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Estradiol Increases IL-8 Secretion of Normal Human Breast Tissue and Breast Cancer In Vivo

Christina Bendrik and Charlotta Dabrosin

IL-8 or CXCL8 has been associated with tumor angiogenesis, metastasis, and poor prognosis in breast cancer. Estrogen is crucial in breast carcinogenesis and tumor progression. Whether sex steroids affect IL-8 secretion of normal breast tissue or breast cancer is not known. Several cell types in a tissue secrete IL-8. Hence, regulatory mechanisms of IL-8 need to be investigated in whole tissue. We used microdialysis to sample IL-8 in normal human breast tissue in situ in pre- and postmenopausal women, preoperatively in breast cancers of women, and in experimental breast cancer in mice. We found a significant positive correlation between IL-8 and estradiol in normal breast tissue and hormone-dependent breast cancer in vivo. Ex vivo, estradiol exposure increased the IL-8 secretion of normal whole breast tissue in culture. In experimental breast cancer, estradiol increased IL-8 whereas the anti-estrogen tamoxifen inhibited the secretion of IL-8 both in vitro and extracellularly in vivo in tumors of nude mice. An anti-IL-8 Ab inhibited endothelial cell proliferation induced by cancer cell produced IL-8 and tumors with low IL-8 levels exhibited decreased angiogenesis. Our results strongly suggest that estradiol has a critical role in the regulation of IL-8 in normal human breast tissue and human breast cancer. IL-8 may present a novel therapeutic target for estrogen driven breast carcinogenesis and tumor progression. The Journal of Immunology, 2009, 182: 371–378.
were cultured and exposed to estradiol and progesterone. Our results revealed that estradiol has a significant effect on IL-8 secretion both in normal breast tissue and breast cancer in vitro and in vivo.

Materials and Methods

Subjects

The local ethical committee approved the study, and all women gave their informed consents. Of the healthy volunteer women, 12 were premenopausal (aged 22–30 years) and 6 postmenopausal (aged 52–55 years). All had been off sex steroid containing medication such as contraceptive methods or hormone replacement therapy for more than 3 mo. All premenopausal women had history of regular menstrual cycles (cycle length 27–34 days). Eight of the premenopausal women were investigated in the luteal phase of the menstrual cycle, whereas four were investigated in the follicular phase. The breast cancer patients were all postmenopausal (aged 51–86) as defined by having no spontaneous menstrual bleedings for at least 1 year. None of the patients had ongoing hormonal treatment.

Microdialysis of healthy volunteers and breast cancer patients

A microdialysis catheter (CMA/Microdialysis AB), which consists of a tubular dialysis membrane (10 mm long × 0.52 mm in diameter, 100,000 atomic mass cut-off) glued to the end of a double-lumen tube (100 mm long × 0.8 mm in diameter), was used. The catheters were inserted guided by a catheter for i.v. use (Venflon 1.4 mm; BOC Ohmeda AB). The catheters were connected to a microinfusion pump (CMA 107; CMA/Microdialysis AB) and perfused with NaCl 154 mmol/L and dextran-70 40 g/L, at a perfusion rate of 0.5 μL/min. The solution entered the catheter through the outer tube and left through the inner tube from which it was collected. After a 90-min equilibration period, the outgoing perfusate was collected and stored at −70°C for subsequent analysis.

Mepivacaine (5 mg/ml) was administrated intracutaneously as a local anesthetic before the insertion of the microdialysis catheters. In the healthy volunteers, one microdialysis catheter was placed in the upper lateral quadrant of the left breast and directed toward the nipple as previously described (24–27). In the premenopausal women, a second catheter was inserted in abdominal s.c. fat. The breast cancer patients were investigated on the day before or on the same day as surgery. In these women, the microdialysis catheters were inserted intratrunomally in the center of the tumors. No complications occurred during or after the microdialysis experiments.

Microdialysis is a technique that allows continuous sampling of the extracellular fluid by passive diffusion of substances over a semipermeable membrane. The recovery, i.e., the amount of substances from the tissue that diffuses into the perfusion fluid, depends on the membrane properties, the flow rate, and the size of the compound of interest (28). Diffusion of low molecular substances over the dialysis membrane is almost complete at low flow rate, and the size of the compound of interest (28). Diffusion of low molecular substances over the dialysis membrane is almost complete at low flow rates using a 30-mm long dialysis membrane (29). However, for larger molecules, the recovery over the membrane decreases and the measured levels in the microdialysis sample will not be absolute concentrations in the tissue. The recovery of certain substance may be measured in vitro by putting a microdialysis in a vial containing the compound of interest, perfuse the catheter, and divide the concentration of the substance in the dialysate by the concentration in the vial. This in vitro recovery can only be an estimate of the in vivo recovery since other factors such as tissue pressure and temperature will affect the diffusion of substances. The in vitro recovery of IL-8 was 15.3 ± 0.35%. The microdialysis results in the present paper are, however, given as the raw data without any re-calculations based on the in vitro recovery.

Breast tissue biopsies

Biopsies from human breast tissue were obtained from premenopausal women, without ongoing hormonal treatment, undergoing routine resection mammoplasty as previously described (23). Tissue biopsies containing epithelium, stroma, and adipose tissue were produced by using an 8-mm biopsy punch (Kai Europe) and placed in a 12-Well plate (Costar). Serum-free medium was used consisting of a 1:1 mixture of nutrient mixture F-12 (Invitrogen) and DMEM without phenol red (Invitrogen) supplemented with transferrin (10 μg/ml; Sigma-Aldrich), insulin (1 μg/ml; Sigma-Aldrich), and BSA (0.2 mg/ml; Sigma-Aldrich) with or without physiological levels of estradiol (17β-estradiol; E2, Sigma-Aldrich) 10−9 M or a combination of 10−8 M estradiol and 10−8 M progesterone (E2 + P4; Sigma-Aldrich). Control biopsies were incubated in media supplemented with the vehicle, ethanol, equivalent to the hormone treated groups (0.001%). The biopsies were treated for 7 days at 37°C in a humidified atmosphere containing 5% CO2 and the medium was changed every day. After the seventh day of incubation, the medium from each biopsy was collected and stored at −70°C and the biopsies were formalin fixed and embedded in paraffin for subsequent analyses.

Cells and culture conditions

MCF-7 (HTB-22; human breast adenocarcinoma, ER- and PR-positive) cells were obtained from ATCC. Cells were cultured in DMEM without phenol red supplemented with 2 mM glucose, 50 IU/ml penicillin-G, 50 μg/ml streptomycin, and 10% FBS at 37°C in a humidified atmosphere of 5% CO2. Cell culture medium and additives were obtained from Invitrogen if not otherwise stated.

Hormone treatment of MCF-7 cells in culture

Confluent cells were trypsinized (0.05% trypsin and 0.02% EDTA) and seeded into six-well dishes (Costar, 20,000 cells/well). Cells were incubated in the DMEM supplemented with estrogen medium for 24 h and then treated with or without 10−9 M estrogen (17β-estradiol; Sigma-Aldrich), 10−6 M tamoxifen (Sigma-Aldrich), or a combination of estrogen and tamoxifen for 7 days. Hormones were added in serum-free medium consisting of a 1:1 mixture of nutrient mixture F-12 (HAM) and DMEM without phenol red, supplemented with 10 μg/ml transferrin (Sigma-Aldrich), 1 μg/ml insulin (Sigma-Aldrich), and 0.2 mg/ml bovine serum albumin (BSA) (Sigma-Aldrich). The hormone medium was changed every day. After hormone treatment, the conditioned media was collected and cells were lysed by repeated freeze-thaw cycles after a PBS wash. Total protein content was determined using Bio-Rad Protein Assay with BSA as standard (Bio-Rad). Samples were stored at −70°C until subsequent analyses.

Animals and ovariecotony of mice

Female athymic nude mice (6- to 8-wk old) were purchased from Taconic M&B. They were housed in a pathogen-free isolation facility with a light/ dark cycle of 12/12 h and fed with rodent chow and water ad libitum. All animal work was approved by the Linköping University animal ethics research board. Mice were anesthetized with i.p. injections of ketamine/xylazine (Apoteket), ovariecotimized, and 3-mm pellets containing 17β-estradiol, 0.18 mg/60-day release (Innovative Research of America) were implanted s.c. in the animal’s back 7 days before tumor induction. The pellets provide a continuous release of estradiol at serum concentrations of 150–250 pM, which is in the range of physiologic levels seen in mice during the estrous cycle. One week after surgery, MCF-7 cells (5 × 105 cells in 200 μL PBS) were injected s.c. on the right hind side flank or in the mammary fat pad. Tumor volume was monitored by measuring length, width, and depth of the tumor every 4 days using a caliper. At a tumor size of ~300 mm3, the mice were divided into two subgroups. One group continued with the estradiol treatment only, while tamoxifen (1 mg/every 2 days s.c.) was added to the estradiol treatment in the other group.

Microdialysis experiments of breast cancer explants in mice

Tumor-bearing mice were anesthetized with an i.p. injection of ketamine/xylazine and thereafter kept anesthetized by repeated s.c. injections of ketamine/xylazine. A heating lamp maintained body temperature. A small skin incision was made and microdialysis probes (CMA/20, 0.5-mm diameter; PES membrane length 10 or 4 mm, 100 KDa cutoff; CMA/Microdialysis) were inserted into tumor tissue and sutured to the skin. The probes were connected to a CMA/102 microdialysis pump (CMA/Microdialysis) and perfused at 1 or 0.6 μL/min with saline containing 154 mM NaCl and 40 mg/ml dextran (Pharma link). After a 90-min equilibration period, the outgoing perfusates (microdialysates) were collected on ice and stored at −70°C for subsequent analysis. At the end of the experiments, the mice were euthanized and the tumors excised. The removed tumors were weighed, formalin-fixed, and subsequently embedded in paraffin for immunohistochemical analysis.

Determinations of estradiol, progesterone, and IL-8

Plasma of women undergoing microdialysis was collected using a glass tube containing sodium citrate 3.8% as an anticoagulant, and were spun down and frozen at −70°C within 20 min of collection. Microdialysates, plasma, and culture samples were analyzed for IL-8, estradiol, and progesterone using commercial quantitative immunoassay kits, IL-8 by using the Fluorokine MAP cytoxine multiplex kits (R&D systems), and analyzed with the Lumexin 100 analyzer. The sensitivity of IL-8 was 0.39 pg/ml and intra-assay variation 4.6–7.8%. Estradiol and progesterone were analyzed using ELISA kits (DRG Instruments). The sensitivity of the estradiol assay was 16 pmol/l and the intra-assay variation 5%. For progesterone, the cut-off level for luteal phase was 13 nmol/L, sensitivity 0.15 mmol/L and intra-assay variation 5%. The intra-assay variation of the kits was confirmed during the experiments.
**Immunohistochemistry**

Formalin-fixed, paraffin-embedded normal breast tissue biopsies and tumors of nude mice were cut in 3-μm sections, deparaffinized, and subjected to anti-IL-8 immunohistochemistry (mouse anti-human IL-8, dilution 1/20 for breast biopsies and goat anti-human IL-8, dilution 1/20 for MCF-7 tumors (R&D Systems), with Envision detection (Dako)) Sections were counterstained with Mayer’s hematoxylin. Negative controls with isotype IgG did not show staining. All sections were first scanned to identify the range of intensity of the staining. Thereafter, the staining on each tumor or biopsy section was scored either as weakly or strongly positive. In a blinded manner, 10 high power fields (×200) were examined per section.

**Intratumoral microvessel density**

Formalin-fixed, paraffin-embedded tumors and breast tissue biopsies were cut in 3-μm sections, deparaffinized, and subjected to anti-von Willebrand’s factor (rabbit anti-human von Willebrand; dilution 1/1000; Dako). Sections were counterstained with Mayer’s hematoxylin. Negative controls did not show staining. In a blinded manner, 10 high power fields (×200) were examined of three different sections in each group. Vessel quantification of tumor sections was conducted as described previously using a Nikon microscope equipped with a digital camera (30). Percentage of area stained positively for von Willebrand’s factor was assessed using Easy Image Measurement software (Bergstrom Instruments). Tumor sections were also subjected to H&E staining.

**HUVECs and in vitro cell proliferation assay**

HUVECs were isolated from female donors by collagenase digestion at 37°C for 20 min as previously described (31). Cells were grown in medium consisting of Medium 199 without phenol red supplemented with 1% non-essential amino acids, 1.6 mM glutamine, 4 IU/ml penicillin G, 4 μg/ml
Results

Significant positive correlation between E2 and extracellular IL-8 in normal breast tissue

There were no subsequent complications after the microdialysis experiments.

In the twelve women subjected to microdialysis in normal breast and s.c. fat, there was a positive significant correlation between extracellular local E2 levels and extracellular breast IL-8, \( r = 0.828, p = 0.0009, n = 12 \), Fig. 1A. There was also a significant correlation between local breast IL-8 and plasma E2, \( r = 0.716, p = 0.009, n = 12 \), Fig. 1B. There was no correlation between plasma P4 and local extracellular breast IL-8, \( r = 0.177, p = 0.6, n = 12 \), Fig. 1C. Microdialysis was also performed in abdominal s.c. abdominal fat. There was no significant correlation between extracellular fat IL-8 and extracellular local fat E2, \( r = 0.237, p = 0.23, n = 12 \), Fig. 1D. There was no significant correlation between extracellular fat IL-8 and plasma E2, \( r = 0.347, p = 0.3, n = 12 \), Fig. 1E; and no significant correlation was found between extracellular fat IL-8 and plasma P4, \( r = 0.043, p = 0.9, n = 12 \), Fig. 1F.

There was no correlation between plasma IL-8 and plasma E2 levels, \( r = 0.172, p = 0.6 \). Six postmenopausal women were investigated with microdialysis in normal breast tissue to include a group with very low endogenous estrogen levels. Fig. 1G shows a significant correlation between local E2 levels and local IL-8 levels in this larger cohort, \( r = 0.82, p < 0.0001, n = 18 \).

Increased secretion of IL-8 by estradiol incubation of normal human breast tissue biopsies

We have previously shown that breast biopsies maintain tissue morphology without developing necrosis during 7 days of culture analyzed with H&E staining and luminal cytokeratin 18 staining (23). We have also shown that ER and progesterone receptors (PgR) are preserved and that the breast epithelial cells proliferate i.e., express Ki67 when the biopsies are harvested after 7 days of culture with and without added hormones (23). In the breast biopsy experiments (n = 6 in each group), E2 exposure induced a significant increase of IL-8 secretion into the media, \( 1071 \pm 70 \) pg/g tissue, compared with \( 407 \pm 72 \) pg/g tissue in the control group, \( p < 0.01, E2+P4 \) treatment to the tissue increased the IL-8 levels in a similar manner as E2 exposure only, \( 868 \pm 55 \) pg/g tissue, \( p < 0.05 \) compared with controls, Fig. 2.

IL-8 and von Willebrand’s factor immunohistochemistry of normal breast tissue biopsies

The immunohistochemistry staining revealed that the epithelial cells showed most intense staining for IL-8 compared with the stroma. There was an increased intensity of staining and a greater...
and Methods section, 10 detected, open triangles. PgR estradiol (E2) and tumor IL-8 in ten postmenopausal patients. In ER/PgR patients, there were no significant correlations between extracellular IL-8 and estradiol or ER, PgR content, stage, tumor histology or grade, or size. Ten postmenopausal breast cancer patients were subjected to microdialysis before surgery. All patients had palpable tumors, and the microdialysis catheter was inserted in the center of the tumor. Routine clinicopathological data such as content of ER and PgR, tumor histology and grade, and stage of the excised tumors were determined. All ten tumors expressed ER, and five tumors coexpressed ER with the PgR. There was a significant positive correlation of ER/PgR-positive human breast cancer cells MCF-7 was cultured in presence of estradiol, tamoxifen, and a combination of the two hormones for 7 days. IL-8 was analyzed in the cell culture media and correlated to total protein content. Estradiol at 10^{-9} M increased the secretion significantly compared with control cells cultured without hormones, p < 0.01, n = 4 in each group, Fig. 6. By increased concentrations of estradiol on the MCF-7 cells the levels of IL-8 increased further; 5.48 ± 0.4 pg/mg protein in 10^{-9} M exposed cells to 7.26 ± 0.5 pg/mg protein in 10^{-8} M exposed cells, p < 0.05 n = 4–5 in each group. Tamoxifen added to estradiol in the media counteracted the increase seen after estradiol exposure only, p < 0.01, n = 4 in each group, Fig. 6. Tamoxifen alone had no significant effects compared with control cells, Fig. 6.

ABX-IL-8 decreased endothelial cell proliferation induced by cancer cell released IL-8

It has previously been shown that IL-8 induces endothelial cell proliferation (32). In a first set of experiments, we cultured HUVEC with rIL-8 50 ng/ml, which induced an increased proliferation of the HUVECs to 0.147 ± 0.007 (OD at 490 nm) vs 0.115 ± 0.007 in the control cells, p < 0.01. The combination of r50 ng/ml IL-8 and ABX-IL-8 at 100 µg/ml decreased the proliferation rate significantly compared with IL-8 alone, 0.147 ± 0.007 in the IL-8 exposed cells to 0.121 ± 0.003 in the combination group, p < 0.01. In a tumor, secreted proteins from the tumor cells affect the surrounding stroma including endothelial cells. To investigate whether the tumor cell derived IL-8 from MCF-7 cells...
had any physiological significance on endothelial cell proliferation, we treated HUVEC with cell culture media from E2-treated MCF-7 cells. ABX-IL-8 was either added to the MCF-7 cells during their culture or freshly added to the HUVEC cells together with the collected MCF-7 culture media. ABX-IL-8 decreased proliferation of HUVECs significantly compared with MCF-7 supernatant, \( p < 0.001 \), 6 in each group. Freshly added ABX-IL-8 was more efficient than ABX-IL-8 added during the MCF-7 cell culture, \( p < 0.001 \), n = 6 in each group, Fig. 7. Control IgG did not affect HUVEC proliferation compared with cells grown without IgG, data not shown.

**Tamoxifen decreased IL-8 secretion of solid breast cancer tumors in vivo**

To verify whether the inhibition of E2 released IL-8 by the anti-estrogen tamoxifen in vitro also were valid in whole tumor tissue, MCF-7 tumors were established in ovariectomized nude mice. One group of mice was treated with estradiol only and in the other group tamoxifen treatment was added. MCF-7 tumors require estradiol for growth in nude mice; therefore, a nonhormone treated group is not possible to achieve in vivo. Microdialysis of the tumors was performed to sample IL-8 from the extracellular space. In the s.c. tumors, a 10-mm microdialysis catheter perfused at 1 \( \mu l/min \) was used. The mammary fat pad tumors were smaller, dependent on the approval of the ethical committee, and these tumors were therefore investigated with a 4-mm long microdialysis catheter with a perfusion rate of 0.6 \( \mu l/min \) to compensate for the shorter membrane. Similar to the in vitro results, tamoxifen treatment resulted in a significant decrease of IL-8 secretion compared with estradiol only exposed s.c. tumors. IL-8 \( 16.3 \pm 2.4 \) pg/ml in E2 tumors compared with \( 10.3 \pm 0.47 \) pg/ml in the E2+T tumors, \( p < 0.05 \), Fig. 8A. The level of decrease was similar, although the absolute levels were lower dependent on the shorter microdialysis membrane, in tumors grown in the mammary fat pad, \( 7.55 \pm 0.4 \) in the E2 exposed group and \( 3.98 \pm 0.3 \) in the E2+T treated group, \( p < 0.001 \), Fig. 8B.

**Immunohistochemistry revealed a significant difference of intensity of staining after tamoxifen treatment.** In the estradiol group, seven out of nine tumors were scored as intensely stained in the E2 group whereas one out of six tumors showed intense staining in the E2+T group, \( p = 0.04 \). Bars 100 \( \mu m \). D, Microvessel area in solid MCF-7 tumors, \( *, p = 0.01 \).
extracellular IL-8 levels in vivo, whereas no correlations were found in s.c. fat. Our in vivo results were confirmed ex vivo where estradiol treatment to normal human whole breast biopsies in culture increased IL-8 secretion significantly compared with biopsies cultured without added hormones. Progesterone had neither a counteracting nor additive effect on IL-8 secretion. In breast cancer tumors of women, extracellular IL-8 and local estradiol correlated significantly in tumors that were positive for both ER and PgR. This was further investigated in ER\(^+/\text{PgR}^+\) MCF-7 breast cancer cells in culture, which increased their secretion of IL-8 after estradiol exposure. An Ab against IL-8, ABX-IL-8, inhibited cell proliferation of HUVEC exposed to media collected from MCF-7 cell culture. Moreover, the anti-estrogen tamoxifen inhibited the estradiol-induced IL-8 secretion. In solid MCF-7 tumors grown in nude mice, extracellular IL-8 in vivo was decreased after tamoxifen therapy compared with estrogen treatment only and these tumors also exhibited a decreased anti-IL-8 staining and decreased vessel density. Our results suggest that estradiol has a direct regulatory effect on IL-8 secretion in normal human breast tissue and in ER\(^+/\text{PgR}^+\) breast cancer.

IL-8 has been shown to be up-regulated in several human cancers including breast cancer (33, 34). Higher levels of IL-8 in breast cancer compared with normal breast tissue has been demonstrated and higher serum levels of IL-8 in breast cancer patients have been associated with poor prognosis, increased tumor burden, and decreased postrelapse survival (6, 33). In experimental studies using breast cancer cell lines, a strong correlation between the metastatic phenotype and IL-8 expression has been shown suggesting a promoting role for IL-8 metastatic potential of tumor cells (9). In another tumor model, no proliferative activities of IL-8 in cancer cell culture were demonstrated but in tumor-bearing mice a neutralizing anti-IL-8 Ab induced decreased tumor growth and metastasis, and reduced angiogenic activity and vascular density (35). This suggests that IL-8 does not function as an autocrine growth factor but rather functions as a proangiogenic factor. IL-8 has also been shown to direct stimulate endothelial cell proliferation, survival, chemotaxis, and migration supporting the evidence of IL-8 as a proangiogenic factor (10, 32, 36).

Estrogens have been shown to increase angiogenesis and vascular endothelial growth factor (VEGF) expression in experimental breast cancer and normal human breast tissue (25, 37–39). Whether sex steroids are involved in the regulation of IL-8 is not known, and published data are somewhat contradictory. Generally, breast cancer cell lines expressing ER are of low metastatic potential and express very low levels of several cytokines and angiogenic molecules such as VEGF and IL-8, whereas ER-negative cell lines are more invasive and express high levels of these proteins. This does not, however, rule out an estrogen-dependent regulation of IL-8 in less metastatic breast cancer cells. We have previously shown that VEGF secretion is increased by estradiol in MCF-7 cells although these cells express VEGF at very low levels (40, 41). Very few studies have investigated direct effects on IL-8 secretion after estrogen exposure in hormone-dependent breast cancer models. Our present results suggest that estrogen has a role in the regulation of IL-8 secretion and the physiological consequence of this cancer cell released IL-8 on endothelial cells was proliferation, efficiently inhibited by a fully human anti-IL-8 Ab, ABX-IL-8.

In conclusion, the control of extracellular IL-8 seems to be dependent on estradiol in normal human breast and breast cancer in vivo. The increase of IL-8 by estrogen in experimental breast cancer caused endothelial cell proliferation, which was efficiently inhibited by an anti-IL-8 Ab, suggesting a physiological role of the estrogen induced IL-8.

The incidence of breast cancer is increasing in the Western world and it has long been known that sex steroids increase the risk, whereas an early oophorectomy reduces the risk, of breast cancer by up to 60% (45, 46). Ovarian ablation is, however, associated with osteoporosis and cardiovascular disease as well as vasomotor symptoms and urogenital atrophy. Anti-estrogen therapies such as aromatase inhibitors and tamoxifen are effective therapies against breast cancer, and tamoxifen may also reduce the incidence of new breast cancers by more than 40% (47–49). However, these treatments may induce severe side effects such as endometrial cancer, thromboembolism, osteoporosis, and vaginal atrophy. Hence, there is an urgent need for studies of the
mechanisms of sex steroids on normal breast tissue and breast cancer to develop novel, more selective preventive and therapeutic strategies against this disease. IL-8 may be one potential target in estrogen dependent breast carcinogenesis and breast cancer progression.

Disclosures

The authors have no financial conflict of interest.

References


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