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CXCL12 as a Metastasis Inducer Chemokine of Breast Cancer

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Abstract

Breast cancer is a worrying challenge nowadays because it represents the most common type of cancer that has been diagnosed in women. Breast cancer deaths mainly result from metastasis instead of primary tumor. C-X-C motif chemokine ligand 12 is a chemokine that belongs to CXC group and has chemotaxis property that makes it able to migrate immune cells. Based on several studies, C-X-C motif chemokine ligand 12 and its receptor C-X-C chemokine receptor type 4 could promote breast cancer metastasis. Breast cancer metastasis is a multistep process in which the C-X-C motif chemokine ligand 12 / C-X-C chemokine receptor type 4 axis has been shown to play a key role in each of these steps such as local invasion, survival, angiogenesis, trafficking to another organ, and adaption to a new microenvironment. Many types of research have proved the crucial role of C-X-C motif chemokine ligand 12 / C-X-C chemokine receptor type 4 axis in breast cancer metastasis into the liver, bone, lung, and brain. Both in vitro and in vivo studies have provided significant results associated with the reduction of breast cancer metastasis in cell lines when they were treated with antibodies against C-X-C chemokine receptor type 4. Additionally, C-X-C motif chemokine ligand 12 / C-X-C chemokine receptor type 4 axis has provided the ability for cancer cells to resist chemotherapy, radiotherapy, and endocrine therapy. This review aims to discuss the investigations about the role of these peptides that will help in the management of a more specific and effective therapy.

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1. Introduction

Chemokines are large parts of small cytokines that have 7 to 15 kDa molecular weight. Chemokines are proteins that can control and regulate all immune cells' movement [1]. Chemokines differ from other types of cytokines in their chemotaxis property. Structurally, chemokines can be categorized according to the sequence of their primary amino acids and the position of cysteine residues within the protein structure [2]. There are four subfamilies of chemokines C, CC, CXC, and CX3C [3,4]. C chemokines contain only two cysteines in their structure, one near the N-terminal and the other located on the peptide chain. CC chemokines have two adjacent cysteines nearby the N-terminal. CXC and CX3C chemokines have two cysteines separated by one and three amino acids correspondingly [5]. Major chemokines are produced by a variety of different cells; however, some chemokines are produced only by specific cell type. Some chemokines are expressed constitutively while others need to be induced [6]. Both lymphoid and nonlymphoid cells can produce chemokines and these chemokines have number of biological roles (figure 1). Some chemokines are induced as a response to inflammation and are known as inflammatory chemokines. Immune cells start producing inflammatory chemokines to direct additional immune cells into the site where infection, injury, or inflammation occurs [7]. Other chemokines are found in lymphoid organs such as bone marrow, spleen, thymus, lymph nodes and are called homeostatic chemokines. Homeostatic chemokines are responsible for developing lymphoid organs and lymphoid trafficking. Lymphoid trafficking is a process in which lymphocytes migrate from their origin sites to another site [9]. Some chemokines also participate in wound healing which is a complicated

process by which damaged tissue integrity is restarted. Wound healing process consists of four steps: hemostasis, inflammation, proliferation, and remodeling [10]. Another biological process that can occur by chemokines is angiogenesis, chemokines that induce angiogenesis are termed as angiogenic chemokines. Angiogenesis is a process that involves the formation of new blood vessels from the existing vasculature. Angiogenesis can occur in healthy and unhealthy organs. Due to the rapid proliferation of tumor cells, angiogenesis is considered an essential rate-limiting step in tumor progression [11]. Chemokines play a major role in controlling angiogenesis [12]. Additionally, chemokines contribute to the recruitment of cells. Cell recruitment refers to the process in which the cells are controlled to perform different biological activities such as proliferation, adhesion, and migration [13]. Furthermore, chemokines are contributors to the development of T cells. T cells are a type of immune cells that have a strong response to chemokines in migration toward injured tissues. T helper (Th) cells are divided into two groups according to the type of chemokines that induce, Th1 and Th2 [14]. Chemokines throughout the migration of cancer cells to other distant organs have played an essential role in the metastasis of tumors.

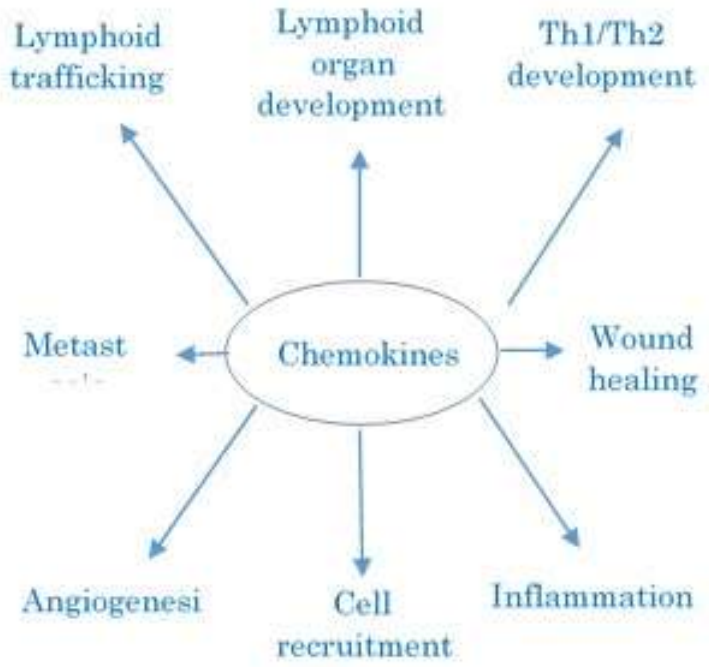

Figure 1. Biological roles of chemokines [8].

2. Aim of study

This study aims to summarize recent findings about the role of CXCL12 chemokine and its receptor CXCR4 in developing breast cancer metastasis.

3. Chemokine's receptors

The biological effect occurs only when the chemokines bind to their receptors. Receptors of chemokines belong to heterotrimeric G proteins and are known as G protein-coupled receptors (GPCRs). A total of 18 receptors have been discovered yet and these receptors can be activated by specific chemokine groups as the following: C (XCR1), CC (CCR1, CCR2, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10), CXC (CXCR1, CXCR2, CXCR3, CXCR4, CXCR5, CXCR6), and CX3C (CX3CR1) [15]. In an inactive state, the chemokine receptor is attached to the heterotrimeric G protein (Guanosine triphosphate (GTP) binding protein) that consists of α, β, and γ subunits. When chemokine binds to the receptor, it causes a conformational change in the heterotrimeric G proteins linked with the receptor. This conformational change results in a separation of α from βγ subunits. The guanosine diphosphate (GDP) molecule which is attached to the alpha subunit converts to GTP after phosphorylation by other external GTP molecules [16-19]. Figure 2 clarifies the process of converting the chemokine

receptor from an inactive form to active form. There is strong evidence that alpha-GTP and beta-gamma subunits act as second messengers in receptor signaling that lead to biological effects [20]. Numerous types of cancer cells express receptors for chemokines These receptors promote growth and motile property which is important for the metastasis of cancer.

4. CXCL12

CXCL12 (also known as a stromal derived factor–1) is a homeostatic chemokine belonging to the CXC group. CXCL12 is widely produced by different immune cells and acts as a strong chemoattractant for both mature and immature hematopoietic cells [21]. CXCL12 is widely known for its role in homing hematopoietic stem cells to the bone marrow. CXCL12 was identified for the first time when it was extracted from murine stromal cell lines, it has acted as a growth-stimulating factor for B cell precursor clone [22,23]. Structurally, there are six isoforms of CXCL12 due to alternative mRNA splicing (CXCL12α, CXCL12β, CXCL12γ, CXCL12δ, CXCL12ε, and CXCL12φ) [24]. CXCL12α and CXCL12β are the highest present isoforms in the tissues and bone marrow.

Oppositely to majority of the other CXC group chemokines that were found on chromosome 10q11.1, CXCL12 was found on chromosome 4q12- q21 [25]. CXCR7 and CXCR4 are the receptors in which CXCL12 bind. Both receptors are G protein coupled receptors (GPCRs) [26]. By comparation, CXCR4 has more biological roles and is considered more important than CXCR7. It was shown that CXCL12 has been expressed by several types of cells including hematopoietic cells such as leukocytes and non-hematopoietic cells such as epithelia and stromal cells. In human and mouse, CXCR4 has shown similarity above 85% in the structure [27]. It was found that CXCL12-CXCR4 signaling contributes in many biological processes [28].

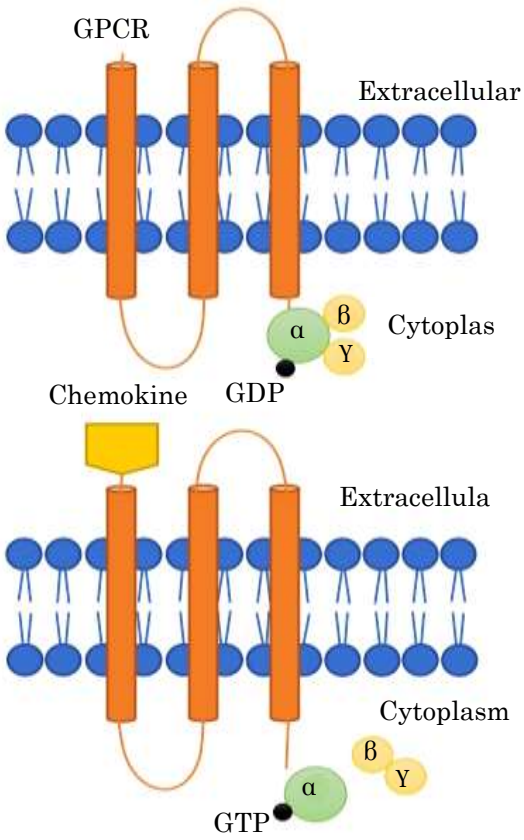

Figure 2. G protein– coupled receptor.
GPCR = G Protein Coupled Receptor.
GDP = Guanosine diphosphate.
GTP = Guanosine triphosphate

5. Breast cancer metastasis

Globally, breast cancer is most prevalent malignant tumor and the second cancer related death among women [29,30]. About 90% of total deaths related to breast cancer caused by metastatic breast cancer rather than primary tumors [31]. Metastasis process can be defined as a biological phenomenon that occurs within some types of cancers, in which the primary tumor cells migrate throughout the blood vessels to other distant sites or organs. For breast cancer, there are favorable organs in which the primary tumor cells migrate to them. According to a Surveillance, Epidemiology, and End Results-based study, 30–60% of metastatic breast cancer patients have metastases in the bone, 21–32% have metastases in the lung, 15– 32% have metastases in the liver, and 4–10% have metastases in the brain. Researches have found that the favorable metastatic locations are highly affected by the subtype of breast

cancer [32]. Breast cancer is a highly diverse disease and has been categorized by many systems and according to different variables. Based on the immunohistochemical expression of hormone receptors, breast cancer subtypes are grouped into four categories: luminal A (oestrogen receptor positive, progesterone receptor positive, and human epidermal growth factor receptor 2 (HER2) negative), luminal B (oestrogen receptor positive, progesterone receptor positive, and human epidermal growth factor receptor 2 (HER2) positive), HER2-positive (oestrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 (HER2) positive), and triple negative breast cancer (all the hormone receptors are negative) [33]. Each subtype has a special mechanism and ability for proliferation and metastasis [34,35]. Recent studies have considered that breast cancer is a metabolic disease as well as a genetic disease. Breast cancer metastasis is multistep process, each of these steps is important and occurs in arranged way. Firstly, local invasion takes place when primary tumor cells overcome the linkages with their surrounding and move away from the primary tumor. Second step is the invasion of detached tumor cells, this step is achieved when the cancer cells detach and enter blood vessels. After survival through circulation, circulating cancer cells escape from the blood vessels and migrate toward the targeted organ [36-38]. Cancer cells tend to promote angiogenesis due to the increasing requirement for more oxygen and nutrients. Several theories have explained the relationship between the microenvironment and cancer metastasis but "seed and soil" theory has been the most acceptable yet. The "seed" refers to certain tumor cells with the ability to spread, and the "soil" is any organ or tissue making up an appropriate environment for the growth of the seeds [39,40]. Adaption of cancer cells to a new microenvironment is very important which causes favorable sites to metastasis. It has been found that with the same amount of blood and oxygen for two microenvironments, the favorable metastasis site in one was more than in the other. It can be concluded that cancer metastasis can occurs only if there is a compatibility between tumor cells and the new microenvironment.

6. CXCL12/CXCR4 in breast cancer metastasis

CXCL12 and CXCR4 are expressed in some of the tissue's cells such as bone marrow, liver, lung, and lymphoid nodes. Because these organs have been determined as the most favorable organs for breast cancer metastasis, it has regraded that CXCL12 and CXCR4 may be contributed to the spreading of breast tumor cells into these organs [41,42]. Moreover, breast cancer cells have shown high expression of CXCR4, this can be considered additional evidence of the implication of CXCL12 and CXCR4 in breast cancer metastasis [43]. It was reported that upregulating of CXCR4 in breast cancer cells causes to move these cells toward the sites where CXCL12 ligand is produced [44]. On the other hand, the effect of CXCR4 down-regulation was investigated by being treated with saikosaponin A (SSA) for triple negative breast cancer in vivo and in vitro. Saikosaponin resulted in a decrease of CXCR4 expression in the breast cancer cells, this has led to a reduction of migration and invasion of these cells and therefore, inhibit metastasis [45]. Figure 3 explains the role of CXCL12 and CXCR4 in each step of breast cancer metastasis into bone, liver, and lung.

7. Liver metastasis

liver is considering as a one of the most favorable organs for breast cancer metastasis. CXCL12 and CXCR4 have shown the ability to enhance breast cancer metastasis to liver in vitro and in vivo. Human breast cancer cell lines (MDA-MB-231 and MDA-MB-468) were used in the investigation. The breast cancer cells were treated with different concentrations of CXCL12 (0, 25, 50, and 100 ng/ml); therefore, the migration and adhesion of these cells were determined using transwell migration assay and static adhesion assay. Both migration rate and adhesion of breast cancer cells have been induced, as the concentration ofCXCL12 increased. In vivo, these breast cancer cells have been injected inside rats to investigate their effect in liver metastasis. It was found that injected rats have liver metastasis more than non-injected rats and this indicates the crucial role of CXCL12 and CXCR4 in developing breast cancer liver metastasis [46]. Other study has confirmed CXCL12 and CXCR4 contribution in breast cancer metastasis into liver throughout determination number of chemokine receptors expression in breast cancer patients. Expression of CX3CR1, CXCR4, CCR7, and CCR6 has determined in 142 patients using immunohistochemical staining All the patients were without any metastasis at the time of diagnosis. Results have showed that CXCR4 expression was higher than other receptors in the patients whose develop liver metastasis later [47].

8. Bone metastasis

Bone metastasis has high possibility in breast cancer because bone is a CXCL12 rich microenvironment which attracts the primary tumor cells of breast cancer. Role of CXCL12 and CXCR4 in bone metastasis of breast cancer has been investigated in vivo and in vitro. Human breast cancer cells of CXCR4+ and fibroblasts have co-implanted in a mouse. Fibroblasts act as a source of CXCL12- γ secretion. Representative bioluminescence images have shown the development of metastasis to bone by the effect of CXCL12 and CXCR4. The role of CXCL12-γ in promoting angiogenesis was investigated human umbilical vein endothelial cells (HUVECs) and 293T cells have been co-cultured. Human umbilical vein endothelial cells represent the part that expressing CXCR4 while 293T cells represent the provider of ligand through secretion CXCL12- γ. The results of culture these cells were stimulation of endothelial tube formation. [48]. Another study examined the relation between CXCR4 and breast cancer bone metastasis in vivo. A total of 191 primary breast cancer patients were selected to follow up them for a total of 5 years. CXCR4 expression was examined using immunohistochemical stanning. Expression of CXCR4 was positive in 107 (56%) of the total patients and was negative in 84 (44%). During the following up of metastasis status for the patients, it was found that patients of CXCR4+ have higher bone metastasis percent (13.1%) than these of CXCR4- (2.4%) [49]. Furthermore, the effect of CXCR4 blocking by treatment was investigated when several mice had been injected by human breast cancer cell lines (cancer cells were colonized from bone and liver). After that, these mice were treated with CTCE-9908 (Chemokine Therapeutics, Vancouver, BC, Canada), a peptide similar to CXCL12 interacts competitively to CXCR4. Bioluminescencent imaging has shown that blocking of CXCR4 results in bone metastasis reduction compared to mice without treatment by CTCE-9908 which have developed bone metastasis after few weeks [50]. Moreover, thymoquinone (TQ) has been investigated in reducing breast cancer metastasis to bone throughout inhibition of CXCR4 signaling axis. Firstly, it has determined the effect of thymoquinone in reduce CXCR4 expression. BT-549 and MDA-MB-231 human triple negative breast cancer cells were used. Treating these cells with 25, 50, 100µl of thymoquinone has shown reduction of CXCR4 compared to the control. Moreover, CXCR4 reduction on bone metastasis was examined MDA-MB-231 was injected in mice followed by treating with thymoquinone. Compared to the control (untreated mouse), treated mouse has shown less metastasis to bone [51]. Collectively, these in vivo and in vitro results indicate the important role of CXCL12/CXCR4 in breast cancer bone metastasis development.

9. Other organs

In addition to liver and bone, there are other sites that can be targets for breast cancer metastasis as secondary sites. Lung and brain are the examples of secondary organs in which breast tumor can be spread. Lung metastasis of breast cancer mainly diagnosed in triple negative subtype, about 40% of triple negative breast cancer patients develop lung metastasis while 20% of non-triple negative patients develop lung metastasis [52]. Assumption of CXCL12 and CXCR4 participation in stimulating breast cancer lung metastasis has been supported by a study in which MCF-7 human breast cancer cells of CXCR+ were used and implanted in mice. After few weeks, images of lungs section showed a metastasis which indicates the contributing of CXC12- CXCR4 signaling in lung metastasis [53]. Other study investigated the effect of treated triple negative breast cancer with everolimus in vivo. Everolimus is a type of targeted drug known as mTOR blocker. mTOR is a type of protein called protein kinase. Everolimus has used to inhibition HER3/Akt/mTOR pathway that increases CXCR4 expression. By comparison, it was found that treated rats have less count of lung metastasis nodules than untreated [54]. With regard to brain, CXCL12 and its receptor CXCR4 play an important role in the migration of primary breast cancer cells into brain and promote a number of processes such as angiogenesis, proliferation, and cell-cell adhesion between the primary breast cancer cells and cells of the new microenvironment [55]. In addition, breast cancer cells of high CXCR4 expression have treated with certain antibodies which caused blocking to these receptors and prevent the CXCL12-CXCR4 interaction in vivo. Results had shown decreasing of metastasis into mice brain [56].

10.CXCL12/CXCR4 in therapy resistance

CXCL12/CXCR4 axis is responsible for the resistance of breast cancer cells against chemotherapy. CXCL12-CXCR4 interaction increases the adhesion of breast cancer cells to fibrotic stroma and this will protect these breast cancer cells from killed by

chemotherapy [57]. It was demonstrated that pancreatic cancer cell lines that express CXCR4 and low express CXCL12 have a certain response to chemotherapeutic. This response has reduced after co-treatment with exogenous CXCL12. This indicates the role of CXCL12/CXCR4 axis in chemotherapeutic resistance [58]. Based on studies, CXCL12 is involved in the stimulation of autophagy in cancer cells after radiotherapy, autophagy is a process that promotes cancer cell growth and recovery [60]. Autophagy results in a reduction of radiotherapy effectiveness. The effect of CXCL12 in decreasing effeteness of doxorubicin against cancer cells, MyLa cells (mycosis fungoides cell line) were investigated. Mycosis fungoides is a type of skin cancer. Inhibition of CXCL12/CXCR4 axis has led to induce the apoptosis of MyLa cells and reduction cells motility. This was due to increasing the response of cancer cells to the doxorubicin effect [61].

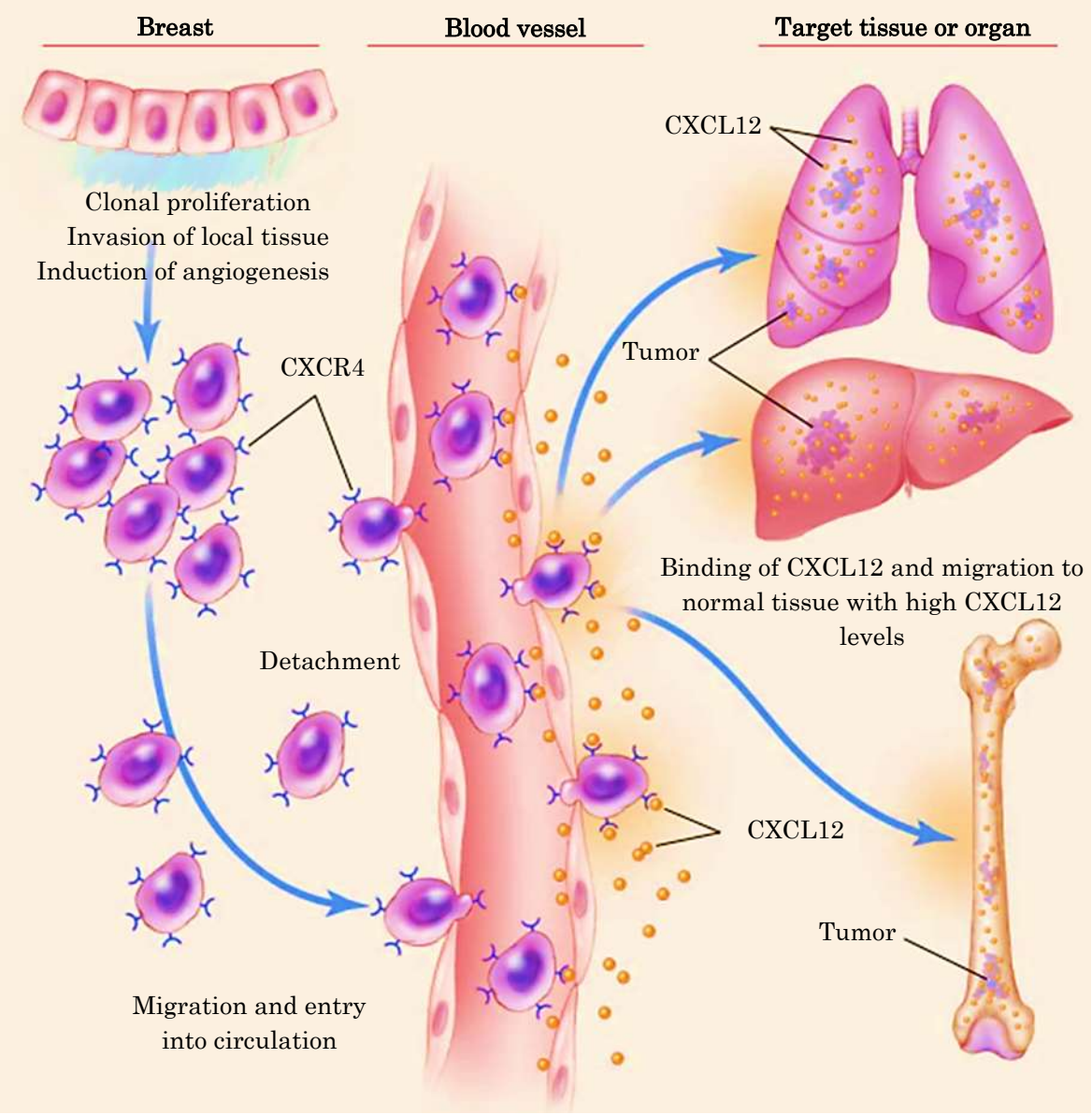

Figure 3. CXCL12/CXCR4 in breast cancer metastasis [59]. Firstly, detachment of breast cancer cells from primary tumor by CXCL12 activity takes place. Secondly, these detachment cancer cells enter the blood vessels and start circulation. Therefore, these circulating cancer cells of CXCR4+ move toward the organs which produce high amount of CXCL12. CXCL12 also participates in proliferation of primary tumor cells and stimulating angiogenesis.

11. Conclusions

It was clear that CXCL12/CXCR4 axis plays a key role in the promotion of breast cancer metastasis. Due to the role of CXCL12 and its receptor CXCR4 in controlling the migration of immune cells toward the damaged tissue, the hypothesis of CXCL12and CXCR4 may contribute to the migration of breast cancer cells to other sites was developed. Both in vitro and in vivo studies have provided results which considered as evidence to prove the important role of CXC12/CXCR4 in breast cancer metastasis. By using human breast cancer cell lines with mice in experimental research, results have shown that the most favorable organs for breast cancer metastasis were bone, liver, and lung. This is because the microenvironment of these organs is rich with CXCL12. CXCL12/CXCR4 signaling has been shown to be a strong promoter for several processes involved in breast cancer metastasis; such as local invasion, angiogenesis, proliferation, and tumor growth. Furthermore, CXCL12 and CXCR4 have shown a negative effect on treatment; CXCL12/CXCR4 axis has reduced the response of cancer cells toward chemotherapy, radiotherapy, and endocrine therapy. Finally, continuous study of chemokines, their receptors, and the role them in cancer metastasis generally will increase the understanding of metastasis. This will lead to making more specific diagnosis for cancer metastasis and then more effective treatment.

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Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript. In addition, the ethical issues, including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been completely observed by the authors.

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