of life for tumor patients will continue to improve with ongoing research and development in this field.

Keywords: Cytokines; tumor microenvironment (TME); tumor immunotherapy

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Introduction

Background

The tumor microenvironment (TME) is a dynamic and complex cellular milieu comprising leukocytes, fibroblasts, extracellular matrix (ECM), and tumor cells. Beyond providing structural support for tumor tissues, the cellular constituents of the TME release a plethora of chemokines, cytokines, and members of the tumor necrosis factor superfamily (TNFSF), all of which facilitate tumor cells proliferation and emigration (1). Moreover, the TME is vitally important for delaying the response of tumor cells to chemotherapy and interfering with immune surveillance, both contributing to tumor growth (2).

The ratio and composition of different cytokines and chemokines within the TME significantly influence the complex intercellular interactions, including promoting cell invasion and migration, evading immune destruction, inducing tumorigenesis, resisting apoptosis, and maintaining cell proliferation signaling (3). Recognizing the pivotal role of the TME in these processes presents an opportunity to target specific components or signaling pathways within the TME for therapeutic intervention. In the process of tumor initiation and development and treatment resistance, cytokines targeting TME have been paid more and more attention in immunotherapy trials.

Rationale and knowledge gap

Despite the potential benefits of cytokine-based therapies, several obstacles must be addressed before their widespread therapeutic application. The safe utilization of cytokines is hindered by their frequent severe toxicities, such as cytokine storm and vascular leakage syndrome. Furthermore, the interconnections and mechanisms of action of cytokines remain poorly understood. Complicating matters, cytokines exhibit a spectrum of effects, including both pro-tumor and anti-tumor actions, adding layers of complexity to their therapeutic potential (4). To overcome these challenges, scientists have developed cutting-edge therapies, including recombinant interleukins (ILs) and antibody-cytokine fusion proteins, laying the groundwork for further advancements. For instance, in a mouse glioma model, the antibody-cytokine fusion protein L19TNF has demonstrated viability. When combined with CCNU, L19TNF enhances immune cell infiltration into the tumor, triggers immune-stimulatory pathways, and suppresses immune-suppressive pathways, resulting in significant tumor regression (5). Another engineered cytokine, F10 IC-CBD, conjugates human IL-2 to anti-IL-2 antibodies. F10 IC-CBD reduces the required dosage and administration frequency by prolonging the half-life of IL-2 and improving its pharmacokinetic and pharmacodynamic properties (6).

Objective

This paper aims to review recent advancements in novel immunotherapy strategies arising from the interactions between TME and tumor cells. Additionally, we aim to synthesize the latest research progress concerning the role of major cytokines in regulating tumor development within the tumor immune microenvironment. Through the presentation of specific examples of tumor immunotherapy, we endeavor to deepen readers' understanding of the application of cytokines in the TME. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-679/rc).

Methods

A thorough literature search was carried out on the PubMed and Web of Science databases to identify pertinent studies elucidating the mechanisms of cytokine utilization in tumor immunotherapy and the regulation of tumor occurrence and development. Key search terms included "tumor immunotherapy", "cytokines", "chemokines", "tumor microenvironment", "recombinant cytokine engineering", and "tumor necrosis factor superfamily". Only English-language literature was considered, and the search strategy is detailed in *Table 1*.

TME

The TME is widely acknowledged as a sanctuary for tumor cells, having a significant effect on the development, metastasis, and carcinogenesis by continually providing essential nutrients and other vital components necessary for tumor cell survival. Previous studies have illustrated that the TME is a dynamic network comprising various elements, including tumor cells, the ECM, endothelial cells, and fibroblasts. The interplay among these components creates physiological and pathological characteristics in tumor cells, such as low pH, hypoxia, hyperthermia, and high pressure (7). The TME, encompassing ECM, immune cells and inflammatory cells, serves as the internal milieu for

Table 1 The search strategy summary

Items	Specification
Date of search	01/08/2023 and 28/07/2024
Databases and other sources searched	PubMed/Web of Science
Search terms used	"Tumor immunotherapy", "cytokines", "chemokines", "tumor microenvironment", "recombinant cytokine engineering", "tumor necrosis factor superfamily"
Timeframe	2005–2024
Inclusion criteria	Restricted to articles published in English
Selection process	After choosing the subject and reviewing the literature, R.Q. and Y.Z. collaborated with other author to produce the final draft of the literature

tumor development and persistence (8,9). Predominantly constituted by immune and non-immune cells (10). These cellular components include tumor cells, neurons, and endothelial cells. Immune cells in the TME comprise tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), dendritic cells (DCs), T cells, B cells, and natural killer (NK) cells, each exerting anti-tumor or pro-tumor effects based on their effector capabilities (11). Furthermore, hypoxia, acidic environments, endogenous hydrogen peroxide, and altered expression of ECM proteins denote crucial TME alterations pivotal for tumor metabolism and progression (12). These distinctive features facilitate the induction of immunological responses by an array of cytokines, including chemokines, TNFSF members, and interleukins, underscoring their potential as therapeutic targets in cancer treatment.

Interleukin

The role of ILs in tumor immunity

ILs play a crucial role in tumor initiation, metastasis, and progression. Among cytokines, specific ILs are intricately involved in the formation and advancement of tumors. Beyond their essential role in anti-tumor immune responses, ILs create an environment conducive to tumor formation (13). Increasingly, research indicates that ILs and their receptors can serve as therapeutic drugs and targets, offering anti-tumor efficacy, as outlined in *Table 2*.

The role of recombinant ILs in tumor immunotherapy

Despite their extensive history of use in treating cancers and other illnesses, cytokines exhibit several unfavorable pharmacological characteristics, including polypharmacy and broad systemic effects, which can limit their therapeutic efficacy and cause significant toxicity (30). Consequently, recombinant ILs are gaining popularity as a novel approach to tumor immunotherapy, aiming to elicit substantial anti-tumor responses. The application of recombinant ILs in tumor immunotherapy, particularly IL-2, IL-10, IL-15, IL-18 and IL-21, has garnered an increase in recent scientific developments. IL-mediated signaling pathways are involved in promoting a role in the development of tumor or antitumor processes, as shown in *Figure 1*.

Activated DCs and $CD8^+$ T lymphocytes serve as the primary sources of IL-2 upon antigen stimulation (31). The first IL effectively utilized in cancer therapy is IL-2, which promotes the proliferation and differentiation of T cells and boosts the activation of NK and T cells, both of which inhibit the development and migration of malignant cells (32). Consequently, IL-2 can be employed as a tumor immunotherapy agent. However, high doses are associated with severe adverse effects that may be life-threatening. Bempegaldesleukin represents a pegylated IL-2 variant designed to mitigate such risks. Bempegaldesleukin has not yet received full approval and is still in the clinical trial stage. Conjugation with polyethylene glycol blocks IL-2's binding site to the high-affinity component IL-2Rα, thereby extending its half-life and reducing the risk of overdose (33).

IL-10 exhibits promise as a prospective anti-tumor treatment, because of its anti-inflammatory properties and capacity to activate cytotoxic T lymphocytes (CTLs). However, IL-10 plays a complex part in regulating anti-tumor immunity, as it can exert inhibitory effects on other effector immunological cells like $CD8^+$ T lymphocytes and NK cells while facilitating the survival, proliferation, and

Table 2 The application of interleukin and its receptors in tumor therapy

Interleukin	Ligand	Receptor	Application	References
IL-1 family	IL-1α, IL-1β	IL-1R1, IL-1R2, IL-1RAcP	Anti-tumor immunity, recruiting anti-tumor immune cells	(14)
	IL-33	ST2, IL-1RAcP	inducing NK cells to generate IFN-γ and releasing perforin and granzyme to eliminate tumor cells	(15)
	IL-18	IL-18Rα, IL-18Rβ	Mainly by activating T cells to generate IFN-γ and inducing apoptosis	(16)
	IL-36α, IL-36β, IL-36γ	IL-1Rrp2, IL-1RAcP	Mainly to inhibit Th1 inflammation and reduce the occurrence of inflammation	(17)
IL-2 family	IL-2	IL-2Rα, IL-2Rβ, IL-2Rγ	Promoting the production of T lymphocytes and NK cells, inducing T cells proliferation	(18)
	IL-7	IL-7Rα, IL-2Rγ	Activating T lymphocytes and B cells to produce growth factors	(19)
	IL-15	IL-15Rα, IL-2Rγ	Activating lymphocytes to produce IFN-γ	(20)
	IL-21	IL-21Rα, IL-2Rγ	Enhancing the cytotoxicity of CTLs	(21)
IL-10 family	IL-10	IL-10RA, IL-10RB	Promoting the proliferation and activity of CTLs, inhibiting the generation of inflammatory cytokines	(22)
	IL-24	IL-20RA, IL-20RB, IL-22R	Inducing cancer cell apoptosis and autophagy	(23)
	IL-28	IL-28R, IL-10Rβ	Inducing apoptosis of malignant tumor cells	(24)
IL-12 family	IL-12	IL-12Rβ1, IL-12Rβ2	Mainly inducing the expansion of Th1 response and cytotoxic immune effector activation (including NK cells and CTLs)	(25)
	IL-27	IL-27R	Limiting the intensity and duration of T cell responses to inhibit T helper cells initiation	(26)
	IL-35	IL-12Rβ2, IL-27R	Mainly secreted by regulatory B cells, thereby inhibiting tumor development	(27)
IL-17 family	IL-17A/F	IL-17RA, IL-17RC	Mainly secreted by Th17 lymphocytes and recruited by neutrophils, promoting the production of inflammatory cytokines; promoting tumor cells infiltration and migration	(28)
	IL-17C	IL-17RA, IL-17RE		(29)
	IL-17E/B	IL-17RA, IL-17RB		

IL, interleukin; NK, natural killer; IFN-γ, interferon-γ; Th1, T helper 1; CTLs, cytotoxic T lymphocytes; Th17, T helper 17.

migration of tumor cells (34,35). As of now, Pegilodecakin is still in the clinical trial stage. Pegilodecakin, a pegylated IL-10 variant, induces systemic immune activation and $CD8^+$ T cell-mediated immune responses in tumor patients by stimulating the production of IFN-γ and granzyme B. This suggests that pegylated IL-10 has the potential to enhance $CD8^+$ T lymphocyte responses and reduce tumor growth, thus achieving a promising therapeutic effect (36).

IL-15 stimulates the proliferation and activation of tumor-infiltrating lymphocytes (TILs) while facilitating the transport of white blood cells, along with the activation and expansion of CTLs and NK cells. BJ-001 is the first IL-15 fusion protein targeting tumors, which is currently in the clinical trial stage. Beyond addressing the issue of its short half-life, BJ-001 also enhances therapeutic efficacy and reduces systemic toxicity through the incorporation of tumor-targeting molecules within its structural domains. These molecules facilitate enrichment in tumors expressing high levels of αvβ3, αvβ5, and αvβ6 integrins (37). In mouse tumor models, ALT-803, a super-agonist compound of IL-15 that enhances the activation and multiplication of NK cells, has demonstrated potent antitumor activity (38). At present, ALT-803 has progressed into multiple stages of clinical trials.

It was initially discovered that IL-18 stimulates Th1 cells to produce the cytokine IFN-γ, thereby inducing Th1

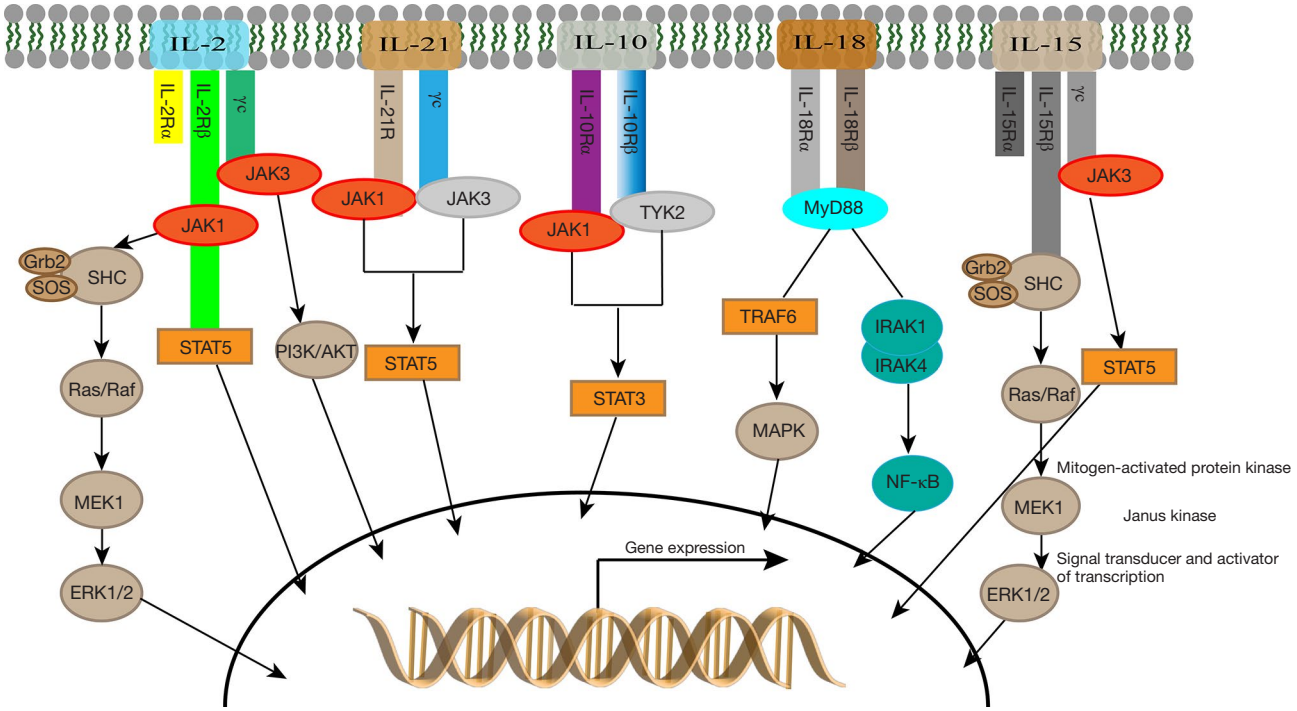

Figure 1 The signaling pathways mediated by interleukins that are involved in anti-tumor responses or the promotion of tumor occurrence and development. JAK, Janus kinase; STAT, signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; ERK1/2, extracellular signal-regulated protein kinases 1/2; PI3K/AKT, phosphatidylinositol 3-kinase/protein kinase B; TYK2, tyrosine kinase 2; TRAF6, tumor necrosis factor receptor-associated factor 6; MyD88, myeloid differentiation primary response 88; IRAK, receptor-associated kinase; NF-κB, nuclear factor kappa-B; IL, interleukin; SHC, Src homology and collagen.

cell proliferation and activation. Additionally, IL-18 can upregulate TILs by activating various signaling pathways, thereby strengthening the immune system's ability to combat tumors (39). Nevertheless, the therapeutic efficacy of targeted therapy is restricted, potentially due to the suppression of IL-18 signaling by IL-18 binding protein (IL-18BP), which exhibits a higher affinity for IL-18 than IL-18R. Currently, scientists have successfully developed the "decoy-resistant" IL-18 (DR-18), which is still in the clinical trial phase. It can stimulate the production of multifunctional $CD8^+$ T cells and boost NK cells activity. Recent research highlights the robust production of IL-8 in the tumor tissues of chemotherapy-resistant patients, primarily secreted by cancer-associated fibroblasts (CAFs) (40,41). These findings offer a novel avenue for enhancing chemotherapy effectiveness and improving the prognosis of tumor patients, underscoring the vital function of IL-8 in mediating tumor cell resistance to chemical treatments.

IL-21 is mainly generated by T follicular helper cells (Tfh) and NK cells. Notably, IL-21 is essential for stimulating Th17 cells proliferation, facilitating Tfh cells formation, and enhancing the survival rates of $CD8^+$ T cells, all of which may be conducive to its anti-tumor effects (42). This multifunctional cytokine also participates in inhibitory regulation, homeostatic maintenance, and lymphocyte differentiation. However, systemic administration fails to achieve sufficiently high concentrations within the TME to activate TILs due to IL-21's short half-life and peripheral depletion (43). To circumvent this limitation, researchers have developed mutant proteins by conjugating IL-21 cytokines with antibodies. These protein conjugates have the potential to enhance the pharmacokinetic properties of IL-21, prolonging its half-life and reducing the frequency of dosing (44).

Chemokine

Chemokines constitute a group of structurally related, small, secreted cytokines that are essential for immune system regulation (45). These chemokines are categorized into

subfamilies including CC, CXC, and CX3C, distinguished by the number and arrangement of their N-terminal cysteine residues, representing the largest subfamily of cytokines. Chemokines have intricate functions as pro- and anti-tumor agents in the setting of tumor immunity, owing to their diverse and dynamically regulated expression by immune cells, stromal cells, and tumor cells (46). Chemokine receptors, comprising a superfamily of seven transmembrane G-protein coupled receptors, are expressed not only on neutrophils and macrophages but also on endothelial and some epithelial cells derived from tumors (47). Chemokines are generated by immune and stromal cells infiltrating tumor tissues in TME, thereby modulating the tumor immune response. Additionally, tumor cells typically exhibit chemokine receptor expression, and the resulting chemokines may influence tumor cell growth, metastasis, and stemness (48). The progression of the disease has a major impact on patient prognosis and treatment, which is partly influenced by chemokines and particular receptors. These molecules participate in all stages of tumor formation, such as angiogenesis, invasion, migration, and proliferation. Due to their crucial roles in tumor formation and metastasis, chemokines and their receptors have garnered increasing interest in research on tumor recurrence, metastasis, and prognosis. This article reviewed the roles and functions of chemokines and their receptors in TME, as detailed in *Table 3*.

The role of chemokines in tumors

Chemotaxis and chemokine signaling to recruit different types of cells to the tumor, which helps shape the TME. The diverse roles of chemokine systems have been clarified by recent research, including immune cell recruitment, tumor cell proliferation and migration.

Chemokines promote immune evasion and immunosuppressive cell recruitment

Chemokines are pivotal in regulating immune cell migration and orchestrating immune responses against tumors (59). However, dysregulated chemokine expression in the TME can lead to the recruitment of immunomodulatory pro-tumor cells and promote cancer cell invasion. This includes TAMs, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs). Tregs are attracted by various chemokines, like the CCR6-CCL20 axis, which stimulates their proliferation and fosters tumor growth (60); TAMs hinder $CD8^+$ T cell activation by suppressing tumor-associated antigens, thereby aiding tumor progression (61). Furthermore, TAMs induce monocyte differentiation into perivascular macrophages, contributing to vascular leakage and tumor endocytosis (62); MDSCs secrete chemokines like CCL3, CCL4, and CCL5, which suppress T and NK cells while promoting Treg recruitment. Additionally, MDSCs support tumor angiogenesis, metastasis, and epithelial-mesenchymal transition (EMT) (63); plasmacytoid DCs (pDCs) can also influence tumor immune response. For instance, the CXCL12/CXCR4 axis facilitates the emigration of pDCs to the TME, potentially promoting tumor emergence and progression (64). CXCL12 also aids in protecting pDCs from apoptosis within tumors (65).

Chemokines promote tumor cell progression and proliferation

Tumor growth is influenced by various factors, among which chemokines play a pivotal role (66). Chemokines generated by tumors, fibroblasts, and infiltrating leukocytes bind specifically to chemokine receptors on the surface of tumor cells, promoting the expression of cyclin D1 (67), Fos, and heparin-binding epidermal growth factor. This induction activates the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated protein kinase (ERK) signaling pathway, thereby enhancing tumor cell proliferation and survival. Additionally, chemokines downregulate Bcl-2 expression while upregulating anti-apoptotic gene expression (68). Previous research has demonstrated that CCL28 effectively inhibits cell apoptosis and stimulates breast cancer cell growth via MAPK/ERK-mediated anti-apoptosis and metastasis signaling pathways (69).

Chemokines promote angiogenesis

Malignant tumor development involves various processes, including local invasion, distant metastasis, clonal proliferation of altered cells, and malignant transformation. One critical process is tumor neovascularization. TAMs within the TME enhance angiogenesis and immunosuppress tumor cells, thereby facilitating tumor development, invasion, and migration. Chemokines act as essential mediators facilitating interaction between TAMs and tumor cells (70). Through chemokine secretion, TAMs accelerate tumor growth. Conversely, tumor-released chemokines mediate TAMs polarization and synthesis. Several chemokines and their receptors control TAMs recruitment,

Table 3 The roles and functions of chemokines and their receptors

Chemokine	Receptor	Ligand	Non-cancer cell recruitment to tumors	References
CC	CCR1	CCL2, CCL3, CCL4, CCL5, CCL7, CCL8, CCL14, CCL15, CCL16, CCL23	Monocytes, TAMs, and TANs	(49)
	CCR2	CCL2, CCL7, CCL8, CCL11, CCL13, CCL16	Monocytes, B cells, and Treg	
	CCR3	CCL5, CCL7, CCL11, CCL13, CCL24, CCL26	Eosinophils and TAMs; primarily involved in allergic reactions and inflammatory responses	
	CCR4	CCL2, CCL17, CCL22	TILs, T helper 17, and Treg	
	CCR5	CCL3, CCL4, CCL5, CCL7, CCL11, CCL14, CCL16	DCs, $CD4^+$ T cells, monocytes, and NK cells; playing a key role in HIV infection	(50)
	CCR6	CCL20	DCs, Treg and B cells	(51-53)
	CCR7	CCL19, CCL21	T cells, DCs	
	CCR8	CCL1, CCL16, CCL18	TAMs, Treg; mainly involved in anti-inflammatory response	
	CCR9	CCL25	T lymphocytes; mainly involved in gut-related immune response	
	CCR10	CCL27, CCL28	TILs, Treg	
	CCR11	CCL2, CCL8, CCL11, CCL13	Monocytes and T lymphocytes; mainly regulating immune and inflammatory responses	
CXC	CXCR1	CXCL1, CXCL8, CXCL17	Neutrophils; mainly involved in inflammation	(54-56)
	CXCR2	CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7, CXCL8	Neutrophils; mainly involved in inflammation	
	CXCR3	CXCL9, CXCL10, CXCL11	T lymphocytes, NK cells and monocytes	
	CXCR4	CXCL12 (SDF-1)	Fibroblasts, endothelial cells	
	CXCR5	CXCL13	B cells, and Tfh	
	CXCR6	CXCL16	NK cells, $CD8^+$ T cells	
	CXCR7	CXCL11, CXCL12 (SDF-1)	T lymphocytes	
CX3C	CX3CR1	CX3CL1	Monocytes, macrophages, and Treg; mainly involved in inflammation and tissue repair	(57)
C	XCR1	XCL1, XCL2	$CD8^+$ T cells, DCs; primarily engaged in antigen presentation and immune response	(58)

TAMs, tumor-associated macrophages; TANs, tumor-associated neutrophils; Treg, regulatory T cells; TILs, tumor-infiltrating lymphocytes; NK, natural killer; DCs, dendritic cells; HIV, human immunodeficiency virus; Tfh, follicular helper T cell.

invasion, and polarization within the TME (71). TAMs, by the formation of angiogenic factors including vascular endothelial growth factor (VEGF) and TGF-β, stimulate tumor angiogenesis. Moreover, chemokines like CCL5 and CCL8 further facilitate tumor development and angiogenesis by recruiting and activating TAMs (72).

Chemokines promote tumor metastasis

Chemokine and their receptors may be vitally important for tumor metastasis, as connections between tumor and stromal cells in the TME often facilitate tumor spread through chemokine signaling. For instance, the CXCL12/

CXCR4 axis activates signaling pathways with diverse effects on tumor cells proliferation, emigration, and gene expression, contributing to metastasis to the liver in colon cancer (73). This axis enables communication between stromal and tumor cells, promoting tumor development, survival, angiogenesis, and migration. Additionally, chemokines implicated in tumor metastasis, such as CCL28, which binds to CCR3, promote angiogenesis in lung adenocarcinomas by activating the MAPK/ERK signaling cascade. This implies that the CCL28/CCR3 axis mediates both the development and migration of lung cancer (74).

Application of chemokine targeting therapy in tumor immunity

Chemokines have impacts that are both pro- and anti-tumor and are pivotal in shaping the TME as mediators of immune cell trafficking. Moreover, chemokine receptors and chemokines can serve as trustworthy biomarkers for promptly detecting and diagnosing malignant tumors (13). This study focused on targeted chemokine receptors, including CXCR4, CXCR2, CCR5, CCR2, CCR1, and CCR6, as they are strongly associated with patient prognosis when expressed on immune cells and malignancies (*Figure 2*).

The recruitment of DCs is significantly facilitated by CXCR4, thereby accelerating tumor cell proliferation and transformation. Activation of the CXCR4/CXCL12 axis stimulates various signaling pathways, like ERK1/2, Ras, p38 MAPK, and PLC/MAPK, promoting tumor cell invasion and distant migration, contributing to cancer cell transformation and progression (75,76). CXCR4 also regulates tumor angiogenesis and EMT, promoting the interaction between tumor and stromal cells (77). Inhibition of the CXCL12/CXCR4 axis significantly reduces M2 macrophage chemotaxis, potentially impeding tumor progression (78,79). Additionally, transmembrane glycoprotein CD248, present in many cancer and tumor stromal cells, facilitates M2 macrophage-induced secretion of CXCL12, promoting non-small cell lung cancer progression both *in vivo* and *in vitro* (80). Small molecule CXCR4 antagonist AMD3100 effectively inhibits gastrointestinal cancer cell invasion and metastasis by targeting CXCR4 (81), indicating that the CXCL12/CXCR4 axis may serve as a promising target for treating malignant tumors.

CXCR2, a major receptor for neutrophil trafficking, recruits TANs to the TME by the CXCR2/CXCL8 axis, stimulating tumor angiogenesis (82). CXCL8, a potent modulator of tumor angiogenesis promotes tumor microvessel growth and endothelial cell recruitment (83). Neutrophils permeate the tissue of tumors and subsequent production of angiogenic molecules like VEGF facilitates tumor vascularization upon CXCL8-induced CXCR2 activation (84). Recent research indicates that CXCR2 antagonists prevent colorectal cancer metastasis to the liver by enhancing cancer cell apoptosis and suppressing tumor angiogenesis in rat models (85).

CCR5 mediates the recruitment of immunosuppressive cells via multiple pathways, including Tregs and MDSCs, thus promoting tumor cell proliferation, invasion, and emigration (86). The CCL5/CCR5 axis exhibits oncogene-like functions, including tumor growth promotion, ECM remodeling, immunosuppressive cell recruitment, and MDSCs polarization (87,88). Furthermore, CCL5/CCR5 promotes TGF-β driven $CD8^+$ CTL apoptosis and immunological escape by recruiting Tregs. Maraviroc, a small molecule inhibitor of CCR5 has been identified as an allosteric inverse agonist. In a mouse model of liver cancer, maraviroc decreases cell metastases to the body, bone, and brain by inhibiting the binding of CCL5 and CCR5, thus reducing cancer cell proliferation and metastasis (89).

CCR2 facilitates the migration of cancer cells and the recruitment of immune-suppressive cells into the TME through its interaction with CCL2 (90). Many studies have emphasized the important role of the CCL2/CCR2 axis in recruiting Tregs within the TME. Radiation therapy induces increased release of CCL2 from cancer cells, consequently activating CCR2 and promoting Treg recruitment in murine models of head and neck squamous cell carcinoma (91). RS504393, a specific CCR2 antagonist, inhibits immunosuppressive cell infiltration into the tumor cell site, thereby impeding tumor growth (92). This underscores the dependence of pro-tumor activation and immune evasion on the inhibitor RS504393, utilized to prevent CCR2 binding to its ligand CCL2.

CCR1, the first identified CC chemokine receptor, mediates the recruitment of MDSCs to malignant tumors through CCL15, promoting immune escape and disease progression (93). The CCL15/CCR1 axis facilitates MDSCs recruitment to tumor tissue through signal transduction (94). Antagonists of CCR1/CCL15 have demonstrated efficacy in reducing tumor burden, inhibiting metastasis, and slowing disease progression in multiple myeloma models (95). The therapeutic benefits of CCR1 targeting primarily stem from diminished MDSCs infiltration, thereby impeding tumor growth, metastasis, and disease advancement.

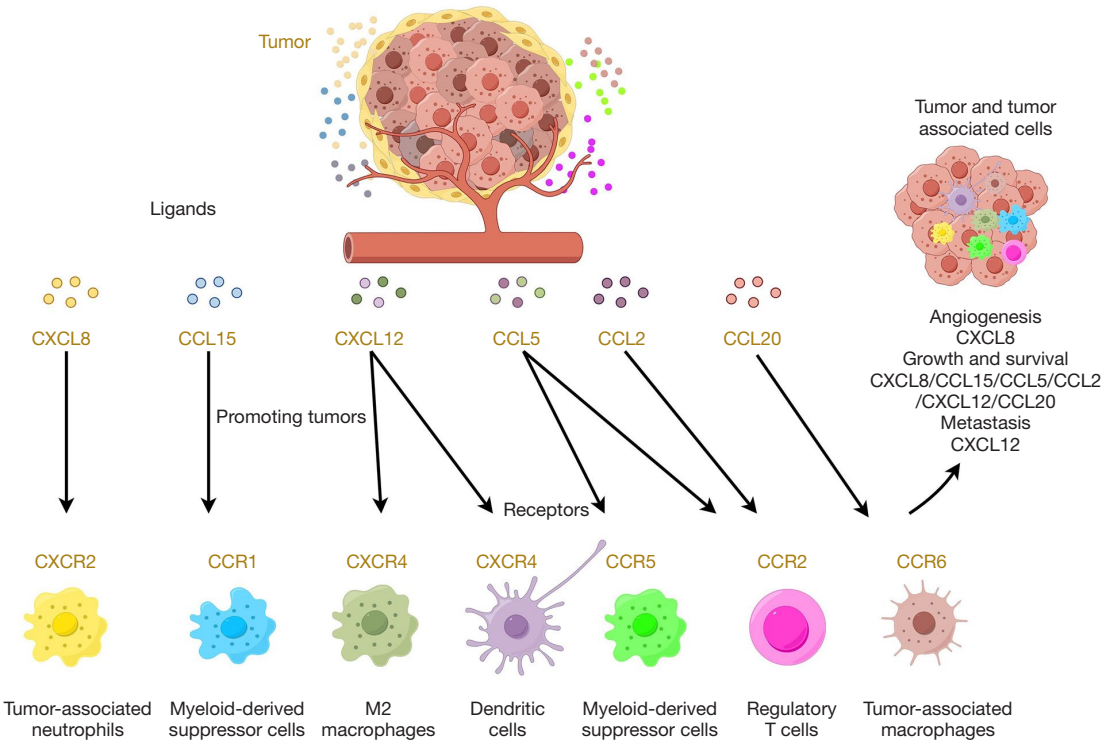

Figure 2 Mediating chemokine signaling of malignant tumors in the tumor microenvironment. Generated by Figdraw. The CXCR2/CXCL8 axis is capable of recruiting TANs, thereby stimulating tumor angiogenesis. The CCR1/CCL15 axis promotes the recruitment of MDSCs to tumor tissue through signal transduction. The CXCR4/CXCL12 axis can recruit dendritic cells and M2 macrophages, promoting the proliferation and growth of tumor cells. The CCR5/CCL5 axis can recruit Tregs and MDSCs, thereby promoting tumor cells proliferation, invasion, and migration. The CCR2/CCL2 axis can recruit Tregs, stimulating cancer cell proliferation and leading to migration and resistance to apoptosis. The CCR6/CCL20 axis helps regulate the infiltration of tumor-associated macrophages and stimulates cancer cell proliferation and migration. TANs, tumor-associated neutrophils; MDSCs, myeloid-derived suppressor cells.

CCR6, in conjunction with CCL20, is found in several immune cell subtypes, including Th17 cells, Tregs, B cells, and DCs (96). CCL20 contributes to the genesis and development of lung and colorectal cancers, along with other conditions like rheumatoid arthritis and immunological responses (97). Prostate cancer progression is facilitated by the CCL20/CCR6 axis, which also promotes TAMs infiltration, M2 polarization, and CD163 expression in macrophages (98). CCL20 serves as a potential prognostic marker for chemotherapy resistance in tumor patients. Blocking CCL20 or its downstream molecules can reduce breast cancer stem cells, reverse chemotherapy resistance, and significantly enhance taxane treatment efficacy for breast cancer (99). Furthermore, cisplatin enhances ovarian cancer cell migration by activating macrophages and increasing CCL20 generation, leading to epithelial-to-mesenchymal transition through CCL20/CCR6 axis activation on ovarian cancer cells. Inhibiting the CCL20/CCR6 axis presents a promising treatment strategy to mitigate tumor cell migration induced by chemotherapy drugs.

TNFSF

The immune system is regulated by the TNFSF and its receptors (TNFRSF), which mediate the proliferation, survival, and development of immune cells. TNFSF is involved in the pathogenesis of numerous diseases, including autoimmune disorders, cancers, and development anomalies, while also contributing to both innate and adaptive immunity. Signaling pathways activated by TNFSF are implicated in both anti-tumor mechanisms such as apoptosis and pro-tumor actions like inflammation and cell survival. Various cytokines within TNFSF, such as TNF-α,

CD137, and CD40, are involved in the formation, invasion, and migration.

Tumor necrosis factor α (TNF-α)

Predominantly secreted by macrophages, TNF-α is a crucial mediator of tumor-associated inflammation. It exhibits dual roles as an anti-tumorigenic cytokine and a pro-tumorigenic cytokine, that encourages angiogenesis, cell migration, proliferation, and disease development in a variety of tumor types (100). According to research, squamous cell carcinoma of the skin is significantly influenced by TNF-α. It is also generated as a proinflammatory cytokine in reaction to ultraviolet B radiation (UVB), promoting apoptosis, which aids in eliminating damaged cells and reduces the risk of tumor development (101). Moreover, TNF-α is necessary for squamous cell carcinogenesis and early stages of skin cancer (102). This suggests that TNF-α participates in immune responses that are both pro- and anti-tumor in cutaneous squamous cell carcinoma.

CD137

CD137 is a surface glycoprotein primarily produced by activated T lymphocytes and is a member of the tumor necrosis factor receptor family 9 (TNFRSF9). On activated DCs, CD137 binds to its native ligand CD137L (TNFSF9), promoting T cell proliferation and cytokine release while preventing T cell death. In numerous animal models, CD137 stimulates $CD8^+$ T cell activation and proliferation of numerous tumor regressions (103). Therefore, CD137 represents a potential target for anti-tumor immunotherapy.

CD40

As a member of the TNFRSF cell surface family, CD40 is a co-stimulatory receptor. In contrast to other costimulatory targets, antigen-presenting cells (APCs), including DC cells, B cells, macrophages, and monocytes, are the primary sites of CD40 expression (104). CD40L, commonly referred to as CD154, is a transmembrane protein that is mostly produced by stimulated $CD4^+$ T lymphocytes and is the sole ligand that interacts with CD40. CD40 agonists activate various immune cell types, enhancing the immune system's anti-tumor response. T cells, particularly CTLs, are necessary for CD40 agonist-induced anti-tumor actions (105). Since antigen cross-presenting DCs is necessary for the anti-tumor effects of CD40 agonists in T cell-dependent models, DCs activation may be a key component of immunological response against tumors. Moreover, by delivering antigens to T cells and generating antibodies to target tumors, B cells stimulated by CD40 can strengthen the immune response against tumors (106).

Conclusions

Cytokine immunotherapy, as a cutting-edge science for the treatment of cancer, autoimmune disorders, and other diseases, constantly demonstrates its significance and promise. When conjunction with other treatment modalities including small compounds and monoclonal antibodies, therapeutic cytokines further contribute to modulating both innate and adaptive immune systems. While cytokines directly impact cancer cells, reports suggesting their role in tumor progression have been made; however, the prevailing view now considers them to predominantly exhibit anti-tumor actions. This article discusses the main functions of cytokines and chemokines in tumor immunotherapy, along with their potential applications in treating solid tumors. Particular attention is given to how these molecules target various cellular components of the TME, like DC cells, TAMs, and other immune cells. Interactions among tumor cells, immune cells, and cytokines constitute key aspects of the TME, providing a theoretical basis for targeting cytokine-mediated signaling pathways, directly and indirectly, to reshape tumor immune and biological phenotypes and enhance the therapeutic efficacy of immunotherapy. Nevertheless, there are certain challenges of cytokine immunotherapy, including high toxicity, brief half-life, and poor effectiveness. Limitations with anti-tumor cytokine therapy are currently being vigorously addressed through various technological platforms. In the future, studies on cytokines will focus on enhancing their efficiency and broaden their use to a wider variety of tumor types. Future endeavors concentrate on devising personalized treatment regimens, employing combination therapies, and conducting research and development of novel medications and therapeutic approaches. By thoroughly investigating the role of cytokines within the TME, we anticipate the development of more potent and precisely targeted immunotherapeutic medications, offering tumor patients with additional treatment options and hope.

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