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REVIEW

Chemokines and Their Receptors: Predictors of Therapeutic Potential in Tumor Microenvironment on Esophageal Cancer

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Abstract

Esophageal carcinoma (ESCA) is an aggressive solid tumor. The 5-year survival rate for patients with ESCA is estimated to be less than 20%, mainly due to tumor invasion and metastasis. Therefore, it is urgent to improve early diagnostic tools and effective treatments for ESCA patients. Tumor microenvironment (TME) enhances the ability of tumor cells to proliferate, migrate, and escape from the immune system, thus promoting the occurrence and development of tumor. TME contains chemokines. Chemokines consist of four major families, which are mainly composed of CC and CXC families. The main purpose of this review is to understand the CC and CXC chemokines and their receptors in ESCA, to improve the understanding of tumorigenesis of ESCA and determine new biomarkers for the diagnosis and prognosis of ESCA. We reviewed the literature on CC and CXC chemokines and their receptors in ESCA identified by PubMed database. This article introduces the general structures and functions of CC, CXC chemokines and their receptors in TME, as well as their roles in the progress of ESCA. Chemokines are involved in the development of ESCA, such as cancer cell invasion, metastasis, angiogenesis, and radioresistance, and are key determinants of disease progression, which have a great impact on patient prognosis and treatment response. In addition, a full understanding of their mechanism of action is essential to further verify that these chemokines and their receptors may serve as biomarkers or therapeutic targets of ESCA.

Graphical Abstract

The poor prognosis of esophageal cancer is related to the early invasion and metastasis of the tumor. Tumor-associated macrophages are highly correlated with the occurrence, development, severity, and prognosis of esophageal cancer in the tumor microenvironment. Studies have shown that tumor-associated macrophages and esophageal cancer cells in the esophageal cancer microenvironment can secrete a variety of chemokines. A comprehensive analysis of the literature on the relationship

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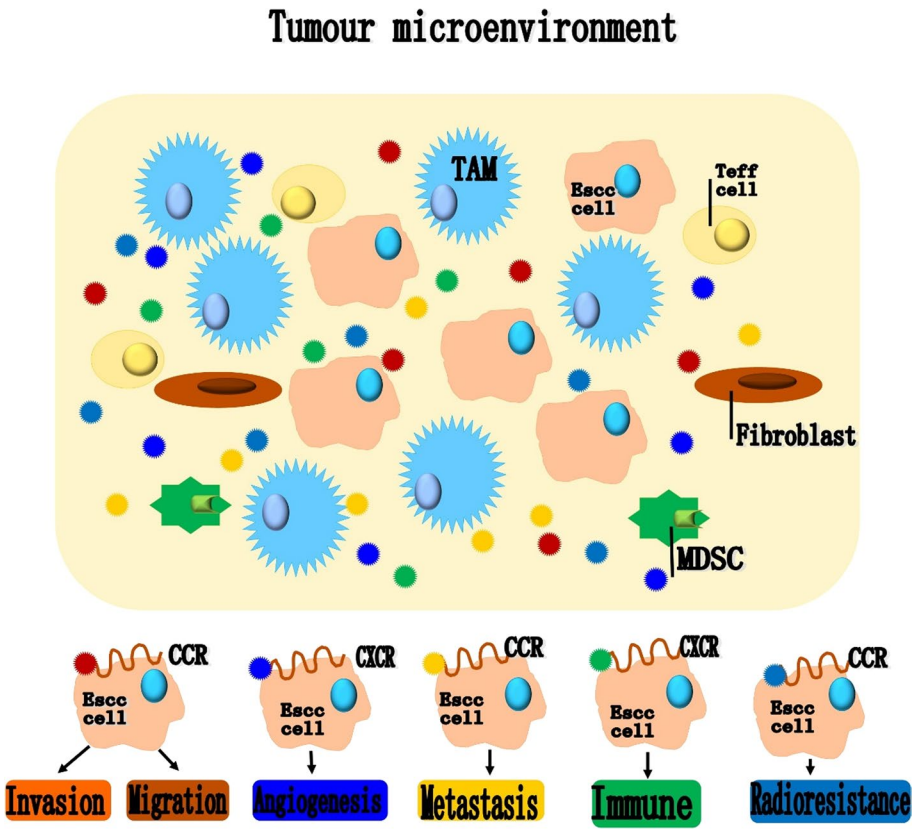
between esophageal cancer cells and chemokines found that the binding of these chemokines with corresponding receptors can regulate the growth, migration and invasion, angiogenesis, radiotherapy resistance and leukocyte invasion of the tumor.



Keywords Chemokine · Chemokine receptor · Esophageal cancer · Therapeutic potential · Tumor microenvironment

Introduction

Esophageal cancer (ESCA) is the seventh most common cancer in the world and the sixth most common cause of cancer-related death, according to new research [1]. Globally, one of the countries with the highest burden of ESCA is China [2]. ESCA can be classified into esophagus adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) by histopathology. The main treatment methods of ESCA include surgery, radiotherapy, chemotherapy, and comprehensive treatment [3]. The overall 5-year survival rate of patients with ESCA is about 20% [4]. The main cause of death is the invasion and metastasis of ESCA cells [5]. However, the 5-year survival rate of patients with early ESCA can exceed 95% if treated promptly [6]. Therefore, it is of great clinical significance to evaluate the biological changes related to ESCA at the molecular level and find the regulatory targets related to the malignant phenotype of cancer invasion and metastasis, to improve the survival rate of ESCA patients.

Chemokines were first described as factors inducing neutrophil migration in 1984 [7]. Chemokines are small cytokines or signal proteins secreted by cells and play an important role in their biology [8, 9]. Chemokines are a family of soluble proteins with a low molecular weight of 8–15 kDa. Studies have shown that human chemokines contain about 50 different types and 20 chemokine receptors [10]. According to the position of the first two N-terminal cysteine residues, chemokines are divided into four major subfamilies, including CC, CXC, C, and CX3C. Chemokine receptors are G-protein-coupled receptors. G-protein-coupled receptors have seven transmembrane domains on the surface of leukocytes. So far, about 20 different chemokine receptors have been identified. According to the type of chemokine they bind, they are also divided into four families, including CCR and CC chemokine binding and CXCR and CXC chemokine binding (Fig. 1). The CC and CXC chemokine are two major chemokine subfamilies, which are mainly expressed in tumor microenvironment (TME) and play an important

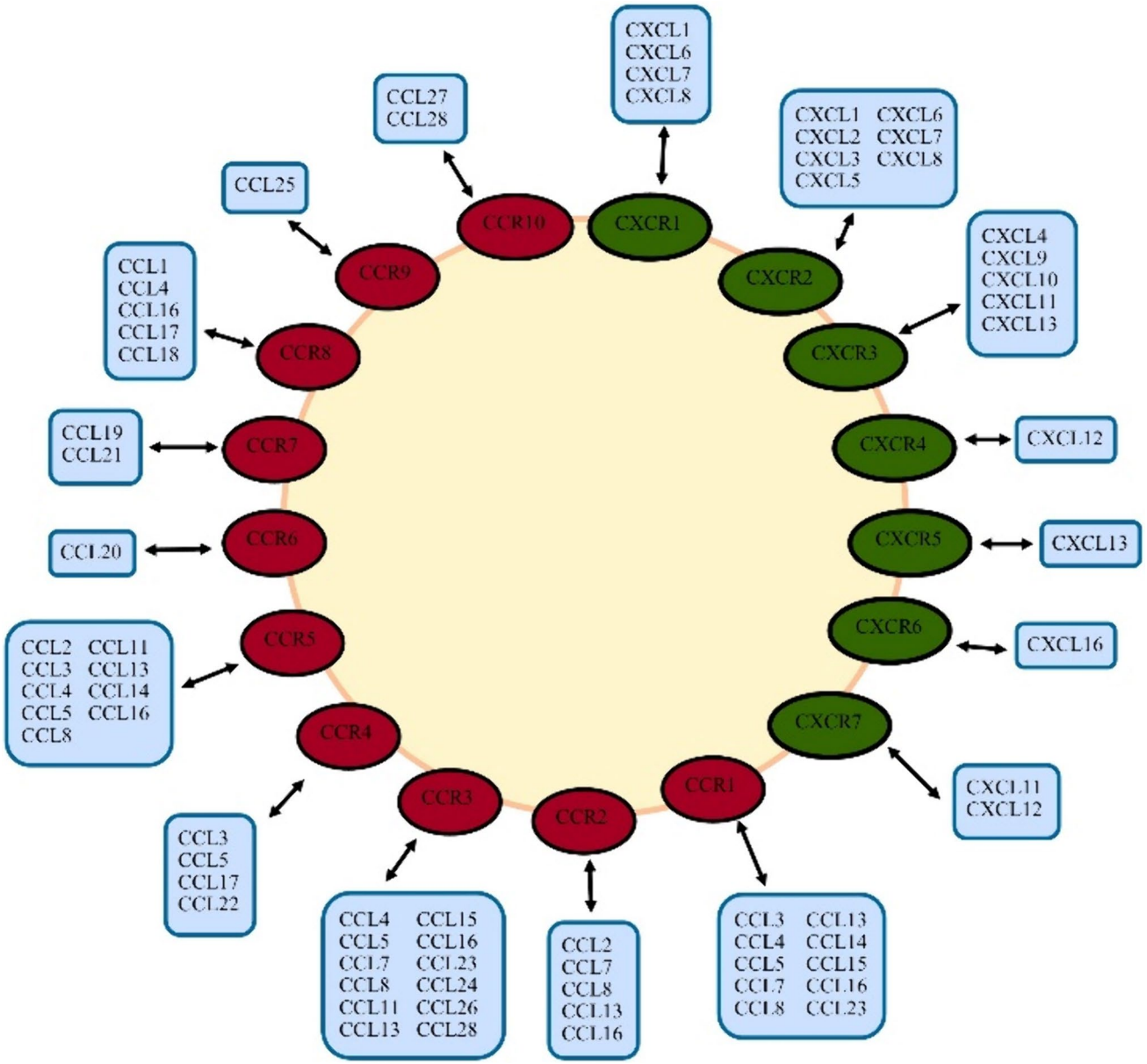


Fig. 1 CC and CXC chemokines and their receptors

role in tumor progression, tumor-related inflammation, immunity, and tumor invasion [11, 12]. Therefore, this review focuses on the role of CC and CXC in ESCA.

Tumor-associated macrophages (TAMs) are macrophages that infiltrate tumor tissue, and their proportion in the TME is highly correlated with tumor occurrence, development, severity, and prognosis. Research has found that TAMs can secrete chemokines. Tumor cells secrete chemokines in the form of autocrine or paracrine. Chemokines mediate host response to cancer by guiding leukocytes into TME. In fact, TME is composed of a wide and diverse mixture of CC and CXC chemokines, which regulate tumor growth, angiogenesis, invasion, and leukocyte infiltration into tumors [13]. Chemokines can directly regulate tumor growth by inducing tumor cells proliferation and preventing tumor cells apoptosis (Fig. 2). The role of chemokines in tumors has been reported in various types of cancers, including breast [14], colon [15], ovarian [16], lung [17], as well as ESCA [18].

More and more evidences show that uncontrolled inflammation is related to the formation of ESCA [19–21]. Chemokines and their receptors play an important role in inflammation and malignant diseases [22–24]. The expression of chemokine in tumor tissue is decreased or up-regulated, which has protective and promoting effects on tumor occurrence. The purpose of this study is to explore the mechanism of chemokine-induced invasion

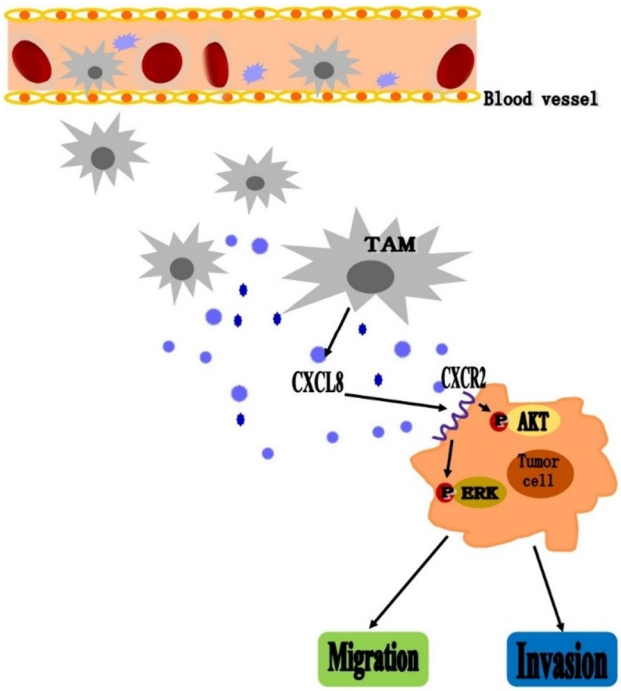


Fig. 2 Tumor-associated macrophages in the tumor microenvironment secrete chemokines that act on the migration and invasion of esophageal cancer cells

and metastasis of ESCA and to provide a strong theoretical and experimental basis for revealing the pathogenesis of ESCA, finding molecular markers for diagnosis of ESCA, identifying, and developing drug targets for clinical treatment, and formulating effective treatment plans.

CC and CXC Chemokine Subfamily in ESCA

We reviewed articles on CC and CXC chemokines and their receptors in ESCA identified by PubMed database (Fig. 3). In the CC chemokines subfamily, there are 28 chemokines, from CCL1 to CCL28. We have not found any research reports on CCL6, CCL7, CCL9, CCL10, CCL12, CCL13, CCL14, CCL16, and CCL27 of ESCA. The role of CC chemokines in ESCA is summarized in Table 1. Most CC chemokines were highly expressed in ESCC and were related to the prognosis of patients. The pathways of CCL1/CCR8 and CCL3/CCR5 in the ESCA are illustrated in Fig. 4. CXC chemokine subfamily includes 17 chemokines from CXCL1 to CXCL17. We did not find the relationship between CXCL4, CXCL7, CXCL15, CXCL17, and ESCA. The role of CXC chemokines in ESCA is summarized in Table 1. Most CXC chemokines were highly expressed in ESCC. The pathways of CXCL6/CXCR2 and CXCR12/CXCR4 in the ESCA are illustrated in Fig. 4.

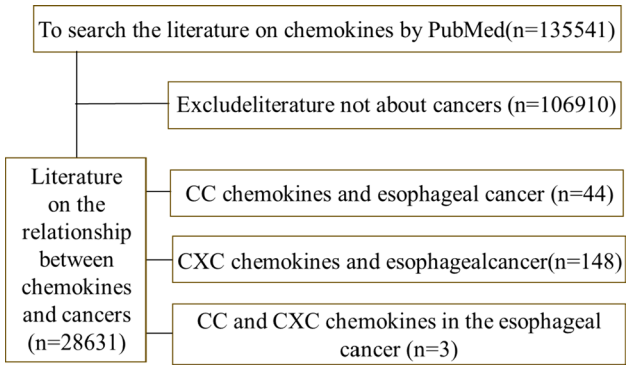


Fig. 3 Diagram of CC and CXC chemokines in the esophageal cancer search

Chemokines and the Invasion and Migration in ESCA

CCL1, CCL3, CCL8, CCL21, CCL25, CXCL5, CXCL8, CXCL12, and CXCL14 are associated with the invasion and migration of ESCA. CCL1 is overexpressed in TAMs, CCR8 (CCL1 receptor) is expressed on the surface of ESCC cells, and the interaction between stromal CCL1 and CCR8 promotes ESCC progression of migration and invasion through Akt/PRAS40/mTOR pathway, thus providing a new therapeutic target [25]. CCL3, derived from TAMs and esophageal cancer cells, promotes cell migration and invasion by binding to CCR5 and phosphorylated Akt and ERK, thus promoting the progression of ESCC and poor prognosis [26]. It is CCL8 that can activate the NF-κB signaling pathway, induce the epithelial-mesenchymal transition, and promote the migration and invasion of ESCC cells in vitro [27]. CCL21 can significantly improve the migration ability of ESCC cell line, can induce the formation of pseudopodia, and can significantly enhance the motility of esophageal carcinoma cells [28]. Among the differentially expressed genes, CCL25 is highly associated with PCSK9, and thus, it is speculated that PCSK9 may promote the migration and invasion of ESCC by affecting the secretion of CCL25 [29]. The results showed that the enhanced expression of miR-145-3p inhibited the proliferation, migration, invasion, and stimulated apoptosis of ESCA by inhibiting CXCL5 [30]. CXCL8 up-regulated in the microenvironment may contribute to ESCC migration and invasion by the phosphorylation of Akt and ERK1/2 [31]. Developmentally down-regulated 9 maintained the stemness of ESCC cells and regulated CXCL8 through the ERK pathway to recruit myeloid-derived suppressor cells into the tumor [32]. Maelstrom could up-regulate CXCL8 through Akt1/RelA to direct myeloid-derived suppressor cells homing into ESCC [33]. Anti-CXCL8 autoantibody had good diagnostic value and may become a candidate

Table 1 The CC and CXC chemokines play a role in the ESCA

Function in ESCA	Chemokines
Chemokines and invasion and migration	CCL1, CCL3, CCL8, CCL21, CCL25, CXCL5, CXCL8, CXCL12, CXCL14
Chemokines and survival	CCL4, CCL5, CCL11, CCL15, CCL18, CCL20, CCL22, CCL23, CCL25, CCL26, CCL28, CXCL1, CXCL5, CXCL6, CXCL10, CXCL11,CXCL12
Chemokines and angiogenesis	CXCL10
Chemokines and metastasis	CCL21, CXCL6, CXCL12
Chemokines and immune	CCL2, CCL17, CCL19, CCL20, CCL24, CXCL2, CXCL3, CXCL9, CXCL10, CXCL11, CXCL13, CXCL16
Chemokines and radioresistance	CXCL1

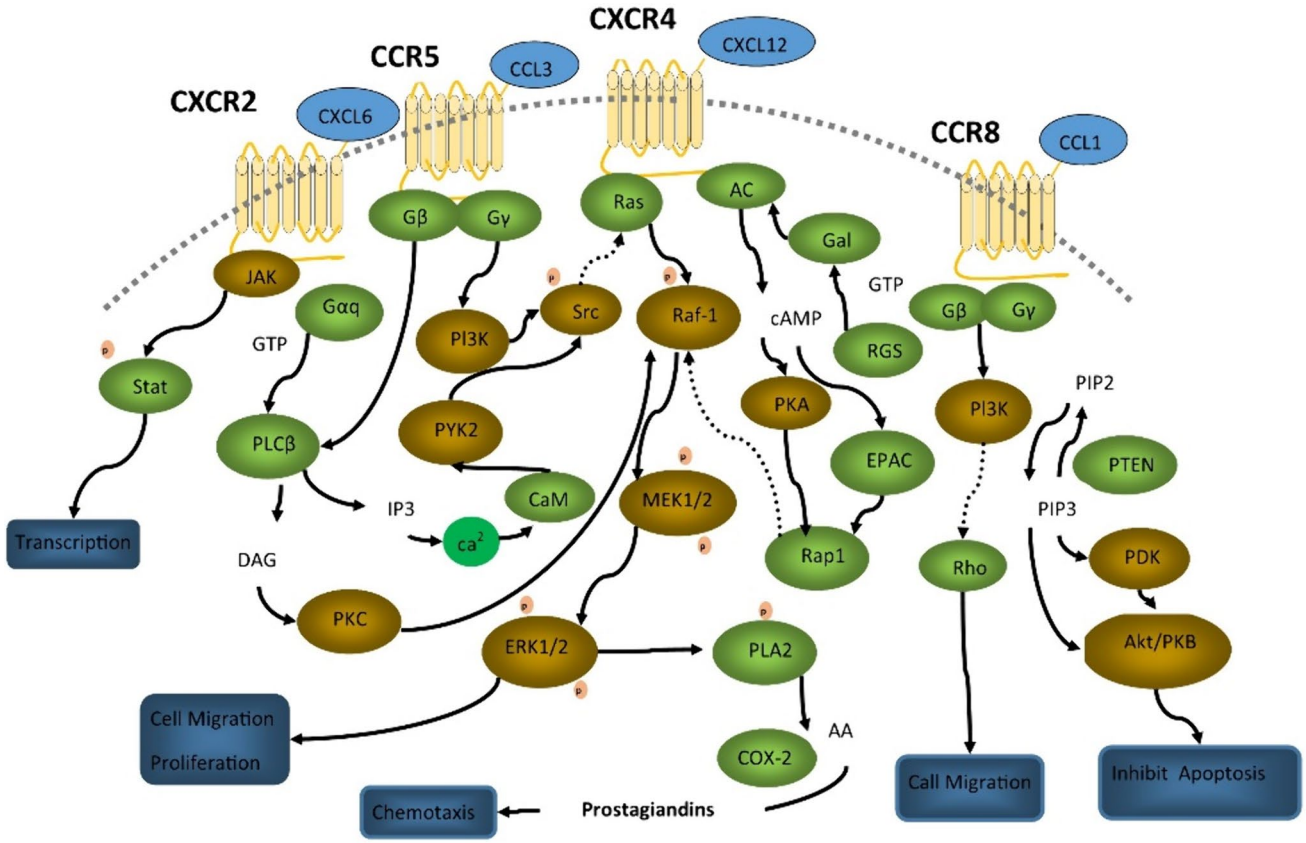


Fig. 4 Schematic model of the CCL1/CCR8, CCL3/CCR5, CXCL6/CXCR2, and CXCL12/ CXCR4 axes in esophageal squamous cell carcinoma. CCL1 binds to the receptor CCR8 on cancer cells, and CCL1/CCR8 interaction promotes cancer cell migration and inhibits cancer cell apoptosis by activating Akt signaling pathway. CCL3 promotes tumor progression and poor prognosis in esophageal squamous cell carcinoma patients by binding to CCR5 on esophageal squamous cell carcinoma cells, activating the PI3K/AKT and MEK/ERK pathways, and promoting cell proliferation, migration, and angiogenesis. CXCL6 enhances transcription by activating the STAT3 pathway and enhances the growth and metastasis of esophageal squamous cell carcinoma cells. CXCL12/CXCR4 is one of the main mechanisms that esophageal squamous cell carcinoma cells transfer through ERK1/2 signaling pathway

biomarker for ESCC [34]. It suggested the potential usefulness of CXCL8 in the diagnosis and progression of ESCA [35, 36]. The decrease of CXCL12 contributes to the inhibition of proliferation and invasion of esophageal cancer cells in vitro [37]. Growth inhibitor 5 inhibits ESCC cells migration and invasion by down-regulating IL-6/CXCL12 signaling pathway [38]. Targeting CXCL12/CXCR4 is also summarized to provide a reference for the clinical diagnosis and treatment of ESCC [39]. Ectopic expression of CXCL14 inhibited the proliferation, invasion, tumor growth, and lung metastasis of ESCC cells

[40]. FAM129A aggravates the progression of ESCA by negatively regulating the CXCL14 level [41].

Chemokines and the Survival in ESCA

The chemokines associated with the survival of ESCA are CCL4, CCL5, CCL11, CCL15, CCL18, CCL20, CCL22, CCL23, CCL25, CCL26, CCL28, CXCL1, CXCL5, CXCL6, CXCL10, CXCL11, and CXCL12. The study showed that CCL4 and CCL20 recruit functionally different T lymphocyte subsets and high levels of CCL4 in the lesions of ESCC patients predicting prolonged survival [42]. High CCL5 expression is associated with poor prognosis in low-grade esophageal cancer, and the therapeutic potential of targeting the CCL5-CCR5 axis in ESCC [43]. CCL5 served as the key chemokine to recruit CD8(+) T lymphocytes into ESCC tissue and may play a role in patient survival [44]. Autocrine CCL5 signaling may promote the progress of ESCC, and targeting CCL5/CCR5 axis may be a potential treatment strategy for ESCC [45]. CCL11 and CXCL10 in tumor tissues of ESCA patients after treatment are related to prognosis, and low levels indicate a good prognosis [46]. CCL15/MIP1D were associated with ESCA [47]. Overexpression of CCL18 was associated with a worse survival in patients with ESCC, and CCL18-induced hox transcript antisense intergenic RNA upregulation promotes malignant progression through the miR-130a-5p-ZEB1 axis [48]. Fusobacterium nucleatum might also contribute to aggressive tumor behavior through activation of CCL20 and be associated with shorter survival in ESCA [49]. CCL20 had been found to be overactivated in EAC tissue infected with the fusobacterium nucleatum [50]. High CCL22 expression was associated with poor patient survival, L1 cell adhesion molecule (L1CAM) promoted CCL22 expression by activating the PI3K/AKT/NF-κB signaling pathway, and CCL22 promoted the recruitment of Treg to ESCA sites, and Tregs secreted TGF-β and then Smad2/3 can promote the expression of L1CAM with a positive feedback mode [51]. Seven biomarkers (CXCL6, CCL23, CXCL5, TGFA, CXCL1, OSM, and CCL4) were inversely associated with HRs 0.57–0.72 in ESCC [52]. ESCA associated with CCL25 as a biomarker for predicting outcome in upper gastrointestinal tumors [53]. Elevated CCL26 was associated with improved overall survival in EAC [54]. The expression levels of CCL28 in the serum of early ESCC were significantly up-regulated [55], and CCL28 is a potential predictor of treatment response in EAC [56]. Histone deacetylase 2 promotes the development of ESCC by down-regulating microRNA-503-5p and promoting CXCL10 [57]. CXCL11/I-TAC was associated with ESCA for prevention and treatment [47]. ESCA patients with high CXCL12 tended to have worse overall and disease-free survival [58].

Chemokines and the Angiogenesis in ESCA

CXCL10 is associated with the survival of ESCA. Poly (A)-binding protein cytoplasmic 1 regulates the stability of interferon alpha (IFN-α) inducible protein 27 mRNA by interacting with eIF4G and promotes angiogenesis through the exosome miR-21-5p/CXCL10, playing a key role in the malignant progression of ESCC [59].

Chemokines and Metastasis in ESCA

CCL21, CXCL6, and CXCL12 are associated with the metastasis of ESCA. The CCL21/CCR7 receptor ligand system may play a role in the lymph node metastasis of ESCC by up-regulating MUC1 [28]. CXCL6 can enhance the growth and metastases of ESCC cells both in vivo and in vitro and promote epithelial–mesenchymal transition by up-regulating PD-L1 expression through activation of the STAT3 pathway [60]. Autocrine CXCL12/CXCR4 was one of the main mechanisms of metastasis of ESCA stem cells through ERK1/2 signaling pathway and may become a therapeutic target for ESCA patients [61].

Chemokines and Immune in ESCA

The chemokines found to be immune related to ESCA are CCL2, CCL17, CCL19, CCL20, CCL24, CXCL2, CXCL3, CXCL9, CXCL10, CXCL11, CXCL13, and CXCL16. CCL2/CCR2 axis recruits tumor-associated macrophages to induce immune evasion through PD-1 signaling in esophageal carcinogenesis [62]. Since CCL2 expressed by tumor cells recruits myeloid cells (monocytes, TAMs, and myeloid-derived suppressor cells) to TME, inhibition of the CCL2-CCR2 axis has been shown to enhance the immune response to tumors [63]. Levels of the chemokines CCL17 in tumors were significantly higher than in tumor-free tissues, and the CCL17/CCR4 axis might play an important role in Th17 cell infiltration of ESCC [64]. CCL17 and CCL22 within the tumor were associated with an increased population of Foxp3(+) Tregs in ESCC [65]. Responders were associated with lower baseline levels of CCL19 of toripalimab plus paclitaxel and carboplatin as neoadjuvant therapy in locally advanced resectable ESCC [66]. Study had shown that CCL20 can chemically regulate T cells (Tregs) through CCR6 (CCL20 receptor), thereby promoting the proliferation of ESCA [67]. The results showed that CCL20 induced by hypomethylation promoted the progression

of ESCA and immune disorders [68]. CCL24 might be promising therapeutic targets for EAC [69]. Interleukin (IL)-17 stimulated ESCC cells to release more of the CXCL2 and CXCL3, which are involved in neutrophil migration [70]. The CXCR3 ligands Mig/CXCL9, IP-10/CXCL10, and I-TAC/CXCL11 are angiostatic and attract anti-tumoral T lymphocytes and may therefore mediate ESCA growth retardation and regression [71]. CXCL10 has been indicated to have anti-tumor effects in ESCC [18]. The high expression of CXCL10 is a clinically useful marker for patients with advanced thoracic ESCC who need adjuvant chemotherapy after surgery [72]. CXCL10, as a key chemokine to recruit CD8 (+) T lymphocytes into ESCC tissues, may play a role in the survival of patients [44]. IL-17A can promote ESCC tumor cells to produce more chemokine CXCL13, which was related to the migration of B cells [73]. CXCL16 induced the expression of CD38 in myeloid-derived suppressor cells in vitro in ESCA [74].

Chemokines and Radioresistance in ESCA

Chemokine CXCL1 is associated with radioresistance in ESCA. Recent studies have shown that cancer-associated fibroblast (CAF)-derived type 1 collagen (Col1) and tumor cell-derived CXCL1 are enriched in unresponsive patient-derived xenografts. Col1 not only promotes radiation tolerance of tumor cells by enhancing DNA repair ability but also induces CXCL1 secretion of tumor cells. In addition, CXCL1 further activated CAFs through the CXCR2-STAT3 pathway, establishing a positive feedback loop. Direct interference with tumor cell-derived CXCL1 or inhibition of CXCL1-CXCR2 pathway can effectively restore radiosensitivity in vivo [75]. Previous studies have shown that CAF-secreted CXCL1 inhibited reactive oxygen species (ROS)-clearing enzyme superoxide dismutase 1, leading to increasing ROS accumulation after radiation and enhancing DNA damage repair mediated by radiation resistance. CXCL1 secreted by CAFs also mediates radiation resistance by activating the crosstalk of CAFs and ESCC cells through the MEK/ERK pathway to induce CXCL1 expression signal cycle in autocrine/paracrine, which further enhances tumor radiationresistance [76].

Summary

ESCA is a highly aggressive tumor with a low survival rate. Chemokines have autocrine, paracrine, and hormone effects and are associated with tumor growth and distant organ metastasis, among others. Understanding their mechanisms of action may provide new therapeutic approaches for a wide range of human malignancies. The role of different chemokines and their receptors in the development of ESCA has been studied and they play a key role in the angiogenesis, growth, aggressiveness, and eventual metastasis of ESCA. It has been found that chemokines regulated the behavior of ESCA mainly by chemically attracting pre-tumor or anti-tumor leukocytes and forming new blood vessels. Wider studies are needed to unravel the complex chemokine network in the development of ESCA to provide more insights, which may enhance therapeutic applications for cancer patients. Further studies are needed to clarify the role of chemokines in ESCA, especially unstudied chemokines.

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Author's contribution HCG made major contributions to the data analysis and manuscript writing. LQ and ZST collected the data and participated in the manuscript writing. LT and TYY collected the data. PTY and CJ participated in the manuscript writing. LXM had the main primary idea and participated in the manuscript writing and revision. All authors discussed, carefully read, and approved the final manuscript.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

References

1. Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 Cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–249.
2. Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 global cancer statistics? *Cancer Commun (Lond).* 2019;39:22.

3. Safran HP, Winter K, Ilson DH et al. Trastuzumab with trimodality treatment for oesophageal adenocarcinoma with HER2 overexpression (NRG Oncology/RTOG 1010): a multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2022;23:259–269.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin.* 2020;70:7–30.
5. Guan X, Liu C, Zhou T, et al. Survival and prognostic factors of patients with esophageal fistula in advanced esophageal squamous cell carcinoma. *Biosci Rep.* 2020;40:379.
6. Pech O, May A, Manner H et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology.* 2014;146:652-660 e651.
7. Sauder DN, Mounessa NL, Katz SI, Dinarello CA, Gallin JI. Chemotactic cytokines: the role of leukocytic pyrogen and epidermal cell thymocyte-activating factor in neutrophil chemotaxis. *J Immunol.* 1984;132:828–832.
8. Chow MT, Luster AD. Chemokines in cancer. *Cancer Immunol Res.* 2014;2:1125–1131.
9. Song X, Greiner-Tollersrud OK, Zhou H. Oral microbiota variation: a risk factor for development and poor prognosis of esophageal cancer. *Dig Dis Sci.* 2022;67:3543–3556.https://doi.org/10.1007/s10620-021-07245-2.
10. Stone MJ, Hayward JA, Huang C et al. Mechanisms of regulation of the chemokine-receptor network. *Int J Mol Sci.* 2017;18:342.
11. Keeley EC, Mehrad B, Strieter RM. CXC chemokines in cancer angiogenesis and metastases. *Adv Cancer Res.* 2010;106:91–111.
12. Thomas JK, Mir H, Kapur N, Bae S, Singh S. CC chemokines are differentially expressed in breast cancer and are associated with disparity in overall survival. *Sci Rep.* 2019;9:4014.
13. Vicari AP, Caux C. Chemokines in cancer. *Cytokine Growth Factor Rev.* 2002;13:143–154.
14. Liubomirski Y, Lerrer S, Meshel T et al. Tumor-stroma-inflammation networks promote pro-metastatic chemokines and aggressiveness characteristics in triple-negative breast cancer. *Front Immunol.* 2019;10:757.
15. Jia SN, Han YB, Yang R, Yang ZC. Chemokines in colon cancer progression. *Semin Cancer Biol.* 2022;86(Pt 3):400–407.
16. Bose S, Saha P, Chatterjee B, Srivastava AK. Chemokines driven ovarian cancer progression, metastasis and chemoresistance: potential pharmacological targets for cancer therapy. *Semin Cancer Biol.* 2022;86(Pt 2):568–579.
17. Khan P, Fatima M, Khan MA, Batra SK, Nasser MW. Emerging role of chemokines in small cell lung cancer: road signs for metastasis, heterogeneity, and immune response. *Semin Cancer Biol.* 2022;87:117–126.
18. Goto M, Liu M. Chemokines and their receptors as biomarkers in esophageal cancer. *Esophagus.* 2020;17:113–121.
19. Saavedra-Garcia P, Fan LY, Lam EW. Multifaceted link between metabolism and cancer. *Mol Cell Endocrinol.* 2018;462(Pt B):65–66.
20. Sethi G, Shanmugam MK, Ramachandran L, Kumar AP, Tergaonkar V. Multifaceted link between cancer and inflammation. *Biosci Rep.* 2012;32:1–15.
21. Sgambato A, Cittadini A. Inflammation and cancer: a multifaceted link. *Eur Rev Med Pharmacol Sci.* 2010;14:263–268.
22. Shrivastava MS, Hussain Z, Giricz O et al. Targeting chemokine pathways in esophageal adenocarcinoma. *Cell Cycle.* 2014;13:3320–3327.
23. Xu J, Li JQ, Chen QL et al. Advances in research on the effects and mechanisms of chemokines and their receptors in cancer. *Front Pharmacol.* 2022;13:920779.
24. Liu H, Yang Z, Lu W et al. Chemokines and chemokine receptors: a new strategy for breast cancer therapy. *Cancer Med.* 2020;9:3786–3799.
25. Fujikawa M, Koma YI, Hosono M et al. Chemokine (C-C Motif) ligand 1 derived from tumor-associated macrophages contributes to esophageal squamous cell carcinoma progression via CCR8-mediated Akt/proline-rich Akt substrate of 40 kDa/mammalian target of rapamycin pathway. *Am J Pathol.* 2021;191:686–703.
26. Kodama T, Koma YI, Arai N et al. CCL3-CCR5 axis contributes to progression of esophageal squamous cell carcinoma by promoting cell migration and invasion via Akt and ERK pathways. *Lab Investig.* 2020;100:1140–1157.
27. Zhou J, Zheng S, Liu T et al. MCP2 activates NF-kappaB signaling pathway promoting the migration and invasion of ESCC cells. *Cell Biol Int.* 2018;42:365–372.
28. Ding Y, Shimada Y, Maeda M et al. Association of CC chemokine receptor 7 with lymph node metastasis of esophageal squamous cell carcinoma. *Clin Cancer Res.* 2003;9:3406–3412.
29. Wang H, Guo Q, Wang M, Liu C, Tian Z. PCSK9 promotes tumor cell proliferation and migration by facilitating CCL25 secretion in esophageal squamous cell carcinoma. *Oncol Lett.* 2023;26:500.
30. Chen G, Teng Z, Zhu Z, Li X. miR-145-3p hampers the malignant progression of esophageal carcinoma via CXCL5 downregulation. *Anal Cell Pathol (Amst).* 2022;2022:5418356.
31. Hosono M, Koma YI, Takase N et al. CXCL8 derived from tumor-associated macrophages and esophageal squamous cell carcinomas contributes to tumor progression by promoting migration and invasion of cancer cells. *Oncotarget.* 2017;8:106071–106088.
32. Yue D, Liu S, Zhang T et al. NEDD9 promotes cancer stemness by recruiting myeloid-derived suppressor cells via CXCL8 in esophageal squamous cell carcinoma. *Cancer Biol Med.* 2021;18:705–720.
33. Li P, Chen X, Qin G et al. Maelstrom directs myeloid-derived suppressor cells to promote esophageal squamous cell carcinoma progression via activation of the Akt1/RelA/IL8 signaling pathway. *Cancer Immunol Res.* 2018;6:1246–1259.
34. Chen H, Sun G, Han Z, et al. Anti-CXCL8 autoantibody: a potential diagnostic biomarker for esophageal squamous cell carcinoma. *Medicina (Kaunas).* 2022;58:1480.
35. Lukaszewicz-Zajac M, Paczek S, Muszynski P, Kozlowski M, Mroczko B. Comparison between clinical significance of serum CXCL-8 and classical tumor markers in oesophageal cancer (OC) patients. *Clin Exp Med.* 2019;19:191–199.
36. Ogura M, Takeuchi H, Kawakubo H et al. Clinical significance of CXCL-8/CXCR-2 network in esophageal squamous cell carcinoma. *Surgery.* 2013;154:512–520.
37. Li J, Gu X, Wan G et al. Rocuronium bromide suppresses esophageal cancer via blocking the secretion of C-X-C motif chemokine ligand 12 from cancer associated fibroblasts. *J Transl Med.* 2023;21:248.
38. Wang Y, Tan J, Li J, Chen H, Wang W. ING5 inhibits migration and invasion of esophageal cancer cells by downregulating the IL-6/CXCL12 signaling pathway. *Technol Cancer Res Treat.* 2021;20:15330338211039940.
39. Wu X, Zhang H, Sui Z, Wang Y, Yu Z. The biological role of the CXCL12/CXCR4 axis in esophageal squamous cell carcinoma. *Cancer Biol Med.* 2021;18:401–410.
40. Guo J, Chang C, Yang LY et al. Dysregulation of CXCL14 promotes malignant phenotypes of esophageal squamous carcinoma cells via regulating SRC and EGFR signaling. *Biochem Biophys Res Commun.* 2022;609:75–83.
41. Cao JW, Cui WF, Zhu HJ. The negative feedback loop FAM129A/CXCL14 aggravates the progression of esophageal cancer. *Eur Rev Med Pharmacol Sci.* 2022;26:4220–4227.
42. Liu JY, Li F, Wang LP et al. CTL- vs Treg lymphocyte-attracting chemokines, CCL4 and CCL20, are strong reciprocal predictive markers for survival of patients with oesophageal squamous cell carcinoma. *Br J Cancer.* 2015;113:747–755.

43. Dunbar KJ, Karakasheva TA, Tang Q et al. Tumor-derived CCL5 recruits cancer-associated fibroblasts and promotes tumor cell proliferation in esophageal squamous cell carcinoma. *Mol Cancer Res.* 2023;21:741–752.
44. Liu J, Li F, Ping Y et al. Local production of the chemokines CCL5 and CXCL10 attracts CD8+ T lymphocytes into esophageal squamous cell carcinoma. *Oncotarget.* 2015;6:24978–24989.
45. Wu YC, Shen YC, Chang JW, Hsieh JJ, Chu Y, Wang CH. Autocrine CCL5 promotes tumor progression in esophageal squamous cell carcinoma in vitro. *Cytokine.* 2018;110:94–103.
46. Blank S, Nienhuser H, Dreikhausen L et al. Inflammatory cytokines are associated with response and prognosis in patients with esophageal cancer. *Oncotarget.* 2017;8:47518–47532.
47. Camargo MC, Song M, Shimazu T et al. Circulating inflammation markers and risk of gastric and esophageal cancers: a case-cohort study within the Japan public health center-based prospective study. *Cancer Epidemiol Biomark Prev.* 2019;28:829–832.
48. Wang W, Wu D, He X et al. CCL18-induced HOTAIR upregulation promotes malignant progression in esophageal squamous cell carcinoma through the miR-130a-5p-ZEB1 axis. *Cancer Lett.* 2019;460:18–28.
49. Yamamura K, Baba Y, Nakagawa S et al. Human microbiome fusobacterium nucleatum in esophageal cancer tissue is associated with prognosis. *Clin Cancer Res.* 2016;22:5574–5581.
50. Maity AK, Stone TC, Ward V et al. Novel epigenetic network biomarkers for early detection of esophageal cancer. *Clin Epigenet.* 2022;14:23.
51. Zhao X, Liu S, Chen X et al. L1CAM overexpression promotes tumor progression through recruitment of regulatory T cells in esophageal carcinoma. *Cancer Biol Med.* 2021;18:547–561.
52. Aversa J, Song M, Shimazu T et al. Prediagnostic circulating inflammation biomarkers and esophageal squamous cell carcinoma: a case-cohort study in Japan. *Int J Cancer.* 2020;147:686–691.
53. Zhu C, Xia Q, Gu B et al. Esophageal cancer associated immune genes as biomarkers for predicting outcome in upper gastrointestinal tumors. *Front Genet.* 2021;12:707299.
54. Donlon NE, Sheppard A, Davern M, et al. Linking circulating serum proteins with clinical outcomes in esophageal adenocarcinoma-an emerging role for chemokines. *Cancers (Basel).* 2020;12:3356.
55. Tong Q, Wang XL, Li SB et al. Combined detection of IL-6 and IL-8 is beneficial to the diagnosis of early stage esophageal squamous cell cancer: a preliminary study based on the screening of serum markers using protein chips. *Onco Targets Ther.* 2018;11:5777–5787.
56. McLaren PJ, Barnes AP, Terrell WZ et al. Specific gene expression profiles are associated with a pathologic complete response to neoadjuvant therapy in esophageal adenocarcinoma. *Am J Surg.* 2017;213:915–920.
57. Li J, Jin C, Sun L, Wang B, Hua P, Zhang Y. HDAC2 enhances esophageal squamous cell carcinoma development through downregulating microRNA-503-5p and promoting CXCL10. *Clin Epigenet.* 2021;13:96.
58. Goto M, Shibahara Y, Baciu C et al. Prognostic impact of CXCR7 and CXCL12 expression in patients with esophageal adenocarcinoma. *Ann Surg Oncol.* 2021;28:4943–4951.
59. Zhang Y, Chen C, Liu Z et al. PABPC1-induced stabilization of IFI27 mRNA promotes angiogenesis and malignant progression in esophageal squamous cell carcinoma through exosomal miRNA-21-5p. *J Exp Clin Cancer Res.* 2022;41:111.
60. Zheng S, Shen T, Liu Q et al. CXCL6 fuels the growth and metastases of esophageal squamous cell carcinoma cells both in vitro and in vivo through upregulation of PD-L1 via activation of STAT3 pathway. *J Cell Physiol.* 2021;236:5373–5386.
61. Wang X, Cao Y, Zhang S et al. Stem cell autocrine CXCL12/CXCR4 stimulates invasion and metastasis of esophageal cancer. *Oncotarget.* 2017;8:36149–36160.
62. Yang H, Zhang Q, Xu M et al. CCL2-CCR2 axis recruits tumor associated macrophages to induce immune evasion through PD-1 signaling in esophageal carcinogenesis. *Mol Cancer.* 2020;19:41.
63. Ko KP, Huang Y, Zhang S et al. Key genetic determinants driving esophageal squamous cell carcinoma initiation and immune evasion. *Gastroenterology.* 2023;165:613-628 e620.
64. Chen D, Jiang R, Mao C et al. Chemokine/chemokine receptor interactions contribute to the accumulation of Th17 cells in patients with esophageal squamous cell carcinoma. *Hum Immunol.* 2012;73:1068–1072.
65. Maruyama T, Kono K, Izawa S et al. CCL17 and CCL22 chemokines within tumor microenvironment are related to infiltration of regulatory T cells in esophageal squamous cell carcinoma. *Dis Esophagus.* 2010;23:422–429.
66. He W, Leng X, Mao T et al. toripalimab plus paclitaxel and carboplatin as neoadjuvant therapy in locally advanced resectable esophageal squamous cell carcinoma. *Oncologist.* 2022;27:e18–e28.
67. Lian J, Liu S, Yue Y et al. Eomes promotes esophageal carcinoma progression by recruiting Treg cells through the CCL20-CCR6 pathway. *Cancer Sci.* 2021;112:144–154.
68. Nan H, Zhou L, Liang W et al. Epigenetically associated CCL20 upregulation correlates with esophageal cancer progression and immune disorder. *Pathol Res Pract.* 2021;228:153683.
69. Zhang X, Yang L, Kong M, Ma J, Wei Y. Development of a prognostic signature of patients with esophagus adenocarcinoma by using immune-related genes. *BMC Bioinform.* 2021;22:536.
70. Chen CL, Wang Y, Huang CY et al. IL-17 induces antitumor immunity by promoting beneficial neutrophil recruitment and activation in esophageal squamous cell carcinoma. *Oncoimmunology.* 2017;7:e1373234.
71. Verbeke H, Geboes K, Van Damme J, Struyf S. The role of CXC chemokines in the transition of chronic inflammation to esophageal and gastric cancer. *Biochim Biophys Acta.* 2012;1825:117–129.
72. Sato Y, Motoyama S, Nanjo H et al. CXCL10 expression status is prognostic in patients with advanced thoracic esophageal squamous cell carcinoma. *Ann Surg Oncol.* 2016;23:936–942.
73. Lu L, Weng C, Mao H et al. IL-17A promotes migration and tumor killing capability of B cells in esophageal squamous cell carcinoma. *Oncotarget.* 2016;7:21853–21864.
74. Karakasheva TA, Waldron TJ, Eruslanov E et al. CD38-expressing myeloid-derived suppressor cells promote tumor growth in a murine model of esophageal cancer. *Cancer Res.* 2015;75:4074–4085.
75. Yang X, Chen X, Zhang S et al. Collagen 1-mediated CXCL1 secretion in tumor cells activates fibroblasts to promote radioresistance of esophageal cancer. *Cell Rep.* 2023;42:113270.
76. Zhang H, Yue J, Jiang Z et al. CAF-secreted CXCL1 conferred radioresistance by regulating DNA damage response in a ROS-dependent manner in esophageal squamous cell carcinoma. *Cell Death Dis.* 2017;8:e2790.