



Chemokines and their receptors as biomarkers in esophageal cancer

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Abstract

Esophageal cancer (EC) is one of the most lethal malignancies of the digestive tract and remains to be improved poor prognosis. Two histological subtypes, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), are major characteristics of EC. Deep understanding about both subtypes is essential to overcome EC. Here, we focus on chemokines and their receptors as biomarkers and their current applications for the prognosis in EC. We reviewed relevant articles identified using PubMed database for the chemokines and their receptors in EC analyzed by immunohistochemistry. The primary objective is to summarize evidences for them as prognostic biomarkers in EC. A total of twenty-one articles were reviewed after exclusion. Most studies have been done in ESCC, and less in EAC. CXCL12 and its receptor CXCR4 have been shown in both subtypes as biomarkers. CXCR7, CXCL8 and its receptor CXCR2, and CCL21 and its receptor CCR7 have been examined in ESCC. Although it was a small number of reports, CXCL10, CCL4, and CCL5 have been indicated to have anti-tumor effects in ESCC. Chemokines and their receptors have the potential to be the biomarkers in EC. Comparative studies between ESCC and EAC will reveal the similarity and difference in these two subtypes of EC. These studies may indicate whether these molecules play important roles in both subtypes or are unique to one or another.

Keywords Esophageal cancer · Esophageal squamous cell carcinoma · Esophageal adenocarcinoma · Chemokine · Biomarker

Introduction

Esophageal cancer

Esophageal cancer (EC) is one of the most lethal malignancies of the digestive tract, the sixth most common cause of cancer-related deaths worldwide [1]. Despite developed surgical techniques combined with various treatment

modalities, the overall 5-year survival rate of EC remains at 16.9% [2]. More than 30% of all patients are diagnosed at an advanced stage, which also makes treatment more difficult [2]. Improvement of its diagnosis and prognosis is urgent, and the need for identification of diagnostic and prognostic biomarkers and new therapeutic targets and strategies are critical. According to the National Institutes of Health of the United States of America, biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [3]. In cancer research, biomarkers are introduced in clinical practice and play an important role.

There are two main histological subtypes of EC, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Worldwide, ESCC is the most common subtype of EC, representing 87% of all cases [4]. ESCC are most common in Central Asia and South-Eastern Africa, with 79% of the total global ESCC cases together forming the so-called “esophageal cancer belt” [5]. The highest burden of EAC is found in Northern and Western Europe, Northern America, and Oceania, with 46% of the total global

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EAC cases [5]. Recently, the incidence rate of ESCC has fallen substantially in many countries, due to changes in diet, reduced tobacco, and alcohol use. In contrast, the incidence rate of EAC has increased remarkably over the past 2 decades and has replaced ESCC as the dominant phenotype in western countries [6].

Regarding the origin, ESCC mostly develops from the squamous epithelial cells that make up the inner lining in the upper two-thirds of the esophagus. EAC typically develops in the lower third of the esophagus and is originated predominantly from Barrett mucosa [7]. High-grade dysplasia is the precursor for both types, while the development of EAC can additionally be characterized by a progression from Barrett's metaplasia to dysplasia and ultimately invasive carcinoma. Regarding the cause of disease, there are similar and different factors between ESCC and EAC. For example, old age, male sex, tobacco smoking, and low intake of fruit and vegetables are the same risk factors for both subtypes, but poverty and consumption of alcohol are considered peculiar risk for ESCC [8]. Furthermore, Barrett's esophagus, gastroesophageal reflux, obesity, and white ethnicity are peculiar risk factor for EAC [7].

Both epidemiologic and functional studies have implicated chronic inflammation in the development of many human cancers [9]. Cytokines, chemokines, and inflammatory enzymes are involved in the process of tumorigenesis [10]. During this process, tumor cells can produce cytokines to enhance their growth and to counteract the host immune response [11]. Several studies demonstrate that expression of inflammatory genes is associated with EC progression and prognosis [12]. Most of these studies, however, examined relatively few genes and focused on patients with ESCC, with far less published information on EAC. Recently, chemokines and their receptors have been identified as biomarkers in EC.

Chemokines and their receptors

Chemokines, in particular chemotactic cytokines, were first described in 1987 as factors that induce neutrophil migration. It has been suggested that chemokines and their receptors play crucial roles in tumor growth, angiogenesis, and metastasis [13, 14]. Chemokines are small molecular weight proteins of 8–10 kDa, classified into four groups (CXC, CC, C, and CX3C) based on the position of the first two *N*-terminal cysteine residues (Supplemental Fig. 1). The chemokine receptors are seven transmembrane receptors coupled to G proteins. There are about 50 chemokines and 20 receptors. CXC and CC chemokines account for majority of them and CXC chemokines play the most extensive role in angiogenesis. Some CXC chemokines have an ELR (Glu-Leu-Arg) motif prior to first cysteine residue. Typically, ELR⁺ CXC chemokines act to stimulate endothelial

cell migration, proliferation, and promote angiogenesis. Conversely, ELR⁻ CXC chemokines inhibit these mechanisms and thus act as angiostatic [15]. In addition to this structural difference, certain chemokines have dual effects on tumor progression, promoting or inhibiting effects, which depends on the types of cells migrated to tumor cells or the types of receptors to bind.

Chemokines and their receptors have been shown to play key roles in the initiation or progression of several cancers [16]. Previously, we reported the expression of chemokines and their receptors in ESCC, and that high CXCR4 expression, especially in nuclei, was associated with worse prognosis [17]. The main purpose of this study is to gain knowledge of chemokines and their receptors in EC, which may improve our understanding in tumorigenesis of EC, and identify new biomarkers for EC diagnosis and/or prognosis.

Materials and methods

We performed a computerized search of PubMed database (January 1990–July 2018) using the following term: (esophageal OR oesophageal OR esophagus OR oesophagus OR gastroesophageal) AND (cancer OR carcinoma OR adenocarcinoma OR squamous cell carcinoma) AND (outcome OR prognosis OR survival OR response OR stage OR potential OR marker OR biomarker) AND chemokine. The references cited by retrieved articles were also assessed for relevant. One reviewer (Goto M) obtained the full texts of relevant articles following the search and reviewed all eligible studies and carefully extracted study characteristics. In this study, we focused on immunohistochemistry (IHC) analysis and excluded studies without IHC-based analysis.

A total of 156 articles were identified, of which 135 articles were excluded due to various reasons and 21 articles were reviewed, of which 20 articles reported studies in ESCC, and 3 articles in EAC, and 2 articles studied both ESCC and EAC (Fig. 1) (Supplemental Table 1).

Evaluation criteria of immunohistochemistry

As tumors were usually heterogeneous, evaluation criteria of IHC should be based on the percentage of positive tumor cells and the staining intensity [18]. Classification criteria for positive immunoreactivity were depending on the following four methods, staining intensity, percentage of positive tumor cells, combination intensity and percentage, and scoring system calculated by multiplying intensity and percentage score. In CXC chemokines and their receptors, there seemed no definite standard criteria. On the other hand, studies on CC chemokines and their receptors used same criteria, scoring system calculated by multiplying intensity and percentage [18].

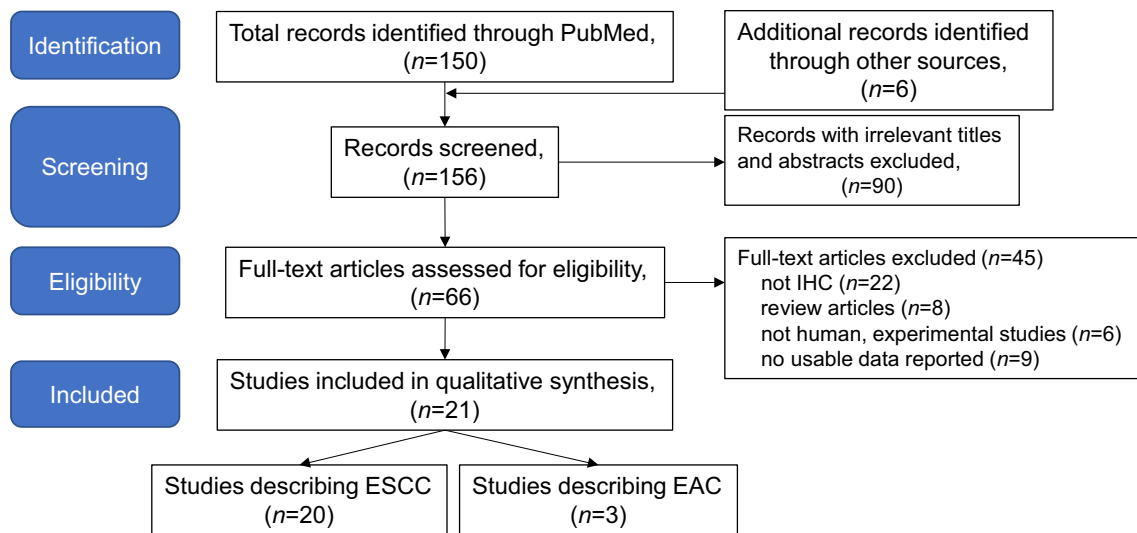


Fig. 1 Literature identification, collection, and selection process for studies related to the role of chemokines and their receptors in esophageal cancer

Results

CXC chemokines and their receptors in esophageal cancer

Expression of CXCL12 and its receptors, CXCR4 and CXCR7, were correlated with poor prognosis

CXC chemokine ligand 12 CXC chemokine ligand 12 (CXCL12), also known as stromal-derived factor 1 (SDF-1), binds to its receptors, CXC chemokine receptor type 4 (CXCR4), and type 7 (CXCR7). CXCL12 is expressed on fibroblasts, endothelial cells, and carcinoma-associated fibroblasts. CXCL12, although an ELR⁻ CXC chemokine, has been involved in angiogenesis (Fig. 2a) and plays an important role in metastatic progression (Fig. 3a). CXCL12 is also expressed at high levels in various organs, including lung, liver, bone marrow, adrenal glands, and lymph nodes, which are frequently involved in tumor metastasis [13, 19].

CXCL12 expression was significantly associated with clinicopathological factors, survivals, and site of recurrence in EC [17, 20–22] (Table 1) (Supplemental Table 2). Carcinoma-associated fibroblasts can be divided into two groups depending on CXCL12 expression, and high CXCL12 expression group contributed to cancer invasion more than that with low expression group in EAC [21]. ESCC patients with positive CXCL12 expression exhibited a higher Ki-67 expression. Positive CXCL12 expression significantly enhanced proliferative ability of ESCC cells in vitro, which was inhibited by selective CXCR4 blockade [22]. CXCL12 expression had no correlation in one article; however, high mRNA expression of CXCL12 was correlated

with recurrence-free survival in ESCC [17]. High CXCL12 expression was associated with advanced tumor stage and high frequency of involvement to lymph nodes, which led poor prognosis in EC.

CXC chemokine receptor type 4 CXCR4 is the predominant receptor for CXCL12 and expressed on myeloid cells, T cells, B cells, mature dendritic cells, and epithelial and endothelial cells [23]. CXCR4 is involved in tumor invasion, angiogenesis, and metastasis in response to CXCL12 (Figs. 2a and 3a). Cancer cells that highly expressed CXCR4 have tendency to migrate toward CXCL12-abundant tissues. Organ-specific metastasis, called homing metastasis, is due to their relationship. CXCL12/CXCR4 interaction can activate phosphatidylinositol 3-kinase (PI3K) and AKT pathway, mitogen-activated protein kinase (MAPK) pathway, especially extracellular signal-regulated kinase 1/2 (ERK1/2) pathway [20, 22, 24, 25]. These pathways are important in the regulation of cell migration, proliferation, and survival.

CXCR4 expression was significantly associated with clinicopathological factors, survivals, and site of recurrence in EC [17, 20, 22, 24–29] (Table 1) (Supplemental Table 2). There was no difference in the intensity patterns of CXCR4 expression between ESCC and EAC [24, 26]. CXCR4 expression in metastatic lymph node was significantly higher than that in primary tumor [25]. CXCR4 expression was observed not only in cytoplasm but also in nuclei of ESCC cells [17, 25, 28, 29]. Positive CXCR4 expression, both in cytoplasm and nuclei in ESCC cells, was correlated with worse survival than the CXCR4 expression in only cytoplasm or negative expression. The prognosis between positive CXCR4 expression in only cytoplasm and

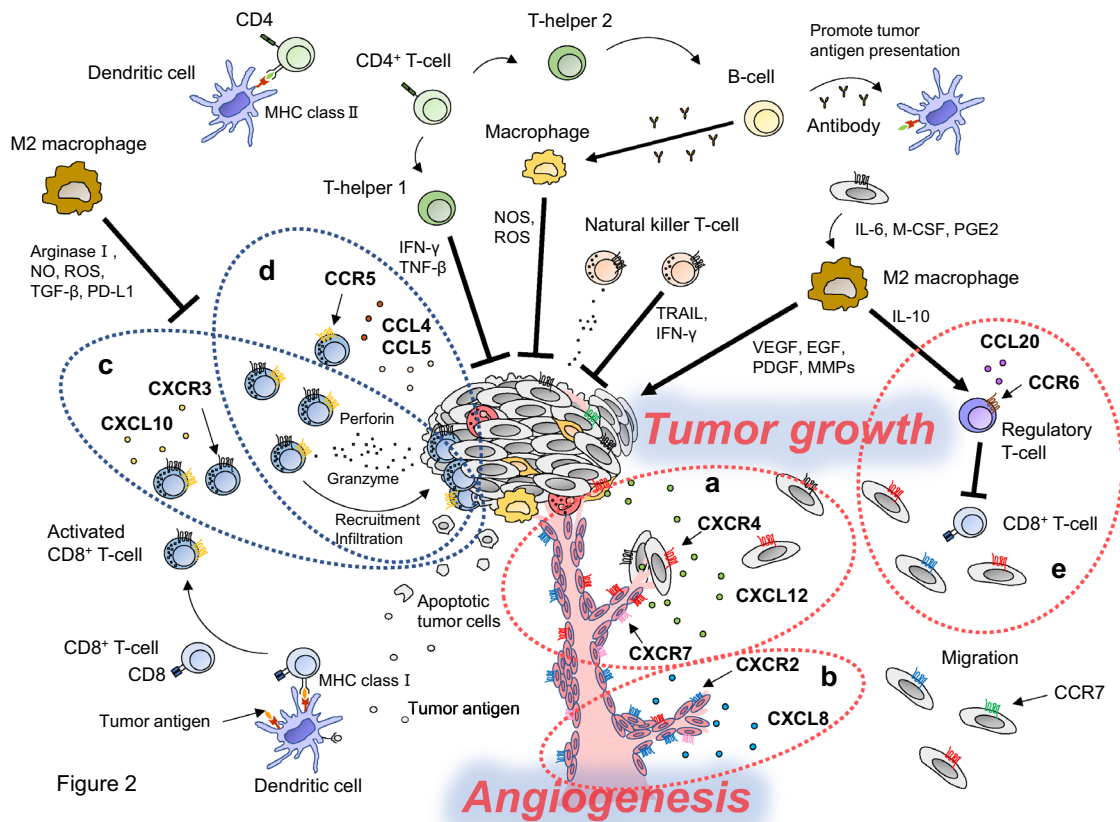


Figure 2

Fig. 2 Potential roles of chemokines and their receptors in tumor growth and angiogenesis. **a** CXCL12 and its receptors, CXCR4 and CXCR7, and **b** CXCL8 and its receptor CXCR2, are involved in angiogenesis, which promotes tumorigenesis. **c** CXCL10 binds to its receptor CXCR3, and **d** CCL4 or CCL5 binds to their receptor, CCR5, respectively, expressed on CD8⁺ T cells, which stimulates recruitment of CD8⁺ T cells to the tumor tissues that leads to inhibition of tumor growth. **e** Regulatory T cells that expressing CCR6 could inhibit CD8⁺ T cell recruitment through binding with CCL20,

and this interaction results in tumor growth. *CD* cluster of differentiation, *CSF* colony-stimulating factor, *EGF* epidermal growth factor, *IFN* interferon, *MHC* major histocompatibility complex, *MMPs* matrix metalloproteinases, *NO* nitric oxide, *NOS* nitric oxide synthase, *PDGF* platelet-derived growth factor, *PG* prostaglandin, *ROS* reactive oxygen species, *TGF* transforming growth factor, *TNF* tumor necrosis factor, *TRAIL* tumor necrosis factor-related apoptosis-inducing ligand, *VEGF* vascular endothelial growth factor

negative expression showed almost same survival curves, which indicated that nuclear CXCR4 expression in tumor cells has malignant potential [17]. Nuclear CXCR4 positivity was recognized in other types of cancers and is often recognized in poorly differentiated adenocarcinoma, which tends to be large and of the infiltrative type, resulting in poor prognosis [30, 31].

Positive CXCR4 expression in ESCC patients, who underwent preoperative chemoradiotherapy followed by radical surgery, was associated with distant recurrence and worse survival; however, it is unclear whether chemoradiotherapy could affect CXCL12-CXCR4 signaling or not, since the status of CXCR4 expression before chemoradiotherapy was not described [27]. CXCR4 expression was positively correlated with matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF). CXCR4 may regulate MMP-9/VEGF expression to promote

hematogenous metastasis [28]. CXCR4 expression was also positively correlated with macrophage migration inhibitory factor (MIF) expression [29]. MIF may bind to its receptor CD74, which can form a complex with CXCR4, to transmit MIF signal to integrins in inflammatory cells, and is involved in cancer progression [29]. CXCR4⁺ cells had stronger migratory ability than CXCR4⁻ cells, and exhibited a significantly higher Ki-67 expression [22, 25]. Positive correlation between CXCR4 expression and clinicopathological features and survivals was identified in tumor cells, but not in tumor-infiltrating lymphocytes [29]. CXCR4⁺ ESCC cells showed high proliferative and migratory ability, and were associated with lymph-node and distant metastasis, and poor prognosis.

CXC chemokine receptor type 7 CXCR7, also known as RDC-1, is a receptor for CXCL12, but also for CXCL11.

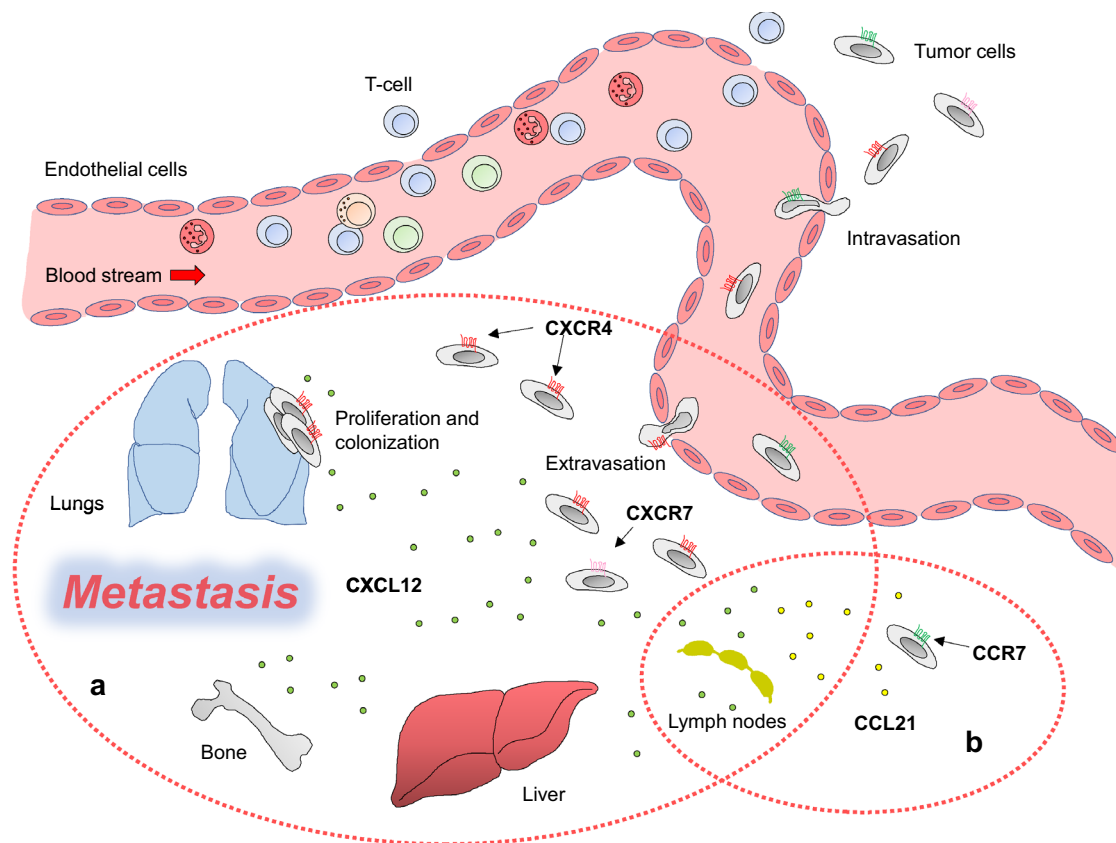


Fig. 3 Potential roles of chemokines and their receptors in metastasis. **a** CXCL12 secreted from specific organs has an effect of attracting tumor cells expressing CXCR4 or CXCR7. This chemoattraction pro-

motes organ-specific, homing metastasis. **b** CCL21/CCR7 axis especially is involved in lymph-node metastasis

CXCR7 is expressed on T cells, B cells, and epithelial and endothelial cells [32]. CXCR7 plays a role in regulating immunity, angiogenesis, stem cell trafficking, and mediating organ-specific metastases of cancer cells (Figs. 2a and 3a). CXCL12/CXCR7 interaction stimulates ERK1/2 pathway, which is involved in cancer cell metastasis and proliferation [33]. Additionally, CXCR7 has several roles as a receptor, such as scavenger of CXCL12, co-receptor for CXCR4, or decoy receptor which interacts with β -arrestin in a ligand-dependent manner [32].

CXCR7 expression was significantly associated with clinicopathological factors and survivals in EC [17, 33–35] (Table 1) (Supplemental Table 2). CXCR7 expression was found in primary tumor lesions and corresponding metastatic lymph nodes and distant lesions in ESCC, but rarely in EAC [34]. Silencing of CXCR7 increased apoptotic rate, and decreased cell viability, chemotaxis, and tumor growth [33]. High CXCR7 expression had high affinity with lymphatic invasion and caused worse prognosis.

Expression of CXCL8 and/or its receptor CXCR2 was correlated with poor prognosis

CXCL8, also known as Interleukin-8 (IL-8), is an ELR⁺ chemokine. CXCL8 binds to CXCR1 (IL-8 receptor A) and CXCR2 (IL-8 receptor B). Both CXCR1 and CXCR2 are expressed on neutrophils, monocytes, basophils, T cells, and endothelial cells [36]. Function of CXCL8 depends on its receptors, increases the proliferation of tumor cells via CXCR1, and promotes angiogenesis via CXCR2. CXCL8 recruits and activates neutrophils and granulocytes to the site of inflammation, and modulates angiogenesis, tumor proliferation, invasion, and migration [37] (Fig. 2b).

High expression of CXCL8 and CXCR2 were correlated with preoperative blood examination values, clinicopathological factors and survivals in ESCC [33, 35, 38, 39] (Table 1) (Supplemental Table 3). Silencing of CXCR2 increased apoptotic rate and cell invasion, and decreased cell viability, chemotaxis, and tumor growth [33]. CXCL8

Table 1 Expression of several CXC/CC chemokines and receptors was correlated with clinicopathological features in esophageal cancer

Chemokines and receptors	Clinicopathological factors		Survivals		Site of recurrence	References
	Patient factor	Tumor factor	Type	Impact		
CXCL12	Gender, age	Tumor depth, lymphatic invasion, LNM, TMN stage	OS, DFS, RFS	Worse	Lymph nodes	[17, 20–22]
CXCR4	Gender	Histological grade, tumor size, tumor depth, lymphatic invasion, venous invasion, LNM, distant metastasis, micrometastasis both in lymph nodes and bone marrow, TMN stage	OS, DSS, CSS, DFS	Worse	Distant organs	[17, 20, 22, 24–29]
CXCR7	None	Histological grade, lymphatic invasion, clinical stage	OS, CSS, PFS	Worse	None	[17, 33–35]
CXCL8	Preoperative blood values ^a	Tumor depth, lymphatic invasion, venous invasion, LNM, TMN stage	DSS, RFS, PFS	Worse	None	[35, 38]
CXCR2	Preoperative blood values ^a	Histological grade, tumor depth, lymphatic invasion, venous invasion, LNM, TMN stage	OS, DSS, RFS	Worse	None	[33, 38, 39]
CCL20	None	Lymphatic invasion, LNM	none	Worse	None	[43]
CCR7	None	Tumor depth, lymphatic invasion, venous invasion, LNM, TMN stage	OS, RFS	Worse	Lymph nodes	[47–49]
CXCL10	None	None	OS, DSS	Better	None	[41, 42]
CCL4	None	None	OS	Better	None	[43]
CCL5	None	Tumor depth	OS	Better	None	[41]

CSS cause-specific survival, DFS disease-free survival, DSS disease-specific survival, LNM lymph-node metastasis, OS overall survival, PFS progression-free survival, RFS recurrence-free survival

^aProinflammatory cytokines, C-reactive protein, and activation of exogenous coagulation factors

and CXCR2 were studied well in EC, but there was no meaningful study examined CXCL8 and CXCR1. Coagulation, as well as chronic inflammation, is often activated in cancer, and positive association between CXCL8/CXCR2 and preoperative coagulation factors in blood indicates its possible use in diagnosis. High expression of both CXCL8 and CXCR2 promoted angiogenesis and was associated with advanced tumor stage and poor prognosis.

Expression of CXCL10 showed anti-tumor effect

CXCL10, also known as interferon- γ inducible protein-10 (IP-10), binds to CXCR3. CXCR3 is expressed on activated T cells, natural killer cells, and B cells. CXCL10 is an ELR⁻ CXC chemokine, and induces apoptosis, regulates cell growth, and attenuates angiogenesis [40] (Fig. 2c).

High CXCL10 expression was associated with better survivals in ESCC [41, 42] (Table 1) (Supplemental Table 3). CXCL10 expression were positively correlated with the

local expression of CD8⁺ T cell marker in tumor tissue, and CD8⁺ T cells were more frequently CXCR3⁺ in tumor than in peripheral blood [41]. In ESCC patient group with low CXCL10 expression, adjuvant chemotherapy could add benefit to overall survival after surgery [42]. CXCL10 expression was positively associated with infiltration of CD8⁺ T cells to tumor tissues and brought better survivals on ESCC patients.

CC chemokines and their receptors in esophageal cancer

Most of studies about chemokines in EC examined CXC chemokines, but some studies examined CC chemokines and showed promising and interesting results. CC chemokines are also implicated in angiogenic progression and tumor development. Details of each study are shown in Supplemental Table 4.

Expression of CCL4 and CCL5 showed anti-tumor effect

CCL4 is also known as macrophage inflammatory protein-1 β (MIP-1 β). CCL4 can be secreted by activated leukocytes, lymphocytes, and endothelial and muscle cells in response to inflammation. CCL4 is a chemoattractant of a variety of other immune cells and plays major roles in recruiting CD8⁺ T cells to malignancies by binding to CCR5 [43] (Fig. 2d).

CCL5 is also known as regulated upon activation, normal T cell expressed, and secreted (RANTES). CCL5 is expressed on T cells, macrophages, platelets, synovial fibroblasts, tubular epithelium, and certain types of tumor cells [44]. CCL5 activity is mediated through its binding to CCR1, CCR3, and mainly CCR5 [44]. CCL5 plays an active role in recruiting a variety of leukocytes to inflammatory sites, including CD8⁺ T cells, macrophages, eosinophils, and basophils. CCL5 production is relevant to inducing proper immune responses against tumors [41] (Fig. 2d).

Both CCL4 and CCL5 were positively associated with CD8⁺ T cell markers, and CCR5 was expressed mainly on CD8⁺ T cells in ESCC [41, 43]. CCL5 expression was elevated in advanced clinical T stage, but high CCL5 expression was associated with a better overall survival in ESCC [41] (Table 1). High CCL4 expression was also associated with a better overall survival [43] (Table 1). Both CCL4 and CCL5 induced the infiltration of CD8⁺ T cells to tumor tissues cells and were associated with a better survival in ESCC.

Expression of CCL20 was correlated with recruitment of regulatory T cells

CCL20 is also known as liver and activation-regulated chemokine (LARC) or macrophage inflammatory protein-3 α (MIP-3 α) or Exodus-1 [45]. CCL20 plays critical roles in the migration of regulatory T cells through its receptor, CCR6. CCL20/CCR6 is responsible for the chemoattraction of immature dendritic cells, effector/memory T cells and B cells, and plays a role in cancer [45] (Fig. 2e).

CCL20 was positively associated with regulatory T cell markers, and CCR6 was mainly expressed on regulatory T cells in ESCC. ESCC patients who expresses high CCL20 showed poor survival rate [43] (Table 1). CCL20 was associated with worse survival due to attraction of regulatory T cells.

Expression of CCR7 was correlated with poor prognosis

CCL19 and CCL21, ligands of CCR7, are also known as EBV-induced molecule ligand chemokine (ELC) and secondary lymphoid-tissue chemokine (SLC), respectively. These are highly expressed in the endothelium of lymphatic vessels and secondary lymph nodes [46]. CCR7 is expressed

on mature dendritic cell and T cells, and has the homing function of these cells to the lymph nodes, in response to CCL19 and CCL21. This relationship is considered for the cause of homing metastasis to lymph node (Fig. 3b). AKT and ERK1/2 pathways are involved in the CCR7-induced migration of tumor cells [47].

In all chemokines and receptors, CCR7 was the first to be described in EC. High CCR7 expression was correlated with clinicopathological factors, survivals, and site of recurrence in ESCC [47–49] (Table 1). CCL21 enhanced the cell migratory, adhesive ability, and pseudopodia formation of CCR7⁺ ESCC cells [48, 49]. CCR7⁺ cells showed high metastatic potential in vivo [49]. CCR7 expression was positively associated with cell surface-associated mucin 1 (MUC1) expression, and CCR7 could promote lymph-node metastasis via up-regulation of MUC1 [47]. High CCR7 expression was associated with lymph-node metastasis and recurrence in lymph nodes, and worse survivals.

Discussion

In this study, we summarized how the expression of chemokines and their receptors is associated with the prognosis of EC by focusing on the different roles of each chemokine and their receptor(s) in tumorigenesis and metastasis of different subtypes of EC. High expression of CXCL12 and their receptors (CXCR4 and CXCR7), CXCL8 and its receptor (CXCR2), CCL21 and its receptor (CCR7) or CCL20 showed worse prognosis on EC patients. These chemokines and receptors are mainly involved in angiogenesis or metastasis, and facilitate tumor growth. Tissue samples were usually collected during the surgery; it may be less helpful for diagnosis. However, they can be considered for prognosis or predicting clinical outcome. As shown above, proliferation of ESCC cells induced by CXCL12 can be inhibited by selective CXCR4 blockade. Accumulation of research data and understanding in CXCR4 are progressing, and it is considered to be the most promising biomarker in EC at the present [14]. On the other hand, high expression of CXCL10 and its receptor (CXCR3), CCL4 and CCL5 and their receptor (CCR5), showed better clinical outcomes. It could be attributed to the types of cells infiltrated to tumor tissues, or the types of receptors which ligand binds [43, 44]. In fact, these molecules could act as tumor promoters in other type of cancers [43]; therefore, results from these studies should be interpreted with cautions [42]. Of the 21 articles identified in this study, 9 articles were published in the last 5 years, and 4 chemokines, CXCL10, CCL4, CCL5, and CCL20, were newly reported as possible biomarkers in EC. Further validation may reveal their values in EC prognosis.

Compared to the numbers of studied in ESCC, there are far less studies and information about chemokines and

receptors in EAC. It is necessary to have comparative studies in both EC subtypes. CXCL12 and CXCR4 were reported to have worse effects on progression of both ESCC and EAC; therefore, they may play similar roles in both EC subtypes. CXCR4 expression was reported to have similar staining pattern both in ESCC and in EAC [24, 26]; however, it is unknown whether the nuclear CXCR4 expression exists in EAC. CXCR7 expression was mainly found in ESCC and rarely in EAC [34]. To determine whether these expressions are ESCC specific or common both in ESCC and EAC will advance our knowledge in EC.

Except for three articles from Germany [24, 26, 34], all of articles which we reviewed were published from Japan and China, which reflect the regional specificity that ESCC is frequently seen in Asia [5]. Recently, incidence rate of EAC is increasing, outside of Asia, due to the changes in lifestyle in Europe and North America; thus, the study on EAC is becoming more important. In addition, because of regional specificity of EC, to study both subtypes of EC in one research group is challenging and collaborations are essential. We should study both subtypes comprehensively by comparing results from EAC studies with that from ESCC studies.

In this study, we focused on and reviewed biomarker studies based on IHC analysis. IHC is the basic method based on investigation in proteins. It is more practical, can be performed widely, and is cost-effective [50]. IHC is also useful to detect specific expression, such as nuclear versus cytoplasmic expression, tumor cells versus stromal cells and infiltrated cells. However, the evaluation criteria of IHC in chemokines and receptors were different among these reports. Developing commonly used criteria will be helpful for comparing results from different research groups, and standardization of the evaluation criteria should be considered. Future investigation and confirmation studies based on DNA analysis of chemokines and their receptors in EC should be developed with the advancement of bioinformatics and transcriptomics.

Conclusions

The prognosis of EC is still worse in cancers of digestive tract, and more studies are required to improve prognosis and detect at early stage. Chemokines are widely known to be involved in inflammation and investigated in many diseases, especially in cancers. Many drugs, including small molecule inhibitors, peptide antagonists, or antibodies, are also developed to target chemokines, and some of them are already introduced in clinical practice. Chemokines and their receptors have the potential to be the prognostic biomarkers in EC. Comparative studies between ESCC and EAC will reveal the similarity and differences in these two subtypes of

EC and may indicate whether these molecules play important roles in both subtypes or are unique to one or another, and will improve our understanding in tumorigenesis of EC, and provide guidance for therapies.

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Compliance with ethical standards

Ethical Statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest.

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