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Review Article

Cytokines in Breast Cancer: Prognostic Marker or Therapeutic Avenue?

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ABSTRACT

Importance of inflammation in cancer initiation has matured through intensive research in recent years resulting in new doctrines. Cytokine is a class of pleiotropic small molecules recruited by immune system for both pro- and anti-inflammatory assignments. Increasing evidence suggest that, various cytokines play important role in tumor initiation, growth and metastasis of breast cancer. Two areas as prognosticator and therapeutic approach cytokines are the possible future course of cytokine biology in context of breast cancer. Expression of several cytokines has been investigated in relation to prognosis and survival of breast cancer patients. Cytokine has also becoming a central part of tumor immunotherapy. Several disadvantages like dual role of tumor promoting and inhibiting effect of several cytokines is one of the important issues to be addressed before establishing cytokine-based therapy. In this review, we tried to have a consolidated view on recent update for the expanding role of cytokines in breast cancer.

Key words: cytokines, interleukin, inflammation, breast cancer

INTRODUCTION

Cytokines and their expanding role in pathogenesis:

Cytokine is a class of small molecular weight secreted pleiotropic proteins mainly involved in regulation of immunity, inflammation and hematopoiesis. They are constituted of diverse group of molecules that includes interferons, chomokines, monokines, and interleukins. Cytokines may act as autocrine, paracrine or endocrine factor. Cytokines and its role in cancer immunity and carcinogenesis, in general, is well-known for a long time. [1] Since chronic inflammation is an important stimulus for initiation of cancer, the pro-inflammatory cytokines are deemed as mediator of such events. Cytokines maintains a balancing network of pro and anti-inflammatory mediator and thus dysregulation of any of these two arms may have important consequences i.e., down-regulation of anti-inflammatory cytokines or up-regulation of pro-inflammatory cytokines.

Cytokines also plays an important role in tumor immunity, immuno-surveillance against tumor initiation, and defense against initiation of tumor. Though pleiotropic molecule, the tissue or cell type specific role of cytokines is less known and

poorly understood. Their tissue specific-regulation mechanism has not been addressed yet. There are also evidences that same cytokine may have different effect at different stage of tumor progression suggesting a more complex interaction of cytokine in the pathology of cancer (double edged sword). Estimation of these cytokines in view of gene-environment interaction and epigenetic modification will be rather more difficult. Recent studies have proved important role of various cytokine in tumor microenvironment and their possible effects in tumor progression and metastasis. Tumor cells hijack the immune-defensive mechanisms, express specific cytokines and employ them as instruments for further progression and metastasis of tumor cells. Cytokines influence patho-biology of cancer in six major ways as below.

1. Tumor promoter: Tumor promoting activity of immune system is known for a long time. [2] Recently, the important mediators of immune enhancer of cancer were discovered. IL-1 promotes angiogenesis, tumor growth, and metastasis in experimental models. [3] The interleukin-1 (IL-1) family consists of two major agonistic proteins, IL-1alpha and IL-1beta, which are pleiotropic and affect mainly inflammation, immunity, and hemopoiesis. The IL-1 receptor antagonist (IL-1Ra) is a physiological inhibitor of pre-formed IL-1. IL-1 promotes carcinogenesis, tumor growth, and invasiveness while IL-1Ra antagonizes these effects of IL-1. [4]

2. Tumor inhibitor: TNF has pleiotropic characteristics, and have the capability to lead apoptosis of tumour-associated endothelial cells that can result in the destruction of the tumour vasculature. [5] Many tumour models studies have shown TNF either with interferon-gamma (IFN-γ) or with chemotherapeutic agents inhibits tumor growth. [6] Exogenous administration of IL-10 mediates regression of tumour growth and breast cancer metastases in mice models. [7] IFN-γ increases the growth inhibitory effect of tamoxifen in breast metastatic carcinomas. [8]

3. Anti-tumor immunity mediator and immunosurveillance: Anti-tumor immunity is mediated by cellular immune cells. Several cytokines facilitates IL-18 facilitates tumour rejection by augmenting cytotoxic effects of NK cells and T cells. [9]

4. Microenvironment modulator: IL-1 is produced by tumor cells and other cellular components of tumor microenvironment. IL-1 patterns of interactions between malignant cells and the host's immune system. [10] IL-1alpha expressed on tumor cells activates immunity, while IL-1beta activates inflammation that promotes invasiveness and also induces tumor-mediated suppression. [11]

The salient functional roles of few important cytokines were summarized in the Table 1.

Cytokines and Breast Cancer

Breast cancer is mostly viewed as disease with endocrine deregulation. Estrogen plays an important role in initiation on breast cancer. The immune factors involved in initiation and progression of breast cancer is thought to play a more of a secondary action in breast cancer.

It has been known for a number of years that there may be there is a significant impairment of the immune system in breast cancer patients. [12] Majority of cytokines have been investigated *in vitro* in breast cancer cell lines like MCF-7, MDA-MB-231 for their mechanistic role in cancer (Refer in vitro roles in Table 2. Several therapy like SERMs, aromatase inhibitor attempts cutting down the estrogen level. [13] Breast cancer is sub-grouped based on the status of estrogen receptor (ER), progesterone receptor (PR) and HER2 receptor. Then progression of tumor towards hormone

independent phenotype and evolving knowledge of hormone receptor negative cancer subtypes have forced to look other tumor cell regulating molecules like cytokines and growth factors. Recent studies on role of cytokines in breast cancer were discussed below and summarized in Table 2.

Table 1: General Role of Important Cytokines in Immunity and Cancer

Cytokines	Producing Cell	Target Cell and Function	Putative Role in Cancer
IL-1	• Monocytes • Macrophages • B-cells • Dendritic cell	• Th cells co-stimulation • B cells maturation and proliferation • NK cells activation	• Promotes angiogenesis, tumor growth, and metastasis in experimental models • Presence in some human cancers is associated with aggressive tumor biology • Antagonist IL-1Ra prevents action of IL-1. [4]
IL-2	• Th1 cells	• Activated T and B cells • NK cells growth, proliferation, activation	• Involved in the control of the equilibrium between proliferation and apoptosis. [31] • Induce Leucocyte Activated Killer cells and LAK cells were thought to invade the tumor and to kill tumor cells. [32]
IL-3	• Th cells • NK cells	• Mast cells growth and differentiation	• Potent hematopoietic growth factors. • Induce signals important for promoting cell survival • Overexpression of IL-3 receptor in AML and possible stimulation of proliferation of AMLs. [33]
IL-4	• Th2cells	• B cells proliferation and differentiation • IgG_1 and IgE synthesis T cells proliferation	• Inhibition of tumour growth by its anti-angiogenic effect. [15]
IL-5	• Th2cells	• B cells proliferation and differentiation • IgA synthesis	• Potent hematopoietic growth factors • Stimulate proliferation, survival, and differentiation of myeloid hemopoietic cells. [34] • IL-5 may be involved in autocrine tumor growth and tumorogenicity. [35]
IL-6	• Monocytes • Macrophages • Th2cells • stromal cells	• activated B cells differentiation into plasma cells for antibody secretion • Stem cell differentiation	• Decreases growth of prostate cancer cells, melanoma cell lines, and M1 leukemia via STAT3. [36]
IL-7	• Marrow stroma • Thymus stroma	• stem cells differentiation into progenitor B and T cells	• Produced by some human tumour cells and involved in tumour development and progression. [37]
IL-8	• Macrophages • Endothelial cells	• Neutrophils (Chemotaxis)	• Role in cell survival, proliferation, inavasion and angiogenesis. [38] • Role in tumor microenvironment and chemoresistance
IL-10	• Th2cells	• Macrophages (cytokines production), B cell activation	• Demonstrates anti-tumour properties. [39]
IL-12	• Macrophages • B cells	• NK cell activation, Activated Tc cells (differentiation into CTL (with IL-2)	• Demonstration of significant anti-tumor activity in several preclinical animal tumor models leading interest in the therapeutic use of IL-12. [40]
IFN- α	• Leukocytes	• Viral replication • MHC I expression	• Viral replication prevention, cell growth inhibition and cell differentiation modulation. [41] • IFN-β induces both direct anti-proliferative and apoptotic effects, as well as systemic immunity against the tumor targets. [42]
IFN- β	• Fibroblasts	• viral replication • MHC I expression	
IFN- γ	• Th1 cells • Tc cells • NK cells	• Macrophages for pathogen elimination • B cell activation for antibody secretion • Th-2 cell proliferation	
TNF-α	• Tissue macrophages • NK cells	• Macrophages for cytokines expression • Tumour cell death	• TNF is also able to induce apoptotic cell death, to induce inflammation, and to inhibit tumorigenesis. [43] • Anti-tumor role in vivo. [44]

Cytokine therapy and Breast cancer:

IL-1Ra, IL-4, IL-6, IFN-gamma, TNFα and several other cytokines are known to inhibit *in vitro* breast cancer cell growth. However, clinical trials till now have failed to demonstrate significant independent benefit of any cytokine in breast cancer. IL-4 inhibits growth and stimulates apoptosis of breast cancer cell lines in the presence of IL-4R, [14] and

inhibits tumour development through its anti-angiogenic effect. [15] Exogenous administration of IL-10 mediates regression of tumour growth and metastases of breast cancer in mice models. [7] These molecules can directly have a tumor regessing therapy for breast cancer.

Table 2: Emerging role of some selected cytokines and their experimental evidences

Cytokines	Emerging Role of Cytokine in Breast Cancer
IL-1	IL-1 antagonize insulin and IGF-I induced mitogenic effects in MCF-7 cells by blocking the receptor tyrosine kinase activity. [44,45] Inhibition of IL-1alpha activity by either neutralizing antibody against IL-1alpha or chemical inhibitor of IL-1alpha processing prevent invasion and metastasis of breast cancer. [46] Interleukin-1α promotes tumor growth and cachexia in MCF-7 xenograft model of breast cancer. [3] Inhibition of IL-1beta activity in vivo result in reduced iFGFR1-induced epithelial proliferation and formation of hyperplastic structures. [47] IL-1beta promoter variants may contribute to risk of developing breast cancer. [48] Carriage of the mutant alleles of IL1RN is independently associated with shortened disease free and overall survival rates in Caucasian patients with breast cancer. [49] IL-1 family and leptin family are adipocytokines which could represent a major link between obesity and breast cancer progression. [30]
IL-2	IL-2 enhances effect of Herceptin on Her2/neu positive MCF-7 cells. [50] Increased expression of IL-2 and its three receptor chain is associated with the development of breast tumors. [51] Have protective effect in male against breast cancer. [19] Trastuzumab and IL-2 regimen results in NK cell expansion with enhanced in vitro targeted killing of HER2-expressing cells. [52]
IL-3	Causes reduction in 17-HSD activity in MCF-7 and cell proliferation. [19] CD4- and CD25- positive T-cell expressing IL-3 is present in non-advanced tumors. [53]
IL-4	Inhibits estrogen induced cell proliferation Inhibits growth and induces apoptosis of breast cancer cell lines via STAT6. [14] IL-4 treatment significantly reduced CD95 (Fas/APO-1)- and chemotherapeutic drug-induced apoptosis in tumor cell lines. [54]
IL-5	IL-5 partially inhibits MCF-7 growth in vitro. [55]
IL-6	IL-6 plays roles in the proliferation and metastasis of cancer cells, in the development of osteolysis and humoral hypercalcemia, and in the regulation of estrogen production in breast cancer tissues. IL-6 may both tumor-promoting and inhibitory effects of IL-6 in breast tumor. [56] IL-6 receptor and of IL-6 cytokine, are produced in an autocrine manner in breast tumors. [57] Reported as a prognostic factor in breast cancer and other malignancies. [21]
IL-7	Lymphangiogenic growth factor and induces lymphangiogenic properties of endothelial cells. [58] Presence of high serum IL-7 levels in patients with bone metastasis and suggested use of serum IL-7 level as a clinical marker of disease progression and of bone involvement. [22]
IL-8	Modulates growth and invasiveness of estrogen receptor-negative breast cancer cells. [59] Levels increased in advanced disease and increase with breast disease progression. Inhibits ER-negative breast cancer cell growth and promotes its metastasis in vivo, which may be correlated with neutrophils infiltration induced by IL-8. [60] IL-8 may be a novel therapeutic target for estrogen driven breast carcinogenesis and tumor progression. [61]
IL-10	Inhibits pro-inflammatory cytokines like IFN-γ, IL-2, IL-3, TNFα and GM-CSF. Reduces natural killer sensitivity and downregulates MHC Class I expression on H-ras-transformed cells and help in escape of tumor cells from host immune system by NK cells. [62] Has potent anti-metastatic activity by inducing NK lysis of tumour cells. [63] Exogenous administration can mediate regression of tumour growth and breast cancer metastases in mice models. [7] Over expressed in breast tumours. [64]
IL-12	Possesses anti-angiogenic activity, and dependent on increasing production of interferon gamma. Induces tumour destruction in murine models of breast cancer by inhibiting angiogenesis and activating CTL. [65] Serum level increases during tumour progression due to alteration in the function of the immuno-competent cells. [66]
IFN- α	IFN-α and IFN-γ have anti-proliferative effect on the growth of MCF-7 cells. [67]
IFN- β	Treatment with IFN-β increases expression of both estrogen (ER) and progesterone receptors (PgR) in breast cancer cell lines and in metastatic breast cancer patients. Antigenic phenotypes of breast carcinoma and astrocytoma cells is modified by IFN-β treatments. [68] Combination of IFN- β and Tamoxifen overcomes clinical resistance to tamoxifen in advanced breast cancer. [69]
IFN-γ	Inhibit the growth of several tumor cell lines, including breast cancer cells. [70,71] Produces anti-tumoral effect up-regulating the expression of p21 and resulting cell cycle arrest in breast cancer cell lines. [72] Local injection of IFNγ results in the total or partial regression of the skin lesions in breast cancer patients with skin metastasis. [73] Increases growth inhibitory effect of tamoxifen in breast metastatic carcinomas. [8]
TNF- α	Enhances anti-tumour effect of DC-based vaccines. Inhibits growth and promotes apoptosis of tumour cells in breast cancer cell lines in vitro. [74] TNF-alpha on down-regulates estrogen receptor and blocks proliferative response of breast cancer cells to estradiol have been demonstrated. [75]
TNF- β	Induces IL-10 killing viral infected cells Homozygous common allele genotype (TNFB*1/TNFB*1) protects against breast cancer. [76]

Conversely, several cytokines have tumor promoting activity in breast cancer. [16] Leukemia-inhibitory factor stimulates aromatase activity, [17] is known to stimulate the proliferation of MCF-7 breast cancer cells. LIF produced by ER- but not ER+ breast cancer cells. [18] It is also possible that another cytokine, IL-3, which has been shown to be secreted by fibroblast derived from male breast tissue but not female and which can inhibit E2DH reductive activity. [19] The over expressed receptors of tumor promoting cytokines may be useful as targeting breast cancer.

Cytokine as prognosticator in Breast cancer:

Study has shown that TNF-alpha and IL-4 are commonly expressed by colon carcinoma TIL, and associated with improved survival. [20] IL-6 is also another prognostic factor in several malignancies such as colorectal cancer, breast cancer. [21] High serum IL-7 and Il-8 levels are observed in patients with bone metastasis of breast cancer. [22,23]

Several clinical studies have showed significant increase in level of few cytokines in breast cancer. Even these changes in expression have been correlated with the stage and progression of breast cancer. For example, serum level of IL6 become higher in breast cancer patients compared to healthy controls and among those with breast cancer, correlate with the stage of the disease. [24] Continuously elevated serum IL-6 levels correlate to poor survival in patients with hormone-refractory metastatic breast cancer (n=12). [25]

Elevated expression of IL-8 in human breast cancer cell lines was associated with breast cancer invasiveness and angiogenesis. Furthermore, IL-8 levels are inversely related to estrogen receptor (ER) status with ER-positive cells generally expressing low levels and ER-negative cells expressing higher levels of IL-8. [26] IL1-beta increases the transcriptional action of ER-alpha in breast cancer cells. [27] ER-alpha is a prognostic factor in breast cancer and IL-8 is a strong angiogenic factor.

CONCLUSION

Malignant diseases pathogenesis is a multifactorial process. Progressive genomic alterations and modifications in gene expression in pre-malignant cells requires tumor-supporting systemic and micro-environment. [28] Some cytokines (IL-1, IL-6, IL- 11, TGF-b) stimulate while others (IL-12, IL-18, IFNs) directly inhibit breast cancer proliferation and/or invasion. In clinical situation, role of cytokine may not only be direct as suggested by failures of single cytokine to significantly improve breast cancer prognosis, but more complex due to its multifunctional role which may be interlinked through other mediators regulated by cytokines. For example, obesity is as a risk factor for post-menopausal breast cancer incidence and morbidity. [29] Recent evidences suggest IL-1 members act as adipocytokines in breast cancer cells may interact with other adipocytokines such as leptin. This represents a major link between obesity and breast cancer progression. [30]

In conclusion, abundant experimental evidence suggest significant role of various cytokines in breast cancer. However, limited favorable clinical responses of cytokine therapy suggest that they may not be sufficient alone for therapeutic management of breast cancer. There may be immense scope to improve clinical outcomes of breast cancer patients post-chemotherapy or with disseminated disease controlled by conventional anti-estrogens using cytokines as supporting therapeutics. Cytokines may serve as important combination therapy lead in combating tumor cells with knowledge of their multifaceted roles in progression of cancer and translation for development of

new strategies to modify the disease progression favorably. Beside genetic and racial differences, cytokine network may greatly influenced by environmental factors such as climatic changes and clinical/subclinical infectious agents exposures altering immune-homeostasis, lifestyle induced immuno-suppression etc. This strategy plays important roles of cytokine as better supportive combination in achieving maximum output in routine therapeutic protocol of breast cancer. However, the cancer promoting role of certain cytokines such as TGF-beta in laboratory models of advanced stage cancer emphasizes that cancer staging, histopathological and serum biomarker profile will be important for such application.

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