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REVIEW

Significance of interleukin-6 (IL-6) in breast cancer (review)

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Abstract Cytokines are factors that are known to have both tumor-promoting and inhibitory effects on breast cancer growth depending presumably on their relative concentrations and the presence of other modulating factors. Different cytokines play an important role in controlling the immune system. Interleukin-6 (IL-6) is a pleiotropic cytokine with obviously tumor-promoting and tumor-inhibitory effects. Here, we review the role of IL-6 in in vitro experiments of breast tumor cells, in breast tumor tissues (BTs) and assess its potential as a prognostic indicator in breast cancer patients. A literature search was conducted using PubMed, restricted to articles published in English language. In summary, results regarding the effect of IL-6 on breast tumor cells and on BTs are not unique indicating both tumor-promoting and inhibitory effects of IL-6. Concerning patients' serum IL-6 levels, data are surprisingly unique showing IL-6 to be a negative prognosticator in breast tumor patients.

Keywords Breast cancer · Interleukin-6 · Prognostic factor

Introduction

Breast cancer is the most common malignancy in women. Its aetiology is multifactorial, the period of development can span decades and clinical course is highly variable. New strategies in the treatment of breast carcinoma are introduced, e.g. Trastuzumab (HerceptinR) belongs to the ''new generation'' agents, a group of drugs used in monoclonal antibody therapy of cancer. Trastuzumab produced objective regression in 15–20% of patients with HER2-overexpressing breast cancer [1] and prolonged survival [2]. But overall results are still unsatisfactory. Recent years focussed on the identification of cytokines as prognostic factors. Both the innate and acquired arms of the immune system are believed to play crucial roles in the anti-tumor response, and the interaction between host immune system and tumor cells has been the subject of intense research over the past decades [3, 4]. Cytokines including transforming growth factor-ß (TGF-ß), tumor necrosis factor-α (TNF-α), several interleukins like IL-1, Interleukin-6 (IL-6), IL-10, and others, and the interferons all play an important role in controlling the immune system.

Briefly, cytokines are secreted principally by lymphocytes and macrophages and act by altering the function of target cells in a paracrine or autocrine fashion. Cytokines have several common structural and functional characteristics: (a) they tend to be glycosylated polypeptides; (b) they are biologically active at very low concentrations (pg/ml–ng/ml); (c) they exert their effects by binding to receptors on the target cell surface; (d) they are pleiotropic; and (e) their effects are additive, synergistic or antagonistic [5]. Therefore, it is the integration of these effects that determines the overall outcome.

It has been known for a number of years that there is a significant impairment of the immune system in breast cancer patients [6]. The lack of an effective

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immune response to tumorigenesis, in spite of the presence of tumor infiltrating lymphcytes in vivo, is believed to be due in some way to the action of inhibitory cytokines in the tumor microenvironment. Also, breast cancer has long been considered to be weakly immunogenic and, hence, is only poorly recognized by the immune system [7]. In contrast to many of the in vivo observations, however, certain cytokines have been demonstrated to promote the generation and/or efficacy of anti-tumor effectors, including dendritic cells and lymphokine activated killer cells and cause inhibition of tumor growth or, in certain instances, regression. Most of this work has been in vitro. In addition to their effects on the immune system, cytokines have also been reported to influence aromatase activity and oestrogen synthesis directly in the tumor vicinity and hence promote tumor growth and aggressiveness [8].

Here, we review the role of IL-6, a pleiotropic cytokine with different biologic activities, in in vitro experiments, in breast tumor tissue (BT), breast cancer patients and its potential as a prognostic marker for assessing disease stage and disease progression.

IL-6 in vitro studies on breast cancer cells

Concerning the biology of in vitro breast cancer cells, IL-6 seems to be a double-edged sword. There are several reports indicating IL-6 to be both a tumor-promoting and a tumor-counteracting cytokine. The IL-6 seems to play an important role in resistance toward apoptosis. It could be shown in esophageal carinoma and multiple myeloma cells, that IL-6 exerts a powerful pro-survival function, which occurs through induction of one or more proteins (e.g., BCL-2, BCL-Xl, and MCL-1) that inhibit apoptosis [9, 10]. In supernatants of multidrug resistant breast cancer MCF-7/ADR cells, high levels of IL-6 were detected, whereas the parental sensitive cell line failed to produce IL-6 [11]. Furthermore, pretreatment of MCF-7 breast carcinoma cells with IL-6 caused an eight to tenfold increase in resistance to doxorubicin indicating that the presence of exogenous IL-6 increased the resistance of breast cancer cells to doxorubicin treatment [11]. Haverty et al. [12] reported that exogenous IL-6 induces GP96, a glucose related stress protein related to drug resistance in tumor cells, in the metastatic breast cancer cell line MDA-MB231, but has no effect on GP96 in the primary cell line BT474. Furthermore, both IL-6 and GP96 are significantly elevated in BT compared to normal breast tissue. However, Chiu et al. [13] could demonstrate in human ER (+) mammary carcinoma cell lines that IL-6 inhibited proliferation via induction of apoptosis. In these cells, 5 ng/ml IL-6 (for 6 days) induced DNA fragmentation in MCF-7 and ZR-75-1 cells, which is characteristic for apoptosis. Again, opposing effects of IL-6 are described.

Besides its questionable role in apoptosis, IL-6 could be shown to promote breast cancer cell motility indicating a role in metastasis [14, 15]. The studies of Asgeirsson et al. [16] support this observation. They showed that in in vitro conditions IL-6 decreased cell adhesion of three breast cancer cell lines and this was associated with a decrease in E-cadherin expression. The responsiveness to IL-6 varied according to the differentiation status of the cell. They have also shown that IL-6 serum levels were raised in a significant number of breast cancer patients and that E-cadherin expression of their tumors was often altered, although they were not able to establish an association between the two. They propose IL-6 and E-cadherin as possible factors important in breast cancer metastasis formation. The finding that the estrogen receptor represses IL-6 expression in breast cancer cell lines, suggests that up-regulation of the cytokine may be involved in the high invasiveness and metastatic capability of estrogen receptor-negative tumors [17].

The IL-6 is a pleiotropic cytokine that plays a significant role in the growth and differentiation, two opposing mechanisms, of cells. Several studies have addressed the role of IL-6 in tumor cell growth in vitro, but its exact role remains varied and unclear. There are reports indicating IL-6 as a growth factor in cancer disease for myeloma/plastocytoma, renal cell carcinoma, cervical carcinoma, AIDS Kaposi's sarcoma-derived cells, and certain T- and B-cell lymphomas [18–23]. Analysis of transgenic mice overexpressing IL-6 in B-cells has shown that IL-6 is involved in the development of plasmacytoma and myeloma [24]. Other studies show growth inhibitory thus anti-cancer properties of IL-6 on prostate cancer xenografts [25] or no effect was seen ([26]: colorectal adeonocarcinoma; [27]: malignant glioma cells; [16]: T47D, MDA-MB-231, and ZR-75-1 human breast carcinoma cells). Honma et al. [28] showed no significant effect on cell proliferation of human breast cancer cell lines (SK-BR-3, MCF-7) but cell proliferation was significantly increased when IL-6 and estrone sulfate (E1-S) were simultaneously added to the incubation medium. The report of Shen et al. [29] showed different results. They demonstrate that IL-6 (and TNF-α and IL-1β) all dose-dependently inhibited IGF-1 promoted DNA synthesis. Flow cytometry confirmed that these cytokines suppress IGF-1 induced MCF-7 cell proliferation by preventing cells from entering the S phase of the cell cycle,

leading to the arrest of these cells in the G0/G1 phase. Consequently they concluded that proinflammatory cytokines suppress growth of breast cancer cells by inhibiting activation of early adaptor molecules used by growth factor receptors to promote cell division.

Taken together, in vitro data are not uniformly consistent underscoring the pleiotropic characteristic of this cytokine in breast cancer.

IL-6 levels in breast tumor tissues

The IL-6 is a multifunctional cytokine produced by non-malignant cells such as T lymphocytes, fibroblasts, or monocytes and a number of malignant cells, e.g., melanoma or renal cell carcinoma [30, 31]. Concerning expression of IL-6 in BT, results are contradictory. Analyzing the IL-6 mRNA expression profile in 19 malignant breast cancer tissues, Marrogi et al. [32] were not able to detect IL-6 mRNA. In opposite to these results, we were previously able to show that BTs produce IL-6 with a mean concentration of 0.47 ng/g (range 0.004–3.10 ng/g) [33]. In good agreement with our results, Ueno et al. [34] showed in human breast cancer samples a median IL-6 concentration of 5.31 ng/g (range 0–24.66 ng/g). Irahara et al. [35] studied the aromatase mRNA expression and promoter usage in axillary adipose tissue (AA), mammary adipose tissue (MA), BT, and adjacent normal tissue (NB) and the relationship between aromatase mRNA expression and IL-6 (and others). They found a significant association between aromatase mRNA levels and IL-6 in BT, AA, and MA but not in NB, indicating expression of IL-6 in breast tumors. The study of Crichton et al. [36], analyzing the expression of transcripts in six breast tumor samples, and also the study of Purohit et al. [37] also showing BTs to produce IL-6, support our results.

Provided that tumor tissue contains IL-6, three hypotheses concerning the significance of intratumoral IL-6 are present. One, indicating IL-6 not to be associated with breast tumor disease, the second to be a positive prognosticator, and the third one suggesting IL-6 to be a negative prognosticator. The study of Green et al. [38] support the first hypothesis. They analyzed the mRNA transcripts for different cytokines in normal and neoplastic human breast tissue and found 32 of 56 (57%) normal breast tissues and 44 out of 77 (58%) breast tumors to be positive for IL-6 with no significant difference in expression between the two groups of tissues.

The second hypothesis is supported by the study of Basolo et al. [39]. They found normal mammary epithelial cells from healthy women to release IL-6, but expression of IL-6 was abolished in ductal infiltrating carcinomas. Consequently they suggest that alteration of IL-6 expression is associated with pathogenesis in breast cancer. Similar results were worked out by Fontanini et al. [40] and Karczewska et al. [41]. The latter group analyzed mRNA of IL-6, IL-6R, and gp130 in 75 tumor samples obtained from breast carcinoma patients. Patients were followed for a maximum of 71 months. Prognostic factors were analyzed in univariate and multivariate analysis. They found mRNA specific to IL-6, IL-6R and gp130 in 57, 53, and 71% of breast carcinoma tissues, respectively. Expression was strongly correlated with earlier stages of the disease. In univariate analysis, expression of IL-6 and its receptor subunits proved to be a positive prognostic factor for overall survival (OS) and disease free survival (DFS). Consequently they concluded that in advanced stages, expression of IL-6 and its receptor subunits predicts better prognosis. The study of Fontanini et al. [40] analyzed the expression of IL-6 in 149 tumor samples of invasive breast carcinoma and the data were correlated with clinico-pathological variables including tumor size, histological grade, nodal status, and oestrogen and progesterone receptors, Ki67 and p53 protein expression. Although the majority of breast carcinomas expressed at least low levels of immunoreactive IL-6, they found that expression of this cytokine was inversely associated with histological tumor grade (not with tumor size and nodal status). These data let them speculate that down-regulation of IL-6 is associated with highly mammary carcinomas.

Concerning IL-6 to be negative prognosticator in BTs, Purohit et al. [37] compared normal and malignant breast tissues and found IL-6 production, expressed in terms of tissue weight, to be significantly higher for tumor tissue compared with normal breast adipose tissue. Similar results were worked out by Garcia-Tunon et al. [42]. This study was done to characterize the expression pattern of IL-6 and its receptors and to relate this pattern to bcl-2 and bax expression (which are related to anti-apoptosis) and to elucidate the effects of the proliferation/apoptosis equilibrium in benign conditions and in situ and infiltrating breast cancer. They found weak expression of IL-6 and its receptors in patients with benign lesions. In the invasive breast tumors, the percentage of cases showing immunoreactivity for IL-6, gp130, and IL-6Rα was much higher than in non-malignant lesions, and the intensity of expression was two to three times higher. Consequently they suggest that breast tumor cells not only produce more IL-6 than normal breast epithelial cells, but also the response on the tumor cells

to this interleukin is greater. Furthermore, they reason that high expression of IL-6 and its receptors in breast tumors might be related to the enhanced cell proliferation occurring in breast cancer.

Taken together, the data concerning the significance of IL-6 within BT are not unique and should be interpreted with caution. Further studies are necessary to elucidate the intratumoral role of IL-6 in regard to development and progression of breast tumors.

IL-6 serum levels and breast cancer patients

Despite the above mentioned sometimes opposing effects of IL-6 on breast tumor cells shown in several in vitro experiments and the ambiguous significance of IL-6 in BTs, there is an increasing number of publications dealing with the up-regulated serum IL-6 level in breast tumor patients indicating high serum IL-6 level to be a negative prognostic marker in mammary carcinoma patients. In Table 1 the published studies analyzing serum IL-6 levels in breast cancer patients are depicted. Several studies analyzed the IL-6 levels between control and breast cancer patients and also between lower stages and higher stages of disease. Kozlowski et al. [43] assessed the concentration of IL-6 (and also IL-8 and IL-10) in blood serum of breast cancer patients to determine whether it correlates with the disease progression. They showed statistically higher serum concentrations of IL-6 (and IL-8 and IL-10) in breast cancer patients in comparison with healthy women, which also correlated with clinical stage of breast cancer. Yokoe et al. [44] showed that serum IL-6 levels in progressive recurrent breast cancer patients, who did not respond the therapy, were significantly higher than the levels in recurrent breast cancer patients, who were stable after therapy. Patients whose serum IL-6 concentration was 20 pg/ml or more died within 4 months of the beginning of treatment. Jiang et al. [45] found serum IL-6 levels were significantly higher in patients with breast cancer (38.3 ± 138.7 pg/ml) than in normal women (0.7 ± 2.5 pg/ml). In that study, they did not determine the relationship between serum IL-6 concentration and prognosis by determining either disease-free or OS. Nevertheless, these results support the studies of Yokoe et al. [44]. Another study, done by Nishimura et al. [46], analyzed the significance of IL-6 in advanced or recurrent breast cancer, the relationship between the IL-6 level and clinical findings or effect of medroxyprogeterone acetate (MPA, presumed to inhibit IL-6 production). They found serum IL-6 to be significantly higher in recurrent cases (6.5 ± 7.48 pg/ml), especially in those with visceral metastasis, than in non-recurrent cases (1.96 ± 1.38 pg/ml). Further, in patients for whom MPA treatment was effective, the IL-6 level prior to treatment was clearly low. Performance status was improved in those cases in which the degree of IL-6 increase was suppressed by MPA. The group of Bozcuk et al. [47] analyzed, among others, IL-6 and correlated it with clinical outcome in 43 metastatic breast cancer patients treated with chemotherapy. They proved in their cohort that IL-6 is negatively correlated with survival. They concluded that their observation that higher serum IL-6 is associated with inferior progression free and OS is in accordance with findings of Zhang and Adachi [48], where they showed in 46 metastatic breast cancer patients that serum IL-6 value greater than a cut off value of 4 pg/ml was associated with 3.86 times increased risk of death as opposed to 5.99 times increased risk of death in their cohort, when the cut off value was 5 pg/ml. Consequently, Bozcuk et al. [47] proposed IL-6 as an independent negative prognosticator in breast cancer patients with metastatic disease. Similar results were worked out by Saldago et al. [49]. The study was designed to evaluate prospectively the independent prognostic importance of circulating IL-6 in 96 patients with untreated metastatic breast cancer, and to evaluate whether there is an association with clinicopathological variables, with tumor load and with tumor extension. The median IL-6 value for the breast cancer population was 6.6 ± 2.1 pg/ml. Patients with two or more metastatic sites had higher IL-6 values compared to those with only one metastatic site (respectively, 8.15 ± 1.7 and 3.06 ± 6.6 pg/ml). Patients with liver metastasis (8.3 ± 2.4 pg/ml), with pleural effusions (10.65 ± 9.9 pg/ml), and with dominant visceral disease (8.15 ± 3.3 pg/ml) had significantly higher values compared to those without liver metastases (4.5 ± 3.4 pg/ml), without pleural effusions (5.45 ± 1.5 pg/ml) and with dominant bone disease (4.5 ± 1.4 pg/ml), respectively. Multivariate analysis showed that high levels of serum IL-6 had independent prognostic value. They concluded that circulating IL-6 is associated with worse survival in patients with metastatic breast cancer and they suggest that at later stages of breast cancer progression IL-6 may have a net stimulatory effect on tumor growth. In a preliminary report, Yokoe et al. [44], investigating the trend of IL-6 and IL-8 in heavily pretreated patients with recurrent breast cancer, found the pretreatment level of IL-6 in the partial response/no change group (11.0 ± 2.1 pg/ml) to be significant lower than that (15.3 ± 2.7 pg/ml) in the progressive disease group. Furthermore, they observed an increase of IL-6 levels in the progressive disease group until the time of patient death. A combination therapy including agents that reduce IL-6 levels was suggested to be a new

Table 1 Different studies analyzing serum IL-6 in breast cancer patients

Study's intention	*n*	Results/mean IL-6 (pg/ml)	Ref
Compares IL-6 levels in healthy persons with breast cancer patients	25 vs 45 36 vs 111	3.3 vs 31.7 (median) 0.7 ± 2.5 vs 38.3 ± 138.7 Both studies showed significantly higher serum IL-6 levels in breast cancer patients compared to controls	43 45
Compares IL-6 levels in healthy persons with patients of different tumor stages	12 9 11	Healthy: 9.81 ± 3.96 Stage II: 16.7 ± 8.7 Stage III/IV: 29.4 ± 12.9 Serum levels of IL-6 were higher in stage II than in the control, stage III/IV patients had increased serum levels of IL-6 compared to stage II	51
Compares IL-6 levels in different tumor stages (median)	6 23 12 4	Stage IIA: 18.7 Stage IIB: 19.3 Stage IIIA: 40.9 Stage IIIB: 44.1 Level of IL-6 correlated with clinical stage of disease	43
Compares different severity of metastasis (median)	24 72 49	One metastatic site: 3.06 ± 6.6 Two or more metastatic sites: 8.15 ± 1.7 Liver metastasis: 8.3 ± 2.4 Patients with two or more metastatic sites had higher IL-6 values compared to those with one metastatic site. The authors suggest that serum IL-6 mirrors the ongoing tumoral growth process	49
Analyses the association between IL-6 levels and clinical outcome in metastatic breast cancer patients	43 80	Higher serum IL-6 (cutoff: >5 pg/ml, median) was associated with inferior progression free and overall survival in metastatic breast cancer patients High level of serum IL-6 (cutoff: ≥55 pg/ml) was significantly correlated to a shorter suvival in metastatic breast cancer patients	47 50
Analyses the association between IL-6 levels and therapeutic success in metastatic and recurrent breast cancer patients, respectively	4 20 12 10 16/10 12	CR: 2.4 ± 1.2 PR: 4.1 ± 1.0 NC: 7.4 ± 3.8 PD: 36.3 ± 13.2 PR/NC: 11.0 ± 2.1 PD: 15.3 ± 2.7 Both studies show that elevation of IL-6 levels indicates poor prognosis in metastatic and recurrent breast cancer patients, respectively	48 44
Compares IL-6 levels in non-recurrent and recurrent breast cancer patients	17 65	Non-recurrent: 1.96 ± 1.38 Recurrent: 6.50 ± 7.48 IL-6 levels were significantly higher in recurrent than in non-recurrent cases	46

Ref reference, *vs* versus, *CR* complete response, *PR* partial response, *NC* no change, *PD* progressive disease

strategy for aggressively treating recurrent breast cancer. Similar results were achieved by Bachelot et al. [50]. They investigated the clinical significance of vascular endothelial growth factor (VEGF) and IL-6 in hormone-refractory metastatic breast cancer and found that the presence of high levels of serum IL-6 (but not VEGF), was significantly correlated to a shorter survival. In a multivariate analysis along with clinical prognostic parameters, serum IL-6 was identified as an independent adverse prognostic variable for OS. With regard to disease extension, they did not find any correlation between IL-6 levels and liver involvement or IL-6 levels and the number of metastatic sites (whereas Saldago et al. [49] found a correlation with liver metastases). Another study by Jablonska et al. [51] found serum levels of IL-6 in breast cancer patients in stage II to be higher (16.7 ± 8.7) than in the control (9.81 ± 3.96 pg/ml), furthermore, breast cancer patients in stage III/IV had increase serum levels of IL-6 (29.4 ± 12.9) compared with stage II, and they concluded that changes in values of certain cytokines could have a diagnostic and prognostic role in cancer disease.

Taken together, there are lots of indications that serum IL-6 level is a negative prognosticator in breast tumor patients, which might eventually present the rationale for introducing an additive anti-IL-6 treatment regiment to the up-to-date therapy. On the other hand, the significance of IL-6 in BT and results of different in vitro experiments are not uniformly clear. Therefore, additional studies are necessary to rule out the significance of IL-6 in breast cancer disease and results should be interpreted with caution.

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