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Targeting chemokine pathways in esophageal adenocarcinoma

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Esophageal adenocarcinoma (EAC) is one of the fastest growing malignancies in the US and needs newer therapeutic and diagnostic strategies. Chronic inflammation plays a role in the pathogenesis of EAC and contributes to the dysplastic conversion of normal esophageal epithelium to Barrett's esophagus and frank adenocarcinoma. Chemokines play important roles in mediating inflammation and recent evidence implicates these ligands and their receptors in the development and spread of various tumors. We demonstrated that the chemokines IL8, CXCL1 and CXCL3 are significantly overexpressed during esophageal carcinogenesis and accompanied by amplification and demethylation of the chr4q21 gene locus. We also demonstrated that IL8 levels can be detected in serum of patients with EAC and can serve as potential biomarkers. We now demonstrate that inhibition of IL8 receptor, CXCR2, leads to decreased invasiveness of esophageal adenocarcinoma derived cells without affecting cellular proliferation. Taken together, these studies reveal the important roles that chemokines play in development of esophageal cancer and demonstrate that these pathways can serve as potential therapeutic targets.

Keywords: barrett's esophagus, chemokines, CXCR2, esophageal adenocarcinoma, IL8

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Introduction

Esophageal cancer is the fastest growing cancer in the United States and other industrialized nations. Esophageal adenocarcinoma like many other malignancies arises in the setting of chronic inflammation and is preceded by a premalignant condition called Barrett's esophagus. Many studies have pointed to a role of chemokines and chemokine receptors in cancer growth and metastasis. Our work and other recent findings have shown that chemokine signaling is also very important in esophageal carcinogenesis and can act as a potential therapeutic target in this disease.

Chemokines and Chemokine Receptors

Chemokines are a group of small (~8–14 kDa), structurally related, mostly basic, molecules that act through 7-transmembrane G protein-coupled receptors (GPCRs).[1] They play important roles in growth, differentiation and activation of various cells including those involved in immune responses.[2]

Since the identification of IL-8 (CXCL8) and MCP1 (CCL2) in the late 1980s, the chemokine family has significantly expanded with identification of over 40 ligands and their receptors (**Table 1**); helping us understand their role not only in inflammatory responses and allergic phenomenon but also in cancers, tissue homeostasis and wound healing.

Chemokine ligands

Structurally chemokines are classified into 4 subfamilies namely CC, CXC, CX3C and (X)C, depending on the arrangement of N-terminal 2 cysteine residues.[1] Functionally they can be seen as inflammatory, homeostatic (regulating bodily functions) or dual function chemokines (i.e., they are homeostatic and also

Table 1. Chemokine ligands and receptors

Chemokine	Receptor	
Ligands	**Agonistic**	**Antagonistic**
CXC Subfamily		
CXCL1	CXCR2	
CXCL2	CXCR2	
CXCL3	CXCR2	
CXCL4	CXCR3-B	
CXCL4L1	CXCR3-B	
CXCL5	CXCR2	
CXCL6	CXCR1, CXCR2	
CXCL7	CXCR1, CXCR2	
CXCL8	CXCR1, CXCR2	
CXCL9	CXCR3	CCR3
CXCL10	CXCR3	CCR3
CXCL11	CXCR3, CXCR7	CCR3, CCR5
CXCL12	CXCR4, CXCR7	
CXCL13	CXCR5, CXCR3	
CXCL14	UNKNOWN	
CXCl16	CXCR6	
CXCL17	UNKNOWN	
CC subfamily		
CCL1	CCR8	
CCL2	CCR2	
CCL3	CCR1, CCR5	
CCL3L1	CCR1, CCR3, CCR5	
CCL3L3		
CCL4	CCR5	
CCL4L1		
CCL4L2		
CCL5	CCR1, CCR3, CCR5	
CCL7	CCR1, CCR2, CCR3	CCR5
CCL8	CCR1, CCR2, CCR5	
CCL11	CCR3, CCR5	CXCR3, CCR2
CCL13	CCR2, CCR3	
CCL14	CCR1, CCR3, CCR5	
CCL15	CCR1, CCR3	
CCL16	CCR1, CCR2, CCR5, CCR8, H4	
CCL17	CCR4	
CCL18	PITPNM3	
CCL19	CCR7	
CCL20	CCR6	
CCL21	CCR7	
CCL22	CCR4	
CCL23	CCR1, FPRL-1	
CCL24	CCR3	
CCL25	CCR9	
CCL26	CCR3, CX3CR1	CCR1, CCR2, CCR5
CCL27	CCR10	
CCL28	CCR10, CCR3	
XC Subfamily		
XCL1	XCR1	
XCL2	XCR1	
CX3C Subfamily		
CX3CL1	CX3CR1	

get upregulated during the inflammatory response).[3] This functional classification is rather operational than mutually exclusive. Inflammatory chemokines are chemo-attractants and the CXC chemokines attract neutrophils and lymphocytes while CC chemokines attract lymphocytes and monocytes.[4] Some inflammatory CXC chemokines have an ELR (Glu-Leu-Arg) motif just prior to first cysteine residue and these exert angiogenic effects through the CXCR1 and CXCR2 receptors. On the other hand chemokines like CXCL4, L9-L10 that lack this ELR motif, are angiostatic.[5] Thus chemokines contributes in new vessel formation at the site of inflammation depending on the molecular signal.

Homeostatic chemokines are constitutively expressed in the lymphoid and other tissues and helps in migration and homing of various cells like lymphocytes and dendritic cells. The inflammatory chemokines are relatively new in evolutionary history and hence show variation between the species while homeostatic chemokines are ancient, well conserved and function in a more predictable manner.[6]

Chemokine receptors

The chemokine receptors are Class A GPCRs coupled with Gαi heterotrimeric G protein. They are also grouped in 4 subfamilies.[7] The inflammatory chemokines are more in number than their receptors and chemokine ligands are shared by multiple receptors.[8] This raises the possibility of functional redundancy also likely to be modulated by both spatial and temporal control of expression. For example natural antagonism is seen between the ligands of CXCR3 and CCR3, thus CXCL9, CXCL10 and CXCL11 are natural antagonists for CCR3 whereas CCL11 is a natural antagonist for CXCR3.[9] The chemokine GPCRs signal through heterotimeric G-proteins which in turn regulate a diversity of signal transduction pathways involved in chemotaxis that include mitogen-activated protein (MAP) kinases, phospholipase-cβ, phospholipase 3-kinase (PI3K) and RAS or Rho GTPases.[10] Interestingly the receptors can also bind with non-chemokine ligands such as Macrophage migration inhibitory factor (MIF) (to CXCR2 and CXCR4),[11] anti-microbial peptides such as β-defensins (to CCR6)[12] and extracellular ubiquitin (to CXCR4).[13] Receptors for the Dual function and homeostatic chemokines on the other hand show a more restricted ligand usage with one or 2 ligands acting on a particular receptor in a specific manner.[6]

In addition to the above-mentioned "typical" receptors, certain atypical receptors are also known namely D6, Duffy antigen receptor for chemokines (DARC) and CCX-CKR (ChemoCentryx,

chemokine receptor).[13] These receptors are also heptahelical but do not transduce the signals due to the lack of DYR motif in the second intracellular loop needed for interaction with Gαi class of G-proteins. These probably function as decoy receptors, scavengers or as transporters for the ligands.[14]

Chemokines also interact with glycosaminoglycans (GAGs) and this binding is essential for presentation of chemokines over the endothelial layers and for migration of leukocytes.[15]

Role of chemokines in cancers

Chronic inflammation plays a key role in the initiation or progression of cancers of the lung, colon, liver, breast, cervix, prostate, bladder, ovary, esophagus, skin and lymphatics.[16-19] Dynamic interaction between the tumor cells and the cells of the tumor microenvironment facilitates tumor growth and spread. Both the tumor cells and stromal cells elaborate chemokines, thereby recruiting different cell types, namely tumor-associated macrophages (TAMs), Tumor-associated neutrophils (TANs) and lymphocytes, cancer-associated fibroblasts (CAFs), mesenchymal stem cells (MSCs) and endothelial cells, to the tumor microenvironment. These infiltrating cells provide additional sources of chemokines that affects, tumor growth, survival, aging, angiogenesis, metastasis to distant sites and immune evasion.[20]

Tumor proliferation and immune evasion

CXCL12 secreted by stromal fibroblasts from the tumor microenvironment can bind CXCR4 on tumor cells and stimulate cell motility/chemotaxis.[21] Interaction of CXCL12 with CXCR7 mediates cellular proliferation.[22] The CXCR4 driven pathways have been shown to drive malignant growth in multiple tumor models.[18-20] The chemokine CCL2, is widely expressed in many carcinomas and its production corresponds to macrophage recruitment.[23,24] For instance, in esophageal and breast cancer cells, CCL2 expression is correlated with high TAM influx, lymph node metastasis and a poor prognosis.[25] TAMs and CCL2 may have pro-tumorigenic role. TAMs stimulated by chemokines produce growth factors such as epidermal growth factor (EGR) and transforming growth factor (TGF-β), benefitting tumor cell proliferation[25] Pro-inflammatory chemokines (specially CCL2)[26] produced by infiltrating leukocytes and the neoplastic tissue may recruit Th2 cells and regulatory-T cell (T_{reg}).[4] T_{reg} ($CD4^+CD25^+$) cells, suppress immune attack against self antigen and avoid autoimmunity. Macrophages stimulated by these Th2 T-lymphocytes (M2 macrophages), promote tumor growth and progression by elaborating the immunosuppressive cytokine, IL-10.[20] Also TAM derived TGF-β can convert infiltrating $CD4^+CD25^-$ T cells to $CD4^+CD25^+$ T cells, allowing immune evasion by the tumor cells thereby helping proliferation.[27]

Fibroblasts also play important roles in secretion of chemokines in the tumor microenvironment. Normal or resting fibroblasts in the tumor microenvironment get activated via effects of TGF-β to become TAFs.[28-30] TAFs form bulk of the tumor stroma and are also the main source of CXCL12; the chemokine implicated in promoting tumor proliferation. TAFs also increase angiogenesis by recruiting endothelial cells.[31] Within the tumor milieu the TGF-β stimulation also polarizes the infiltrating neutrophils to N2 state (increased expression of arginase and chemokines such as CCL2 and CCL5). These N2 TANs display pro-tumoral properties.[31]

Angiogenesis and metastasis

Formation of blood vessels and blood vessel density is correlated with higher incidence of metastases and more rapid disease recurrence.[32,33] ELR+ Chemokines such as CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7 and CXCL8, that are promoters of tumor angiogenesis, bind to the CXCR2 and CXCR1 recptors.[34-36] CXCR2 is the primary receptor for angiogenesis, and is required for endothelial cell chemotaxis.[37,38] This receptor binds to all the ELR+ chemokines and regulates the response of endothelial cells to CXCL8.[39] In-vitro studies have shown a link between prostaglandins and chemokines in promoting angiogenesis. Prostaglandin E2 (PGE2) increases expression of CXCL1 in a MAPK-dependent manner thus favoring endothelial cell migration and tube formation.[40] Similarly, CXCL8 down-regulation using prolylhydroxylase (PHD)2 was shown to reduce angiogenesis.[41] Knockdown of PHD2 in colon cells increased tumor growth and angiogenesis, possibly mediated by an increased NF-κB activity as well as by induction of CXCL8 and angiogenin.[41] Decoy receptors for the chemokines such as D6 and Duffy antigen/receptor for chemokines (DARC) have been shown to have inverse relationship with angiogenesis. D6 has been shown to reduce CCL chemokine recruitment in a mouse model of skin inflammation.[42] Studies using the TRAMP transgenic model of prostate cancer showed that mice with null DARC showed increased tumor growth and vascularization compared to TRAMP mice with DARC expression, probably due to defect in clearing of angiogenic chemokines in DARC null-mice.[43] DARC overexpression has been inversely correlated to microvessel density, lymph node status and distant metastasis.[44] CXCL12 although not an ELR+ CXC chemokine is also involved in promoting angiogenesis. It increases the expression of vascular endothelial growth factor (VEGF) by endothelial cells. VEGF in turn up-regulates CXCR4 expression over endothelial cells,[45] the receptor implicated in metastasis. Tumor angiogenesis thus can be viewed as impaired balance of pro- and anti- angiogenic factors between normal and cancer tissues. In tumor angiogenesis there is thus, not only an increase in angiogenic chemokines levels, but also decrease in decoy receptors and other triggers, further favoring angiogenic switch.

Metastatic tumors express embryonic stem cell transcription factors and utilize stromal cell-derived factor-1 (SDF-1) /CXCR4-mediated migration,[46] as seen in migration of embryonic and adult stem cells.[47] Concentration gradient based metastasis to distant sites was described for the binding pairs such as CXCR4/CXCL12 (bone metastasis), CCR9/CCL9-CCL21 (lymph node metastasis) and CCR10/CCL27 (skin metastasis).[48] Certain other chemokine receptor/ligand pairs that favor tumor metastasis to

specific sites based on concentration gradient of the ligands has been discovered such as CX3CR1 producing pancreatic ductal carcinoma metastasizing to neurons and nerve fibers (higher concentration of CX3CL1)[49]; CCR9 positive melanoma to small intestines (higher levels of CCL25)[50] and CXCR2 positive breast cancer cells to lungs (higher CXCL1 levels).[51] Studies have proposed that tumors might be generating the gradient and actively promoting their own metastasis[52] and tropism, as observed during cell migration toward lymphatic endothelia in a CCR7-dependent manner; more pronounced in slow interstitial flow conditions.[53] This raises the possibility that cancer cells may control their own rolling capacity by affecting overall expression of surface molecules as they flow toward the specific organs.[54]

Metastasizing cells leave the favorable tumor microenvironment and face hostile conditions. It has been shown that CCR7 and CXCR4 could possibly help cancer cells in surviving anoikis (detachment-induced cell death) by down-regulating pro-apoptotic Bcl2-modifying factor (Bmf) thereby assisting metastasis.[55]

Reflux disease, Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC)

Esophageal cancer is the eighth most common cancer worldwide.[56] Lifetime risk of esophageal cancer in United States is ~1 in 125 men and 1 in 400 women.[57]

There has been a steady increase in the incidence of EAC in past 2–3 decades in US, (Surveillance Epidemiology and End Results –SEER program).[58] The rate of increase in EAC in the last 25yrs is greater than that of any other solid tumor in the US over the same time interval.[59] Similarly increase in the incidence has been noted in the European[60] and Australian[61] populations. EAC has a very high male: Female ratio ~7:1 and higher incidence among whites compared with blacks.[62,63] EAC is commonly a disease of mature; peaking around 55–65years,[64] obese[65] males with gastroesophageal reflux disease (GERD).[66] Other risk factors implicated in disease development are tobacco smoking,[67] high calorie, fat and red meat diet[68-69]; medications that relax lower esophageal sphincter (LES)[70] and hiatus hernia.[71] Genetic and familial preponderance is also sought.

GERD is defined by recurrent heartburn, cardinal symptoms and acid regurgitation occurring at least weekly[72,73] and has long been regarded as important risk factor of several upper gastrointestinal cancers.[74,75] In a Swedish nationwide case-control study, GERD and obesity were identified as strong and independent risk factors for EAC.[76]

Barrett's esophagus

Long standing GERD is strongly associated with development of Barrett's esophagus; the transformation of esophageal mucosal lining from normal stratified squamous to "intestine like" columnar epithelium with goblet cells (intestinal metaplasia).[77] Case control studies have shown that subjects with heartburn are around 6–10 times more likely to have BE than those without it. Furthermore the more frequent and chronic the GERD is, the more likely for them to have BE.[78]

The progression of BE to EAC is a multiple step process where this metaplastic epithelium is thought to sequentially undergo low-grade dysplasia (LGD), high-grade dysplasia (HGD), early EAC (non invasive disease) and eventually invasive carcinoma[79-81.] Virchow first linked inflammation to carcinogenesis in 1863.[82] Up to 25% of human cancers are considered inflammation-related,[83] gastroenterological organs in particular have a notably strong association, viz. colon cancer and inflammatory bowel disease,[84] chronic Helicobacter pylori gastritis and gastric cancer,[85] hepatitis B & C and liver cancer[86] and reflux esophagitis/BE and EAC.[87] Inflammation can act as a classical tumor promoter, increasing the risk and tumor progression.[88] In addition inflammation also generates tumor-initiating DNA alterations.[89,90] Reactive oxygen species-mediated DNA damage is a critical factor in carcinogenesis,[91] leading to altered transcription, genomic instability and replication errors.[92,93] Microsatellite instability with defect in mismatch repair genes[94] and nucleotide excision repair pathways,[95] genetic instability with allelic loss and ploidy abnormalities leading to loss of heterozygosity (LOH) viz. p53 LOH, p16LOH,[96] copy number alterations and deletions at fragile sites of the genome,[97,98] spindle checkpoint function failure like APC gene inactivation by promoter methylation,[99] pro-inflammatory cytokines and nitric oxide induced suppression of p53 activity,[100,101] increased human telomerase reverse transcriptase and human telomerase-associated RNA expression,[102] have all been demonstrated in patients progressing from BE to dysplasia and EAC. Alterations in p53 and p16 are early events in the metaplasia-dysplasia-adenocarcinoma sequence, followed by loss of cell cycle checkpoints.[103]

Chronic inflammation is also pivotal in triggering epigenetic alterations in addition to DNA damage and genetic alterations as described above. These epigenetic events occur early on in tumorigenesis and not restricted only to malignant tumors, but also seen in pre-malignant lesions. Most important epigenetic alterations are aberrant DNA methylation and histone modifications.[104-106] We conducted an analysis of genome-wide DNA methylation on endoscopic biopsies of dysplastic and malignant lesions to understand the role of epigenetic events associated with the progression of Barrett esophagus. We observed that the previously reported global hypomethylation phenomenon in cancer has its origins at the earliest stages of epithelial carcinogenesis and was seen in low grade dysplasia. Integration of methylation analysis with copy number analysis demonstrated that promoter demethylation synergizes with gene amplification and leads to significant upregulation of a chr4q21 chemokine cluster and other transcripts during Barrett neoplasia. This chromosomal region contains the genes for CXCL1, CXCL3 and IL8 chemokines. We observed that these ligands are significantly upregulated in Barrett's and dysplastic lesions. Importantly we were also able to show that IL8 levels in the serum are elevated in patients with esophageal cancer and can potentially serve as biomarkers of disease.[107] Likewise molecular signatures are being sought for many other malignancies, which can help us diagnose or monitor the treatment of specific cancers.[108]

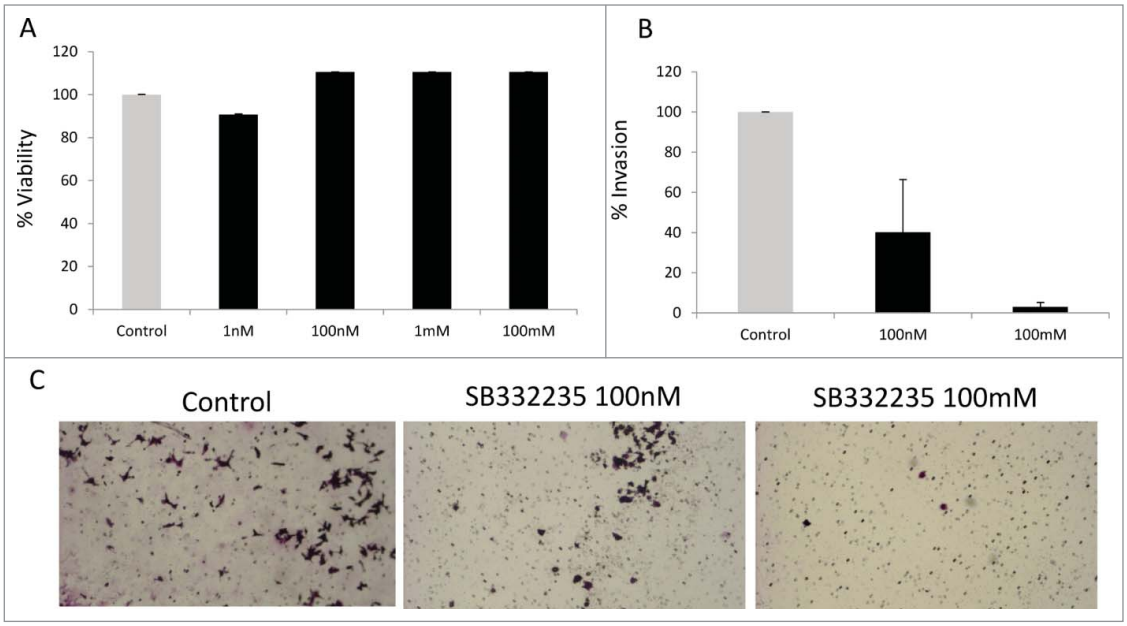

Figure 1. CXCR2 inhibition leads to reduced invasiveness of esophageal adenocarcinoma cells. Treatment with CXCR2 inhibitor, SB332235, did not lead to inhibition of proliferation of OE33 cell lines at 48 hrs by MTT assay (Mean +/− s.e.m of 3 independent experiments is shown) (**A**). Treatment with CXCR2 inhibitor, SB332235, led to inhibition of matrigel invasion of OE33 cell lines at 48 hrs at different dose levels (Mean +/− s.e.m of 3 independent experiments is shown; TTest with *P* value < 0.05 (*) (**B**). Representative pictographs shows decreased invasion after CXCR2 inhibition (**C**).

Other studies have also suggested that chemokines are involved in esophageal carcinogenesis. Fitzgerald et al.[109] found that, in patients with reflux esophagitis, the inflammation is maximal at squamous-columnar junction and was accompanied by an increased expression of IL-8 and IL-1β. CXCR1 and CXCR2, the receptors for IL8, have also been shown to be constitutively expressed in esophageal mucosa.[110-112] Infiltrating neutrophils have also been shown to contribute to the pool of IL8 thereby facilitating the progression of BE and EAC.[113] Nguyen et al. in their study demonstrated a relation between increased IL8 expression and poorer prognosis in esophageal cancer confirming the pro-tumoral role of IL8.[114] Thus our previous work and these studies promoted us to further examine the effect of IL8 pathway inhibition in esophageal cancer.

Chemokine receptor (CXCR2) blockade can inhibit invasiveness of esophageal cancer cells

To determine the role of CXCR2 in esophageal adenocarcinoma we used a specific inhibitor of the receptor. SB332235 is a small molecule inhibitor that has been shown to be a specific inhibitor of CXCR2.[115] Esophageal adenocarcinoma derived OE33 cells were exposed to CXCR2 inhibitor and proliferation was assessed by a MTT assay. We observed that CXCR2 inhibition did not result in any significant effect on proliferation (**Fig. 1A**). Since invasiveness is the hallmark of cancer, we next used matrigel invasion assay to test the role of CXCR2 in this process. We observed a dose dependent decrease in cancer cell invasion with CXCR2 inhibition (P Value < 0.05, T Test)(**Fig. 1B, C**).

Taken together, we have shown that IL8 is significantly upregulated during esophageal carcinogenesis; can be detected in the serum of patients with adenocarcinoma and the IL8-CXCR2 pathway is a potential therapeutic target in this disease.

Conclusions

Chemokines and chemokine receptors play pivotal role in tumorigenesis and metastasis of many malignancies including esophageal adenocarcinoma. Therapeutic targeting the chemokines or their receptors may represent novel strategies to prevent tumor development at an early stage.

Materials and Methods

OE-33 cell proliferation

OE-33 (ATCC) were passaged in DMEM containing 10% FBS, 2 mM L-glutamine, 100 U/mL penicillin and 100 ug/mL streptomycin. Growth of cells was measured after 3 days using MTT assay. CXCR2 inhibitor SB332235 was provided by GSK pharmaceuticals.

Matrigel invasion assay

The invasiveness of the OE33 cells were assessed with the modified Boyden chamber assay. Matrigel invasion chambers (BD BioCoat™ BD Matrigel™ Invasion Chamber) with 8 μm pore sizes in a 24-well plate format were used as per the manufacturer's recommendation. After the cells were allowed to invade, the matrigel was wiped off the membrane, and then it was fixed with 4% paraformaldehyde, stained with 0.2% crystal violet and the number of cells that had invaded

through to the other side of the membrane were counted.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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