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The Role of Interleukin-8 and Its Mechanism in Patients with Breast Cancer: Its Relation with Oxidative Stress and Estrogen Receptor

Robab Sheikhpour[1,*]

[1]Hematology and Oncology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[*]*Corresponding author*: Robab Sheikhpour, Hematology and Oncology Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran. Tel: +98-9131522462, E-mail: r.sheikhpour@yahoo.com

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Abstract

Context: Breast cancer is one of the leading causes of death among women all over the world. Prognostic markers can be used for patient survival. Likewise, these biomarkers are able to generate main information related to clinical manner of breast gland tumors. Interleukin-8 (IL-8) is a chemotactic cytokines caused initiation of an inflammatory response.

Evidence Acquisition: We performed a computerized search in Medline/PubMed databases with key words: IL-8, breast cancer, and oxidative stress.

Results: IL-8 secretion motivates the expression of adhesion molecule, including fibronectin in human inflammatory breast cancer cells. IL-8 activates PI3K/Akt pathway, which in turn activates NF-κB resulted up-regulation of integrin β3 expression and increases the invasion of breast cancer cells. Therefore, it seems that IL-8/PI3K/Akt/NF-κB/integrin β3 axis may be used for therapeutic intervention of breast cancer with metastasis status. NF-κB plays an important role in IL-8 gene transcription via several signals, such as LPS, TNF-alpha, and oxidative stress. Oxidative stress caused angiogenic factor production, such as vascular endothelial growth factor and IL-8 via cancer cells. Moreover, there is inverse relation between ER level and IL-8, but the mechanism of IL-8 action in estrogen receptor-negative breast cancer is largely unknown. Estrogen receptor and growth factor in breast cancer cells is influenced by mitogen activated protein kinase (MAPK) cascade, as a part of IL-8 signaling pathway.

Conclusions: According to these studies, interleukin-8 may be as a main biomarker for breast cancer. It seems that signaling pathway of IL-8 may be used for therapeutic intervention of breast cancer. Also oxidative stress and breast cancer cells with lacking estrogen receptor generate more interleukin-8.

Keywords: Breast Cancer, Interleukin-8, Estrogen Receptor, Oxidative Stress

1. Context

Breast cancer is one of the leading causes of death among women all over the world (1), containing approximately one-third of all illness in women. It affects 1 of every 8 women in the United States (2). Also, it is one of the most frequent malignancies among Iranian women (1). This cancer consists of erratic growth of cells in breast tissue, forming tumors, which can be either benign (non-cancerous) or malignant (cancerous). The correct and early detection of breast cancer can ensure a long survival of the patients. Early detection of breast cancer with an accurate and reliable diagnosis procedure causes physicians distinguish benign breast tumors from malignant tumors (2). Breast cancer involved different signaling cascade deregulation (3), and early prognostic markers can could be used for routine diagnosis and patient survival. These biomarkers are able to generate main information related to clinical manner of breast gland tumors (4). Iinterleukin-8 (IL-8) is also over-expressed in various human tumors (5, 6) and increased with malignancy (7). The influence of IL-8 in migration and invasion of tumor cells is important for progression and metastasis formation of tumors (8). IL-8 secretion also motivates the expression of adhesion molecule, including fibronectin in human inflammatory breast cancer cells (5). Neoplastic mammary tissues have high levels of IL-8 concentration in comparison to normal tissue (4). Studies showed that IL-8 expression in patients with breast cancer is associated with metastasis of mammary gland cancer (4), advanced disease, and poor survival (9).Thus, high level of IL-8 is associated with metastatic invasiveness (10) and early recurrence (11, 12). It seems that it has significant potential as a prognostic and/or predictive cancer biomarker (5). Another study confirmed previous study and reported that IL-8 is associated with stage disease, detected as a prognostic factor (13, 14). Kamalakar reported

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that interleukin-8 plays a main role in osteolysis of patients with breast cancer, and anti-interleukin-8 therapy may be useful in the treatment of skeletal-related events associated with breast cancer (15). However, Zuccari et al. reported that the decreased level of IL-8 is associated with local recurrence and/or metastasis in patients with breast cancer (4). Therefore, the aim of the present study is to evaluate the mechanism and action of IL-8 in patients with breast cancer and its relation with oxidative stress and Estrogen receptor in these patients.

2. Evidence Acquisition

In order to collect data about the role of Adiponectin and obesity in prostate cancer, we performed a computerized search in Medline/PubMed databases with key words: Breast cancer, Interleukin-8, Estrogen receptor, and Oxidative stress.

2.1. Interleukin-8 (IL-8) and its Action

Chemotactic cytokines, which is produced by tumor and endothelial cells, can play an important role in cancer including angiogenesis, progression of tumor, migration, and facilitating evasion of immune surveillance (16). Among chemokine family (17), IL-8 is known as chemotactic (16, 18) cytokine (8, 16, 19-21) factor for neutrophils and causes the initiation of an inflammatory response (22). Yoshimura et al. in 1987 discovered interleukin-8 (16) as a protein with molecular weight of 8.4 KDa (23). Its gene is placed on chromosome 4q12-21 and contains 4 exons and 3 introns (16). Interleukin-8 (IL-8) is encoded by CXCL8 gene (24) and acts as a member of Glu-Leu-Arg (ELR) motif positive Cysteine- X-Cysteine (CXC) (25) chemokine (26-28) secreted by tumor cells (25). It is also mainly secreted by monocytes and endothelial cells (4, 29). Likewise, IL-8 and CXR-2 gene polymorphisms are associated with increased risk and disease progression (5).

IL-8 act as transcription target of Ras and has a necessary role in Ras-induced tumor growth and angiogenesis in vivo (30). IL-8 expression in mammary gland is associated with positive status of Lymph nodes (4). Down regulation of IL-8 arrested G1-S phase. Besides, the proliferation mechanism of IL-8 was associated with the alteration of inhibitors of cell cycle, such as p27Kip21 and the CDK regulator cyclin D1 (25). IL-8 via increasing Cyclin D1 and Cyclin B1 level and via the activation of phosphatidylinositide 3-kinases PI3K/Akt and Extracellular signal-regulated kinases Raf/MEK/ERK stimulates proliferation (12). In another study, it was reported that interleukin-8 also upregulated the anti-apoptotic gene Bcl-2, down-regulated the pro-apoptotic gene caspase-3, and significantly inhibited the apoptosis of MCF-7 cells, and these effects were blocked by phosphoinositide 3-kinase protein kinase B (PI3K/AKT) (31). IL-8 also controlled apoptotic pathway via protein kinase-B (Akt) and NF-κB interaction (25) Moreover, protein kinase A (PKA) and protein kinase C (PKC), activated by cyclooxygenase (COX-2), play an important role in regulation of IL-8. The activation of PKC, but not PKA, increased the production of IL-8 and inhibition of PKC, but not PKA, decreased the production of IL-8; hence, it seems that invasive effect of COX-2 is done via the mediating of PKC, not PKA. Because of the effect of IL-8 on different cell type, interleukin-8 signaling pathway may be therapeutic targets for sensitizing tumors to chemotherapeutic and biological agents (4).

2.2. IL-8 Receptors

The tumorigenic (4) and proangiogenic activities of interleukin-8 (32) is done via its binding to high-affinity cell surface receptors CXCR1 (IL-8RA) and CXCR2 (IL-8RB) (25). These receptors, as members of 7 transmembrane G-protein-coupled receptor (GPCR) family, are largely expressed on different cells, including normal and malignant (33). CXCR1 and CXCR-2 are expressed in all breast cancer cells, whereas these receptors are expressed in only 50% of the benign breast tissues.

Because of the incidence of 2 receptors in tumor cells, IL-8 could be as an autocrine and growth factor, which provide additional growth and progression of tumor (5). Il-8 signaling can induce mitogen activated protein kinase (MAPK) signaling cascade activation with downstream phosphorylation of Erk1/2 in cancer (34). Therefore, it can stimulate the growth of cancer cells and contributes metastasis and recurrence (4). Furthermore, it acts as a short-lived intercellular mediator in cancer pathogenesis (22).

3. Results

3.1. Idea About the Role of Interleukin-10 in Breast Cancer

The results of different studies considering the role of Interleukin-10 in breast cancer are shown in Table 1.

3.2. Interleukin-8 (IL-8) and NF-κB

NF-κB, as a dimeric transcription factor, composed of various homo-or heterodimeric combinations of 5 subunits including RelA (also called p65), RelB, c-Rel, p50 (generated from the precursor p105/NF-B1), and p52 (generated from p100/NF-B2) (24) was show to have an important role in carcinogenesis as well as in the immune and inflammatory response regulation (25). IL-8 expression can be deregulated in metastasis breast cancer due to the aberrant activity of NF-κB (34). NF-κB also plays an important role in

Table 1. Different Studies Considering the Role of Interleukin-10 in Breast Cancer

Researcher	Results	Population	References
Reed et al. (1992)	High IL-8 expression level has been observed in patient with breast cancer sera and in breast tumor samples.	U.K	(35)
Green et al. (1997)	Higher IL-8 level is seen in neoplastic breast tissues than normal tissue.	U.K	(36)
Bendre et al. (2002)	IL-8 mRNA expression is elevated in a variety of human cancer cell lines with different metastatic potential in vivo.	USA	(37)
Benoy (2004)	Serum IL-8 is increased in patients with breast cancer and has an independent prognostic significance for survival.	Belgium	(38)
Freund et al. (2004)	The highly metastatic breast carcinoma cells with lacking estrogen receptor produce moreIL-8.	France	(39)
Simeone et al. (2007)	Exogenous IL-8 increased the invasiveness of MCF-7 cells.	USA	(40)
Derin et al. (2007)	There is correlation between IL-8 levels and poor prognosis and metastasis in breast cancer.	Turkey	(41)
Lyon et al. (2008)	Levels of cytokines like IL-8 were significantly different in women with breast cancer than those who did not suffer breast cancer.	USA	(42)
Chen et al. (2011)	Interleukin-8 (IL-8) plays an important role during tumor angiogenesis and metastasis.	China	(11)
Singh et al. (2013)	IL-8 levels regulate breast cancer stem cell activity.	UK	(43)
Shao et al. (2015)	Interleukin-8 (IL-8) possesses tumorigenic and proangiogenic properties and is overexpressed in many human cancers.	China	(25)
Kim et al. (2015)	IL-8 expression is correlated positively with overall survival in basal-type patients with breast cancer.	Korea	(44)

IL-8 gene transcription via several signals, such as LPS, TNF-alpha, and oxidative stress (23). This study showed that although NF-κB is principal for the expression of IL-8 gene, cooperation with either AP-1 or C/EBP is required for the activation of optimal IL-8 gene in breast cancer cells. Studies showed that in mammary cancer cells, NF-κB promotes cell survival via apoptosis inhibition (23). NF-κB is a main factor for controlling the expression of IL-8 in MDA-MB-231 cell. It regulates multiple genes encoding a number of cytokines, cytokine receptors, and growth factors (23). The constitutive activity of NF-κB is associated with the aggressive forms of diverse type of cancers. Several studies reported that NF-κB transcription factors participate in the development and growth of cancer (23). NF-κB activity inhibition results in IL-8 expression down regulation and inhibition of cell proliferation and metastasis (23). Chavey et al. reported that IL-8 gene expression activation in breast cancer is also acetylation-dependent and needs the activation of NF-κB. Given that IL-8 can have higher aggressiveness for breast cancer cells, Histone deacylase (HDAC) inhibitors in anticancer strategies can have adverse effect through increasing pro-inflammatory molecules expression (34). Moreover, increasing IL-8 secretion is similar to increasing IL-8 RNA, gene transcription, histone H3 acetylation on the IL-8 promoter, and increased activity of the IL-8 (CXCL8) (45).

3.3. Interleukin-8 (IL-8) and Integrin β3

Some studies demonstrated that cooperation between integrin and cytokine signaling is important for the progression of tumor (25). There is positive correlation between integrin β3 level and IL-8 (25). The depletion of IL-8 caused significant reduction of integrin β3 transcription and protein expression. IL-8 can up regulate integrin β3 expression to promote the invasion of breast cancer cell line. Therefore, IL-8 promotes the invasion of breast cancer cell by integrin β3 expression up regulation (25). On the other hand, human breast cancer cells with metastasis status expressed the high levels of IL-8 and integrin β3 (25). Exogenous IL-8 increased chondosarcoma cell migration via increasing the expression of integrin β3 through signaling pathway of PI3K/Akt/AP1 (25). Furthermore, this study showed that there is positive correlation between the expression of integrin β3 and IL-8 in ER negative breast cancer tissues and cell lines. The mechanism of action is as follows: interleukin-8(IL-8) activates the PI3K/Akt pathway, which in turn activates NF-κB, resulting in the up regulation of integrin β3 expression and increased invasion of breast cancer cells. Therefore, it seems that IL-8/PI3K/Akt/NF-κB/integrin β3 axis may be used in therapeutic intervention of breast cancer with metastasis status (25).

3.4. IL-8 and Estrogen Receptors

The expression of IL-8 is significantly different between ER-negative and ER-positive breast cancer cells (23). IL-8 RNA and IL-8 secretion level is low in ER positive breast cancer cell line. The mechanism of IL-8 action in estrogen receptor-negative breast cancer is largely unknown (25). The high level of IL-8 in estrogen receptor (ER) negative

breast cancer cell is associated with higher invasion potential of these cells (41, 42). Malonia et al. reported that breast cancer cells with lacking estrogen receptor generate more interleukin-8 (34). It seems that Interleukin-8 is more expressed in ER-negative in comparison to ER positive breast cancer cells (23). Therefore, inverse relation was seen between ER level and IL-8 (23). Shao et al. showed that the expression of intrinsic IL-8 is associated with Estrogen receptor condition and metastasis in human breast cancer (25). Yao reported that IL-8 expression in ER negative breast cancers may play a main role in aggressiveness via promotion of invasion and angiogenesis (46). Paradoxically, interleukin-8 also inhibited growth of tumors via its chemotactic effects on neutrophils (46). Furthermore, the existence of ER-α and ER-β in ER negative cancer cells decreased the expression of IL-8 about 40% (23). Kamalkar et al. showed that primary human invasive ductal carcinoma may have IL-8 and its expression dose not correlate to Estrogen receptor status (15). Besides, Estrogen activity inhibition with anti-estrogens did not increase the expression of interleukn-8 in breast cancer cells (23). Lin et al. reported that during the progression of breast cancer, the inactivation of estrogen receptors is led to IL-8 up-regulation. This researcher believed that this is a main step for progression of breast cancer, because IL-8 upregulation may lead to angiogenesis and cell invasion (10). Also, the overexpression of IL-8 in ER negative breast cancer cells can be done at the transcriptional level, including NF-κB members binding p50 and p65 to IL-8 promoter. In addition, AP-1 and minor extent C/EBP transcription factors, which are highly expressed in ER-negative breast cancer cells, are necessary for the full activity of promoter of interleukin-8 (23). In another study, it was reported that Estrogen receptor and growth factor in breast cancer cells is influenced by MAPK cascade as a part of IL-8 signaling (5). On the other hand, IL-8 signaling transactivates growth factor receptors and MAPK signaling activation which is associated with cell proliferation (5).

Kim et al. reported that the invasiveness of triple negative breast cancer cell (TNBC) and invasion-related proteins, such as matrix metalloproteinase (MMP)-2 or MMP-9 were increased through treatment with IL-8. They also reported that elevated IL-8 mRNA expression and protein secretion were suppressed by a specific MEK1/2 inhibitor. It seems that the expression of IL-8 is regulated via MEK/ERK-dependent pathways in TNBC cells (44).

3.5. IL-8 and Oxidative Stress

Free radicals are reactive molecules (47). Increased free radical production is due to misbalance between generating and clearing free radical. This process causes oxidative stress (48-50), which is produced during metabolic activity (51). Oxidative stress drives the initiation and progression of cancer via mutations caused by DNA damage and plays the angiogenesis and metastasis of breast cancer. Therefore, oxidative stress caused angiogenic factor production, such as vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8) via cancer cells (52). Likewise, vascular endothelial growth factor (VEGF) increased IL-8 and both were modulated by hypoxia (38). The migration of type of cells, such as endothelial cells, keratinocytes, and melanocytes is induced through IL-8, which shows the strong activity of chemotactic. Furthermore, IL-8 over-expression was shown in breast cancer tissues. It also correlated with a highly invasive potential and metastatic phenotype of breast cancer cells (52). Therefore, it seems that IL-8 inhibition could be therapeutically important for the inhibition of invasion and metastasis of breast cancer (52). Hence, oxidative stress significantly motivated the migratory potential of poorly invasive breast cancer cells MCF-7 via Erk signaling activation, resulted in pro-migratory chemokine IL-8 secretion (52). Moreover, reactive oxygen species (ROS) increases the expression and activity of activator protein one APE-1/Ref-1 in fibroblasts, macrophages, B cells, and other cell types (53). Another study reported that the level of serum interleukin-8 was higher in dogs with inflammatory mammary cancer (IMC) than non-IMC group (7). Thyagarajan et al. reported that G. lucidum, as an Asian medicinal mushroom, can suppress oxidative stress in MCF-7 cell line via MAPK signaling down regulation. The inhibition of oxidative stress stimulated extracellular signal-regulated protein kinases (Erk1/2) phosphorylation, which led to the down-regulation of c-Fos expression and the inhibition of transcription factors AP-1 and NF-κB (53).

Since Il-8 through intracellular molecular signaling can cause tumor aggressive behavior and increase survival in answer to chemotherapy drug toxicity, the inhibition of IL-8 via RNAi or inhibitors of IL-8 or IL-8 receptor may sensitize ER-negative breast cancer to a diverse of chemotherapeutic agents and enhance patients' survival with end-stage disease (25).

4. Conclusions

According to the results of these studies, Interleukin-8 may be a main biomarker for breast cancer. It seems that signaling pathway of IL-8 may be used for therapeutic intervention of breast cancer. Also, oxidative stress and breast cancer cells with lacking estrogen receptor generate more interleukin-8.

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Footnotes

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