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CXCL12-CXCR4 AXIS: ITS ROLE AND THE DRUG INHIBITORS ON EACH TYPE OF CANCERS

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Abstract – *Objective:* *Chemokine 12, C-X-C Motif Chemokine Ligand 12 (CXCL12), and its receptor C-X-C Motif Chemokine Ligand 4 (CXCR4), both play essential and critical roles in the development of different types of cancers. Almost, in all of the cancers, overexpression of these two chemokines is a key to diagnose of cancers and lead them to progress, an increment in proliferation, the invasive feature of different cell lines, metastasis, and a noticeable decrement in apoptosis. Although the impact of this axis on cancer development is known and investigated, there was no review article about this molecular pathway and the drug effects on this cascade is not written. In this regard, we probed the researches about this intracellular process and the drugs that are useful for suppressing it on one-by-one cancer.*

Materials and Methods: *We reviewed this study with scientific keywords in ScienceDirect, Google Scholar, and PubMed. Our research process was to review every study that has looked at this process in every cancer, as well as the drugs selected to treat cancer from 14 years ago onwards.*

Results: *Our researches showed that there are some inhibitors that are introduced in order to block the pathway in many cancers. In addition, the data related to the effect of this pathway on some types of cancers are not enough.*

Conclusions: *Summing up, the present study clears a route to suppress the invasion of cancers and bold the tips that have not been worked on yet.*

KEYWORDS: *Cancer, CXCL12, CXCR4, Neoplasm metastasis.*

INTRODUCTION

Chemokine 12, C-X-C Motif Chemokine Ligand 12 (CXCL12), also known as stromal cell-derived factor-1 (SDF-1) and a member of the chemokine subfamily is ubiquitously expressed in many tissues and cell types. It interacts specifically with the ligand for the trans membrane G protein-coupled receptors C-X-C Motif Chemokine Ligand 4 (CXCR4) and C-X-C Motif Chemokine Ligand 7 (CXCR7). The CXCL12/CXCR4 axis takes part in a series of physiological, biochemical, and pathological processes, such as inflammation and leukocyte trafficking, cancer-induced bone pain, and post-surgical pain, and also is a key factor in the cross-talking between tumor cells and their microenvironment. Aberrant overexpression of CXCR4 is critical for tumor survival, proliferation, angiogenesis, homing, and metastasis[1]. SDF1/CXCR4 axis facilitates angiogenesis via activating the PI3K/AKT pathway in degenerated intervertebral discs. The SDF1/CXCR4 axis in nucleus pulpo-

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sus cells can significantly accelerate angiogenesis by regulating the PTEN/phosphatidylinositol-3-kinase/AKT pathway[2]. PTEN/PI3K/AKT constitutes an important pathway regulating the signaling of multiple biological processes such as apoptosis, metabolism, cell proliferation, and cell growth. PTEN is a dual protein/lipid phosphatase whose main substrate is the phosphatidyl-inositol, 3, 4, 5 triphosphates (PIP3); the product of PI3K. CXCR4 is upregulated in many tumors. SDF-1α induces Matrix Metallopeptidase 2 (MMP-2) and Matrix Metallopeptidase 9 (MMP-9) upregulation which is associated with increased cancer cell proliferation and invasion. SDF-1α leads p38 (p38 proteins are a class of mitogen-activated protein kinases (MAPKs) that are major players during inflammatory responses), especially in macrophages to be phosphorylated and p38 inhibition reduced the level of SDF-1α-stimulated MMP-2 expression. SDF-1α/CXCR4 upregulates MMP-2 expression and induces cancer cell invasion by activating p38 MAPK[3].

During our scientific research in Science Direct, PubMed, Scopus, MedLib, Google Scholar sites, we realized that the information about this molecular pathway is not enough. So, researches about this molecular cascade on each of these cancers are insufficient or non-existent. Also, limited drugs have been used to block this route so far.

Therefore, we decided to categorize the available information, identify the strengths and weaknesses of the existing research, and make the present study a resource for those who want to study the effect of this pathway on any type of cancer. The present study also helps to find the drugs that block this pathway by separating each type of cancer. The drugs that we found in this regard are listed in Table 1.

PROSTATE CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

The chemokine receptor CXCR4 belongs to the large superfamily of G protein-coupled receptors and has been identified to play a crucial role in a number of biological processes, including the trafficking and homeostasis of immune cells such as T lymphocytes. CXCR4 has also been found to be a prognostic marker in various types of cancer, including leukemia and breast cancer, and recent evidence has highlighted the role of CXCR4 in prostate cancer. Furthermore, CXCR4 expression is upregulated in cancer metastasis[4]. SLUG is a zinc-finger transcription factor of the Snail/Slug zinc-finger family that plays a role in the migration, and invasion of tumor cells. Forced expression of SLUG elevated CXCR4 and CXCL12 expression in human prostate cancer cell lines. Migration and invasion of prostate cancer cells were increased by ectopic expression of SLUG and decreased by SLUG knockdown. Notably, knockdown of CXCL12 by shRNA impaired SLUG-mediated migration and invasion in prostate cancer cells. Lastly, our data suggest that CXCL12 and SLUG regulate migration, and invasion of prostate cancer cells independent of cell growth[5]. According to the significance of this chemokine in terms of growth, angiogenesis, and metastasis of prostate cancer, blocking it with anticancer drugs would be an effective method for the treatment of this type of cancer.

Acetyl-L-Carnitine (ALCAR) suppresses invasion (CXCR4/CXCL12), and angiogenesis of prostate cancer. ALCAR reduces cell proliferation, induces apoptosis, hinders the production of pro-inflammatory cytokines [Tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ)], CXCL12 and receptor CXCR4 involved in the chemotactic axis and impairs the adhesion, migration, and invasion capabilities of prostate cancer (Pca) *in vitro*. This *in vitro* experiment has been done on 4 different prostate cancer cell lines and the data were evaluated by flow cytometry. ALCAR exerts angiopreventive activities on PCa by reducing production/release of pro-angiogenic factors (vascular endothelial growth factor (VEGF), C-X-C Motif Chemokine Ligand 8 (CXCL8), C-C Motif Chemokine Ligand 2 (CCL2), angiogenin[6]. The researchers also examine the effects of ALCAR on PCa cell growth using tumor xenografts. Oral administration (drinking water) of ALCAR to xenografted mice with two different PCa cell lines resulted in reduced tumor cell growth *in vivo* [6]. The result was shown that ALCAR had the capability to down-modulate growth, adhesion, migration, and invasion of prostate cancer cells by reducing the production of several crucial chemokines and cytokines. The authors suggested ALCAR be a new therapeutic compound for prostate cancer interception and treatment, similar to aspirin, or beta-blockers[6]. A different study reveals the impact of aspirin (ASA) on the prevention of prostate cancer. In men using aspirin, the overall PCa incidence was significantly lower, but the multivariate Cox regression analysis showed no significant decrease in risk of PCa diagnosis. Total prostate-specific antigen (PSA) values were significantly lower in ASA users[7]. Also, a study on beta-blockers suggests that beta-blocker use was associated with reduced cancer-specific mortality among prostate cancer patients taking beta-blockers[8].

TABLE 1. Effective anticancer drugs on the CXCL12-CXCR4 axis.

Drug	*Molecular Formula*	*PubChem CID*
Tamoxifen	$C_{26}H_{29}NO$	2733526
Tranilast	$C_{18}H_{17}NO_5$	5282230
Methotrexate	$C_{20}H_{22}N_8O_5$	126941
Vinblastine	$C_{46}H_{58}N_4O_9$	13342
CXCR4 antagonist 1	$C_{27}H_{43}N_7$	58801930
CXCR4 antagonist 22	$C_{26}H_{29}C_1N_2$	137321154
Wogonin	$C_{16}H_{12}O_5$	5281703
Acetyl-L-Carnitine	$C_9H_{17}NO_4$	7045767
Plerixafor (AMD3100)	$C_{28}H_{54}N_8$	65015

BREAST CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

The chemokine CXCL12 and its receptor CXCR4 colonize the human breast cancer cells to their metastatic target organs. The effects of chemokine stimulation on adhesion and migration of different human breast cancer cell lines *in vivo* and *in vitro* with particular focus on the liver as a major metastatic site in breast cancer were investigated. *In vitro* stimulation with CXCL12 induced increased chemotactic cell motility. This effect was dependent on adhesive substrates (type I collagen, fibronectin, and laminin) and induced different responses in small GTPases, such as RhoA and Rac-1 activation, and changes in cell morphology. In addition, binding to various extracellular matrix proteins (ECM) components caused redistribution of chemokine receptors at tumor cell surfaces. *In vivo*, blocking of CXCR4 decreased the extravasation of highly metastatic cells, but initial cell adhesion within the liver sinusoids was not affected[9].

Forkhead box P3 (FOXP3) is expressed by epithelial cells of organs including the breast, where it is considered a tumor suppressor. The chemokine receptor CXCR4 also regulates the development of breast cancer by stimulating cell migration towards CXCL12-expressing sites of metastatic spread. During activation, human T cells show reciprocal regulation of FOXP3 and CXCR4. Human breast cancer samples showed significantly decreased FOXP3 protein expression but an increased number of CXCR4 transcripts. In comparison with normal primary breast epithelial cells, FOXP3 was down-regulated at both transcript and protein levels in the breast cancer cell lines. In the invasive cells, the remaining FOXP3 was located predominately within the cytoplasm. Following stable FOXP3 overexpression in those cells, significant decreases were observed in the expression of CXCR4. In contrast, an increase in cyclin-dependent kinase inhibitor 1 (p21) expression led to inhibition of cell proliferation, with a greater proportion in the G1 phase of the cell cycle suggesting the induction of senescence. Specific knockdown of FOXP3 in normal human breast epithelial cells with siRNA significantly increased CXCR4 and decreased p21 expression. These cells also showed a significantly increased chemotactic response towards CXCL12, consistent with a role for FOXP3 in the regulation of cell migration. Results consist that FOXP3 function is an important tumor suppressor in breast cancer. Indeed, the potential functions of FOXP3 in breast epithelium can now be extended to include regulation of CXCR4 expression and response to the pro-metastatic chemokine CXCL12[10]. The effects of anti-estrogen tamoxifen and anti-allergic tranilast drugs as a single or in combination on invasion by two *in-vitro* invasion assays, wound-healing, and matrigel invasion on human breast cancer cell lines were examined. Both *in-vitro* invasion assays markedly showed a synergistic effect of tamoxifen when combined with tranilast drug. Tranilast increases the antimetastatic effect of tamoxifen. The mRNA expression levels of CXCR4 and CXCL12 were measured by quantitative real time-RT PCR and CXCL12 protein levels were evaluated by ELISA assay. The data showed that treatment with tamoxifen and tranilast as a single or in combination resulted in decreased CXCR4 and CXCL12 mRNA and CXCL12 protein expression levels[11].

LUNG CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

The alpha-chemokine receptor CXCR4 for the alpha-chemokine stromal cell-derived-factor-1 (SDF-1) is most widely expressed by tumors. The CXC chemokine SDF-1 or CXCL12 is highly expressed in lung cancer tissues and is associated with lung metastasis. CXCL12/CXCR4 axis is a major cause of lung cancer and has a crucial role in lung cancer initiation and progression by activating cancer stem cells. Together, CXCL12/CXCR4 axis can be a potential therapeutic target for lung cancers and has additive effects with immunotherapy[12]. Although the importance of this axis is clear, there are no experiments of inhibiting CXCL12/CXCR4 using inhibitor agents, either *in vivo* or *in vitro* (only clinical trials).

BLADDER CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

It is known that chemokine receptors and their ligands can affect tumor growth. In this case, bladder cancer is not an exception. Data have

shown that in bladder tumor tissues, expression of CXCR4 and CXCL12 is highly increased so it is significant that the chemokine receptor CXCR4 and its ligand CXCL12 can lead to the development of the cancer[13]. Another study shows that transcription-3 (stat3) activation can affect tumor growth and survival, while its relation with CXCR4/CXCL12 is unclear. Higher expression of CXCR4 attributes to phosphorylation of stat3. It is known that CXCR4/CXCL12 can promote invasion in bladder cancer by activating the stat3 transcriptional activity[14]. Importantly, in order to suppress the growth of tumor cells, investigating the inactivation of stat3 can be useful for the treatment of bladder cancer; however, there is no experiment to examine this idea.

KIDNEY CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

There is not enough updated data about the role of CXCR4 and its ligand CXCL12 and different ways to block this axis, upstream and downstream related molecules in kidney cancer.

LIVER CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

No study is available about the importance of CXCR4/CXCL12 and inhibitors of this axis if it plays any role in spreading the invasive cells of liver tumor tissues.

MELANOMA CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

The role of receptors CXCR4 and CXCL12 in the development of melanoma cancer is not investigated. It may be a good idea to examine the impact of this axis and its inhibitors to find an appropriate therapeutic pathway.

PANCREATIC CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

Chemokine networks have various roles in different cellular processes so they can be a suitable target for cancer cells in order to develop their growth, invasion, and proliferation particularly pancreatic cancer. High expression of CXCR4 may be an indicator of this type of cancer[15]. Pancreatic cancer cells respond to these chemokines and their ligands, therefore they can be a target for therapy. High-mobility group box 1 promotes the CXCR4 and CXCL12 interaction, promoting angiogenesis and lymphangiogenesis. Hypoxia-inducible factor 1 stimulates the CXCR4 and CXCL12 expression while promoting potential tumor growth. Novel imaging is being investigated as a probable therapy for this type of cancer[16]. Perineural invasion (PNI) is known as a possible route for metastatic spread of pancreatic cancer, although there is not enough study about it. According to a previous study[17], PNI correlates with the high expression of CXCR4. Both *in vitro* and *in vivo* PNI models were applied to investigate the function of the CXCL12/CXCR4 signaling in PNI progression and pathogenesis. Vascular Endothelial Growth Factor C (VEGF-C) and the nuclear protein Ki-67 are two important biomarkers, through which CXCR4 initiates metastatic behavior in pancreatic cancer. Therefore, angiogenesis inhibitors will continue to be effective agents in treating pancreatic cancer[18]. Another study reveals that the CXCR4/CXCL12 axis has drug resistance, but a combination of cytotoxic drugs can be effective on tumor growth[19]. The important role of CXCR4/CXCL12 in pancreatic cancer is known, in order to block this axis; there are also some ideas that may be effective in the therapy of this cancer. Downregulating the expression of Hypoxia-inducible factor 1, Novel imaging, suppressing PNI, and also downregulating the expression of VEGF-C and Ki-67 are several of these therapeutic pathways.

THYROID CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

Thyroid cancer is not an exception from the roles of the CXCR4/CXCL12 in developing and spreading metastasis. MiR-455-5p is an RNA that can target the CXCR4 and its ligand CXCL12 and prevent thyroid tumor growth but circPVT1 (a circular RNA derived from one exon of the PVT1 gene and flanks two long introns), actually promotes invasion, metastasis, and proliferation of tumor tissues[20]. Overexpression of CXCR4 in K1 cell lines of thyroid can increase the phosphorylation of protein kinase B (PKB or AKT) and a type of serine/threonine-protein kinase (ERK) and afterward induce the expression of matrix metalloproteinase-2 (MMP-2)[21]. Thus, in order to block the CXCR4, we can examine some agents whether they can be therapy. Increment in the expression of MIR-455-5p and downregulation of expression of circPVT1 and also suppressing the phosphorylation of AKT and ERK are the subjects that are worth investigation.

COLON CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

The CXCR4-CXCL12 mediates metastasis formation and its expression is an independent prognostic factor in colon cancer[22]. Liver metastasis is the major obstacle to prolonging the survival of colon cancer patients. Studies show that Low-Molecular-Weight Heparin (LMWH) disrupts the interaction of CXCR4 and CXCL12 and prevents the seeding and subsequent growth of hepatic metastases of colon cancer cells by downregulating of expression of CXCR4 and CXCL12. The experiment that supports this idea was done *in vivo*[23]. Another study determines that elevation of Dipeptidyl peptidase-4 (CD26) terminates the activity of CXCR4s ligand, CXCL12. 5-Fluorouracil, oxaliplatin, and SN-38 (the active metabolite of irinotecan), as well as cisplatin, methotrexate, and vinblastine, cause decreases in cell-surface CXCR4 and concomitant increases in CD26[24]. A key role of CXCR4-CXCL12 is the Wnt/β-catenin pathway. The canonical Wnt pathway (Wnt/β-catenin pathway) is the Wnt pathway that causes an accumulation of β-catenin in the cytoplasm and its eventual translocation into the nucleus to act as a transcriptional coactivator of transcription factors that belong to the TCF/LEF (T cell factor/lymphoid enhancer factor) family that is a group of transcription factors which bind to DNA. So, blocking this pathway can be a new target to investigate to introduce other inhibitor agents and treat colon cancer[25]. Although it is known that the major hindrance for therapy of colon cancer is liver metastasis, there are not satisfying investigations on it. Moreover, a blocker of liver metastasis can also be an inhibitor of colon tumor growth.

RECTAL CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

Distant recurrence is the major cause of mortality in rectal cancer patients with preoperative chemo radiotherapy (CRT). A noticeable percent of patients shows high levels of CXCR4 and its ligand CXCL12 and patients who developed distant recurrence have a higher rate of expression of these chemokines. CXCR4 and CXCL12 expression determined using immunohistochemistry was observed not only in cancerous cells but also in stromal cells[26]. Researches reveal that with genes and the expression of these chemokines, rectal cancer can be diagnosed better but there were not found investigations on their inhibitor agents and blockers.

ENDOMETRIAL CANCER AND INHIBI TOR AGENTS OF CXCR4/CXCL12

As it is known, chemokines have important roles in the progression of cancers. In patients who suffer from endometrial cancer, the expression of CXCR4 was predominant. CXCR4 is related to cancer differentiation but not CXCL12. Also, endometrial cell cancers can generate diffuse metastases in the peritoneum, lung, and liver of mice. Fortunately, with anti-CXCR4 monoclonal antibody and neutralization of it, metastasis will be reduced[27]. Moreover, CXCL12 not only induces invasion and cell proliferation but also reduces apoptosis and CXCR4 will silence all these functions[28]. Although, there is a lot of information about the CXCR4-CXCL12 axis, the inhibitors agents and blockers of these chemokines are not investigated. Using drugs such as methotrexate and vinblastine that are effective on colon cancer may be effective on endometrial cancer too. This case has the chance to be examined.

LEUKEMIA AND INHIBITOR AGENTS OF CXCR4/CXCL12

Chemokine control homing and trafficking of leukocytes in the bone marrow and lymphoid organs. In particular, CXCL12 and its receptors CXCR4/CXCR7 control the homeostasis of multiple organs and systems. Their overexpression is linked to tumor development and causes drug resistance of tumor tissues[29]. Leukemia is defined as an aggressive disorder that contains immature malignant cells in the bone marrow. As it is known, CXCR4 and its ligand CXCL12 are involved in this type of cancer. Studies demonstrate that targeting these chemokines in both leukemic and stromal cells and disrupting their interaction with CXCR4 and CXCL12 can effectively treat leukemia[30]. Another study shows that the high expression of CXCR4 can be a prognostic factor and the CXCR4-CXCL12 axis may be inhibited by some agents such as peptides, small molecules, and monoclonal antibodies[31]. Deletion of CXCR4 in tumor cells suppresses tumor growth; in contrast, CXCL12 does not have the role of its receptor on the development of leukemia. Thus, in *in vivo* experiments, overexpression of CXCR4 is essential for leukemia independent of CXCL12 stimulation[32]. Oroxylin A and Adriamycin are two agents that can be used to inhibit the CXCR4-CXCL12 axis. It is demonstrated that CXCL12 enhances the resistance of the first human immortalized myelogenous leukemia cell line (K562 CELLS) to Adriamycin by increasing the expression of

CXCR4, up-regulating the downstream phosphatidylinositol 3-kinase (PI3K)/Akt pathway (an intracellular signaling pathway important in regulating the cell cycle), and promoting translocation of NF-κB (a family of heterodimers and homodimers which are generated from subunits encoded by five genes) dimers into the nucleus and subsequently decreasing the expression of apoptosis-related proteins in K562 cells. This resistance will be partially reversed by CXCR4 siRNA transfection. Experiments on both Oroxylin A and Adriamycin, *in vitro* and *in vivo* revealed that they serve as leukemia treatment by increasing apoptosis in leukemic cells and decreasing the expression of CXCR4[33]. Another study shows that the combination of inhibitors of tyrosine kinase with anti-CXCR4 antagonists may lead to the treatment of leukemia[34]. It is investigated that upregulating Interleukin-8 (a chemokine produced by macrophages and other cell types such as epithelial cells, airway smooth muscle cells, and endothelial cells) promotes the bone marrow microenvironment and the CXCR4-CXCL12 axis to act in the pathogenesis of leukemia[35]. A study discusses the Wogonin potentials to down-regulate the expression of CXCR4 and CXCR7 and increase the sensitivity of cells[36]. Therefore, the impact of CXCR4 on the development of leukemia is proved and some agents are investigated to decrease the expression of this chemokine receptor such as Oroxylin A, Adriamycin, Wogonin. Moreover, examining the inhibitors of tyrosine kinases and the agents which downregulate Interleukin-8, could lead us to a new and effective therapeutic pathway.

APPENDIX CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

There is no investigation into this type of cancer. With all information that exists, examining the roles of CXCR4-CXCL12 on developing cancer and its inhibitor agents or the drugs that respond appropriately to reduce tumor growth in other cancer types may demonstrate treatment of appendix cancer, too.

BONE CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

The CXCR4-CXCL12 sensitizes neurons and activates astrocytes and microglia, so it is contributed to the development and maintenance of bone cancer[37]. As it is clear, the importance of these chemokine is demonstrated. Investigating other effective agents to inhibit this axis may lead us to treatment for bone cancer.

LYMPHOMA AND INHIBITOR AGENTS OF CXCR4/CXCL12

Lymphoma is a common cancer and CXCL12/CXCR4 expression is associated with disease progression. CXCL12/CXCR4 axis plays an essential role in the occurrence and development of T-cell lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia (T-LBL/ALL). There may be other factors that play different roles in the progress of tumor growth[38]. Tumor cells have resistance to treatment and decrement of chemokine factors, so combining CXCR4 inhibitors and cytotoxic agents may be a solution to this problem[39]. The experiments, *in vitro* and *in vivo*, on this cancer, restrict to investigate both increment and decrement of CXCR4 and CXCL12. It is known that the increment of these chemokine at least slows down the tumor growth. There is not any investigation on inhibitor agents of CXCR4-CXCL12, but it is so potential to be examined.

EYE CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

Eye cancer is not common, but this will not make it unimportant. There is no research about the effect of the CXCR4-CXCL12 axis on this type of cancer. It is probable that this axis plays an essential role in the development of eye cancer just like other types. If the impact becomes clear, examining agents such as Adriamycin and Wogonin may cause a new treatment for this cancer.

ANAL CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

Also, this type of cancer is not investigated from the aspect of the CXCR4-CXCL12 role. The impact of this axis is wide and known, so investigation of such an important factor may be a key to new and effective treatment, not only for anal cancer but also for other types of cancers.

BILE DUCT CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

This cancer is not so common and the researches on it are very restricted. The impact of the CXCR4 and its ligand CXCL12 is not investigated yet.

BRAIN CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

Neurons proliferation is nearly zero unless in rare conditions the brain needs to recover itself, so this type of cancer is not that common to be investigated from the aspect of chemokines like CXCR4, but yet it can show the researchers different and new therapeutic pathways.

CERVICAL CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

The chemokine CXCL12 is overexpressed and has an essential role in tumor growth and spread in cervical cancer. Researches show that CXCL16 and CXCL6 participate in the development of cancer in correlation with CXCR4 and CXCL12. These 4 proteins promote the progression of cervical cancer. Each of these chemokines led to different metastasis. In Kaplan-Meier analysis, patients with high CXCR6 expression had significantly shorter overall survival than did those with low CXCR6 expression. Moreover, CXCR6, in addition to CXCR4 and CXCL12, may be useful as a biomarker and a valuable prognostic factor for cervical cancer[40]. This type of cancer is so common that is the fourth leading cause of cancer death in women. Cervical cancer is not curable with surgery, radiotherapy, or cisplatin chemotherapy. The CXCL12/CXCR4 chemokine pathway is ubiquitously expressed in many normal tissues and cancers, including cervical cancer. New studies show that the combination of cisplatin and the CXCR4 inhibitor Plerixafor (AMD3100) can improve the responses to suppress tumor growth without increment inside effects[41]. Thus, the CXCR4-CXCL12 chemokine pathway in the development of this cancer is known. Also, there are two more chemokines, CXCL6 and CXCL16 that correlate with the progression of cervical cancer. The old therapeutic pathways do not respond appropriately, so experiments must go on about new inhibitor agents of CXCR4. A combination of drugs such as tamoxifen and tranilast, in addition to cisplatin and AMD3100, may lead us to a new and effective treatment of this cancer.

ESOPHAGEAL CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

This cancer is one of the most common cancers of the digestive tract. The most important obstacle for curing this type of cancer is its wide metastasis. While clinical evidence suggested that continuous up-regulation of CXCL12/CXCR4 was significantly associated with poor prognosis in patients with esophageal cancer, the role and mechanism of CXCL12/CXCR4 in the invasion and metastasis of esophageal cancer has not been reported by far. Studies show that esophageal cancer stem cells produce a high amount of both CXCR4 and CXCL12. The ability of esophageal cancer stem cells to spread and metastasize could be inhibited by blockage of CXCR4 with inhibitors or shRNA approaches both *in vivo* and *in vitro* studies. These chemokines play their role in the development of cancer through the ERK1/2 pathway[42]. An experiment supports the previous information. Eighty-six patients with submucosal ESCC underwent curative resection from 1985 to 2002. Immunohistochemical staining of CXCL12, CXCR4, and CD34 (a trans membrane phosphoglycoprotein protein encoded by the CD34 gene in humans, mice, rats, and other species) was performed with primary tumors, and staining of cytokeratin was carried out with dissected lymph nodes. Microvessel density (MVD) was calculated from CD34 expression, and lymph node micro metastasis (LMM) was detected by cytokeratin staining[43]. Thus, the impact of CXCR4-CXCL12 is clear on this type of cancer. In order to block this axis, a new pathway may lead us to the cure of it. The ERK1/2 has the potential to be investigated for an effective treatment.

SKIN CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

Sunlight causes skin cancer by suppressing anti-tumor immunity. It alters mast cells migration via the CXCR4-CXCL12 chemokine pathway. AMD3100 is an inhibitor agent for this pathway that prevents both UV radiation-induced immune suppression and skin cancer. AMD3100 completely prevents the outgrowth of latent tumors that occurs once UV irradiation is ceased. This protection correlates with a decrement of mast cell migration[44].

OVARIAN CANCER AND INHIBITOR AGENTS OF CXCR4/CXCL12

A study reveals that there is a close correlation exists between the chemokine axis CXCL12-CXCR4 and the pathogenesis, metastasis of epithelial ovarian cancer. This axis is important in the case of this cancer; therefore, it can be a target in order to cure ovarian cancer. This study originates from SKOV3 transfected with plasmids

that was cultured *in vitro*. Methyl thiazolyl tetrazolium (MTT) was used to analyze the effects of different concentrations of CXCL12 on the proliferation, migration, and invasion of three cell lines and examine the inhibition of neutralizing CXCR4 antibody or antagonist AMD3100[45]. An *in vitro* study shows that CXCL12 promotes proliferation, migration, invasion of ovarian cancer cell line CAOV3, and up-regulates integrin beta1 and VEGF-C expression, and these effects are strongly inhibited by neutralizing CXCR4 antibody, thus the CXCR-CXCL12 chemokine pathway plays an important role in the development of cancer[46]. As other cancers, these chemokines can be a prognostic clue in ovarian cancer. A study supports that AMD3100 can interrupt the CXCR4-CXCL12 chemokine pathway and in this way, cisplatin can be also effective[47]. Another study suggests that Lysophosphatidic Acid (LPA), which possesses growth factor-like functions, is a major regulatory factor in the peritoneal metastasis of ovarian cancer. LPA stimulates the expression of numerous genes that are associated with angiogenesis and metastasis. LPA promotes invasiveness of ovarian cancer by up regulating CXCL12-CXCR4 axis expression[48]. In ovarian cancer, it is known that CXCL12 induces epithelial-mesenchymal transition (EMT) phenotypes including spindle-like cell morphology, podia, and stress fiber formation, a decrease in E-cadherin expression, and increases in mesenchymal N-cadherin and vimentin expressions[49]. Cancer-Associated Fibroblasts (CAFs) activate the Wnt/β-catenin pathway in ovarian cancer cells via CXCL12/CXCR4 axis and then induce EMT and cisplatin resistance[50]. Thus, AMD3100 can be a therapy for ovarian cancer. Moreover, using some factors that lead to an increment in E-cadherin and a decrement in mesenchymal N-cadherin and vimentin can also be a therapeutic pathway.

CONCLUSIONS

We came to the conclusion that one of the most promising pathways to cancer therapy is to block the CXCR4-CXCL12 chemokine axis. In prostate cancer, investigations represent that ALCAR, ASA, and beta-blockers can inhibit this axis. In breast cancer, using both tranilast and tamoxifen can cause a synergic effect which is practical and appropriate therapy. Also, in breast cancer, the FOXP3 will be decreased by overexpression of CXCR4 and the p21 get increased, thus we can examine the factors that lead to an increment in FOXP3 and a decrement in p21. In bladder cancer, the amount of phosphorylation of stat3 will be increased and help the tumor growth, so we can suggest the drugs which are effective like tranilast, tamoxifen, ALCAR, ASA, beta-blockers, and also, a factor that decreases the phosphorylation of stat3. In pancreatic cancer, we can use cytotoxic drugs and also, examining the factors which cause decrement in VEGF-C, HIF1, and ki-67 can be a new and probable therapeutic pathway. In thyroid cancer, the use of agents that suppress the phosphorylation of the AKT/ERK pathway and the factors, which increase MIR-455-5P and decrease circPVT1, is a promising subject that is worth investigating. In colon cancer, there are some drugs that have their effects to block the chemokine pathway are known such as 5-fluorouracil, oxaliplatin, SN-38, cisplatin, methotrexate, and vinblastine. Moreover, the agents which increase the expression of CD26 (CD26 neutralize the impact of CXCR4) and decrease the expression of beta-catenin, can lead us to new cancer therapy. There are different effective agents available to treat leukemia. Oroxylin A and adriamycin which increase apoptosis and decrease the expression of CXCR4 and wogonin, are the drugs that are used to suppress tumor growth. Also, the combination of tyrosine kinases and anti-CXCR4 is a probable therapeutic pathway while we can investigate the factors that decrease the amount of interleukin-8, as in the effect of overexpression of CXCR4, this cytoplasmic chemokine gets increased. In esophageal cancer, there are not any introduced agents, but we can block the axis by suppressing the phosphorylation of the ERK1/2 pathway in addition to using other drugs and inhibitor agents which are effective in cancer therapy. In order to treat cervical and skin cancer, AMD3100 is an appropriate agent that can be used. In ovarian cancer, we can use the drugs that we mentioned in addition to AMD3100. For other cancers, there was no investigation on inhibitor agents of CXCR4-CXCL12, so we can examine the other drugs and realize their effects.

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A. Ghanbari was responsible for overall supervision. I. Rashidi, M. Pazhouhi, C. Jalili revised the manuscript. N. Akhshi wrote the manuscript. All authors performed editing and approved the final version of this paper.

Conflict of Interest:
The authors declare no conflict of interest.

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