

Elucidating the Role of Chemokines in Infectious Diseases and Gastric Cancer

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Abstract

The fourth most frequent cancer in the world is Gastric cancer and also the second leading cause of cancer-related fatalities. Despite substantial research into new diagnostic and therapeutic agents, patients with advanced stomach cancer have a low quality of life and a dismal prognosis, and treatment is mostly cytotoxic chemotherapy. A deeper knowledge of the underlying molecular pathologies, as well as their application toward the development of innovative therapeutic strategies, is essential for improving the quality of life and survival of gastric cancer patients. Chemokines are a family of tiny proteins linked to cytoskeletal rearrangements, directed several cell movements throughout development and physiology, and the host immunological responses by interrelation with G-protein coupled receptors. Presently there is growing proof that chemokines are involved in the development and progression of malignancies, in addition to their involvement in the immune system. Cell transfer in and out of the tumor microenvironment in gastric cancer is regulated by CXC chemokines and chemokine receptors. CXC chemokines and their receptors can affect carcinogenesis directly by regulating tumor transformation, survival, growth, metastasis, and invasion and also by indirectly controlling angiogenesis and tumor-leukocyte interactions. The significance of CXC chemokines and their receptors in the formation, progression, and metastasis of gastric cancers will be discussed in this review, as well as their therapeutic potential for gastric cancer.

Keywords: Chemokine; Chemokine receptor; Gastric neoplasm; Therapeutic target

Introduction

Although the prevalence of gastric cancer is decreasing in many developed nations, it is the fourth most prevalent cancer and the second leading cause of cancer-related deaths globally. Around 8 percent of recently diagnosed malignant tumors are stomach cancer, more than 7,00,000 individuals die from gastric cancer yearly. Despite extensive research into new diagnostic and therapeutic methods, the prognosis for individuals with advanced stomach cancer remains dismal, and survival rates have hardly improved [1]. In recent years, many latest innovations have improved our understanding of the molecular mechanisms and modifications that contribute to gastric cancer's beginning and progression, including

several genetic and molecular modifications and mutations [2]. Molecular variations in gastric carcinogenesis have been recognized in Her-2/neu (c-erbB2) [3], semaphorin-5A, c-Myc, c-MET, BCL2-like-12 (BCL2L12), and K-sam, whilst mutations have been described in K-ras, TP53, E-cadherin, and adenomatous polyposis *E. coli* (APC) [4,5]. Relevantly, the ToGA (Trastuzumab for Gastric Cancer) experiment recently found that adding trastuzumab, a monoclonal antibody against Her-2/neu, to standard chemotherapy, increased the patient survival with advanced gastric or gastro-esophageal junction cancer significantly compared to chemotherapy alone. Despite these advancements, the success of advanced or metastatic stomach cancer treatment is still largely dependent on the tumor's response to standard cytotoxic

chemotherapy. Identifying the unique molecular processes behind stomach cancer growth and treatment resistance might lead to new therapeutic possibilities, improving patient quality of life and overall mortality. Chemokines are a family of tiny (8-14 kDa) proteins that interface with cell-surface receptors to guide cells to appropriate sites throughout the body during development, for immune response, and other physiological functions [6]. Chemokines were first introduced as an abbreviated version of chemotactic cytokines in 1992, shortly after the discovery of the first chemokine, interleukin-8 (IL-8; also called CXCL8) [7]. Chemokines were subsequently known as a wide family of heparin-binding proteins that affect cell trafficking and immune cell targeting [8]. Chemokine ligands are encoded by around 50 human genes, together with more than 20 chemokine receptor genes, which produce seven- transmembranes G protein-coupled receptors. [9]. Chemokines are divided into four categories based on the location of cysteine residues around the N-terminus (CXC, CC, CX3C, or C), with X representing any amino acid. The CXC and CC groups contain the majority of chemokines [10]. All chemokines, excluding the "C" subgroup, have a similar four-cysteine residue motif connected by disulfide bonds at conserved sites: one between the first and third Cys, and one between the second and fourth Cys, resulting in a triple-stranded β -sheet structure. CXC chemokines can be additionally subclassified based on the existence or non-existence of a glutamic acid-leucine-arginine (ELR) pattern located before the first preserved cysteine residue (ELR+ or ELR-) [11].

Chemokine's Function in Infectious Disease

Many cell types, including leukocytes, endothelial cells, fibroblasts, epithelial cells, and tumor cells, produce chemokines [12]. Recent proof has disclosed that Chemokines and their receptors are now known to have a function in tumor initiation and development in addition to their role in the immune system [13]. Chemokines link to chemokine receptors' of an extracellular domain, which includes the N-terminus and extracellular loops. The intracellular domains (containing three loops and the C-terminus) detach from G-proteins, which are made up of three subunits (α , β and γ heterotrimers) after activation. This causes the formation of the second messenger's diacylglycerol (DAG) and inositol triphosphate (IP3) which leads to cytoplasmic calcium mobilization and the activation of several downstream signaling pathways, along with the Mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/Akt, Ras and Janus kinase/signal transducer and generator of transcription (JAK/STAT) pathways [14]. Chemokines and related receptors play a significant role in the movement of cells into and out of the tumor microenvironment in cancer, influencing tumor activity. During inflammation, chemokines cause directed cell movement, especially among leukocytes. Long-term inflammation can promote carcinogenesis by

creating an attractive microenvironment for tumor growth and progression [15]. Chemokines can affect carcinogenesis in two ways: indirectly through angiogenesis and tumor-leukocyte interactions, and directly through altering tumor growth, invasion, transformation, survival, and metastasis. But, the activities of chemokines and associated receptors in carcinogenesis are complicated, since some members of the family encourage tumor development and progression while others indicate anti-tumor properties [16]. For example, ELR+ CXC chemokines like CXCL8 can promote tumor development by causing angiogenesis and chemoattraction of neutrophilic granulocytes. The release of angiogenic tumor stimulating factors [such as vascular endothelial growth factor] matrix-degrading enzymes [such as matrix-metalloprotease (MMP)-9] by neutrophils further increases angiogenesis, tumor development, and metastasis (VEGF) [17].

Chemokine's Receptors in Gastric Cancer

CXCR4 is expressed differently in gastric cancer at the transcriptional, cell membrane, and protein levels [18]. Gene expression analysis also identifies the differential expression of CXCR4 in gastric cancer [19]. Furthermore, circulating CXCR4 mRNA levels in the plasma of patients with stomach cancer are higher pre-operatively than in normal controls, but decline post-surgery. Increasing CXCR4 activity in gastric cancer cells is linked to peritoneal carcinomatosis, which is a frequent cause and a leading cause of death in gastric cancer patients. Furthermore, CXCL12 was shown to be overexpressed in peritoneal mesothelial cells, indicating that CXCR4-positive gastric cancer cells are attracted to the peritoneum, where large quantities of its ligand CXCL12 are generated [20]. CXCR4 expression has also been linked to aggressive tumor activity, which includes poor differentiation, tumor invasion, and metastasis, suggesting that it might be utilized as an independent prognostic factor for gastric cancer patients' survival rates. According to several investigations, CXCL12 expression is also changed in gastric cancer cells. However, the findings are contradictory, since higher CXCL12 expression has been linked to lymph node metastases, tumor growth, invasion, and poor prognosis, while the alternative data has been documented. CXCL12 gene upregulation was revealed using cDNA microarrays, and CXCL12 secretion was also seen in gastric cancer cells. Another possible procedure by which CXCL12 may also contribute to tumor growth is by generating a favorable tumor microenvironment by drawing endothelial cells to the tumor site or recruiting immune suppressive cells to the tumor site, resulting in angiogenesis and immune evasion, correspondingly. CD8⁺ T cells release IL-17, which causes stomach cancer cells to generate CXCL12, according to Zhuang et al [21]. CXCL12 then attracts myeloid-derived suppressor cells (MDSCs) into the tumor microenvironment, in a CXCR4-dependent way, where MDSCs promote gastric cancer growth. Furthermore, Ingold et al. [22-27] found that the activity of CXCL12 in tumor cells and CXCR4 in the

microvessels enclosing the tumor is linked to increased local tumor growth and a relatively high tumor stage, implying a major part of the CXCL12-CXCR4 alliance plays an important role in tumor neo-angiogenesis in gastric cancer. CXCL12 transgenic mice model was applied by Shibata et al. [28-31] to show that elevated CXCL12 expression contributed to the early stages of gastric carcinogenesis by attracting CXCR4-positive mesenchymal stem cells as well as stimulating the growth of myofibroblasts in the gastric stem cell niche, increasing epithelial progenitors.

CXCL12 binds to CXCR4 and stimulates a multitude of intracellular signaling pathways and effector molecules that control cancer cell proliferation, migration, invasion, and metastasis. The diverse effects of the CXCL12-CXCR4 axis in the biology of gastric cancer are likely due to the huge number of downstream effectors regulated by CXCR4. The functions of the numerous CXCR4-induced effectors on specific gastric cancer processes, such as cell proliferation and adhesion, are yet unknown. Identifying CXCR4 downstream effectors *in vivo*, however, is crucial for understanding the molecular mechanisms by which CXCR4 encourages stomach cancer [32]. CXCL12 binds to and activates CXCR4, which then activates the p110 β isoform of PI3K, leading to the formation of phosphatidylinositol (3,4,5)-triphosphate and phosphorylation of the protein kinase B/Akt and mTOR pathways. Activated mTOR causes p70S6K (S6K) and eukaryotic initiation factor 4E binding protein 1 to become activated (4E-BP1). The activity of the Akt kinase is activated when stomach cancer cells are treated with CXCL12, which triggers the release of its downstream aims 4E-BP1 and S6K. Furthermore, CXCL12-prompt activation of 4E-BP and S6K can be inhibited specifically using the mTOR inhibitor rapamycin [33-36].

Conclusion

Patients with advanced gastric cancer, especially those who have peritoneal seeding, have a very low quality of life and a dismal prognosis. A deeper knowledge of the underlying molecular pathophysiology of gastric carcinogenesis, as well as its application for the development of innovative targeted therapeutics, is urgently required to enhance the quality of life and mortality rate in these patients. Chemokines, also known as chemotactic cytokines, were once thought to control the direction of leukocyte migration to inflammatory sites. Moreover, now it is clear that Chemokines and their receptors, also now appear to have a role in the progression and development of carcinogenic conditions, such as tumor growth, survivability, angiogenesis, invasions, and metastasis. CXC chemokines and receptors are found in a wide range of gastrointestinal cancers, including gastric cancer, and have been linked to prognosis. CXCL12 and its receptor CXCR4 have an important role in gastric cancer growth in a variety of ways, including cell proliferation, migration, invasion, peritoneal seeding, and therapy resistance. This implies that

they might be potential therapeutic possibilities in the future. About CXCL16 and CXCR6, both CXCL16 as well as its receptor CXCR6 are both abnormally expressed in gastric cancer, indicating that they are involved in gastric carcinogenesis. However, due to a lack of evidence, the importance of CXCL16 and CXCR6 in gastric cancer remains unknown. Overall, the involvement of chemokine receptors and chemokines in the development and progression of stomach cancer is complicated. Furthermore, the functions of alternative CXC chemokines and chemokine receptors in gastric cancer are moderately understood. More research is needed to better understand the functions of the complex chemokine and chemokine receptor network in gastric carcinogenesis, which might lead to therapeutic applications for gastric cancer patients.

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