Biochemical and Biophysical Research Communications 431 (2013) 729–733

Contents lists available at SciVerse ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Estrogen represses CXCR7 gene expression by inhibiting the recruitment of NFκB transcription factor at the CXCR7 promoter in breast cancer cells

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ARTICLE INFO

Article history:
Received 9 January 2013
Available online 23 January 2013

Keywords:
Estrogen
Estrogen receptor
NFκB
CXCR7
Breast cancer cells

ABSTRACT

Although many studies reported mechanisms involved in the positive regulation of estrogens (E2) target genes, very little is known concerning the repressive effect of E2. In this study, we explored the molecular mechanisms by which E2 regulates CXCR7 expression in breast cancer cells. Our results show that E2-mediated down-regulation of CXCR7 occurs at the transcriptional level as demonstrated using actinomycin D and requires estrogen receptor alpha (ERα). In addition, CXCR7 is a primary ERα-target gene because the effect of E2 does not require the synthesis of an intermediary protein as revealed by the translational inhibitor cycloheximide treatment. Using an inhibitor of the NFκB pathway and chromatin immunoprecipitation assays, we demonstrated that NFκB is necessary for the high expression of CXCR7 gene and is recruited to the proximal promoter of the CXCR7 gene. Interestingly, the chromatin immunoprecipitation analyses also showed that E2-treatment significantly prevented the recruitment of NFκB to the promoter. Altogether, our results demonstrate that E2, through ERα, directly down-regulates CXCR7 expression by interfering with NFκB transcription factor at the promoter level.

1. Introduction

The close link between the signaling network of chemokines and immune response associates these proteins to autoimmune, inflammatory and infectious diseases (for review: [1]). Recent research has also demonstrated the importance of the chemokines and their receptors in cancer progression. The chemokine CXCL12 and its receptor CXCR4 play crucial roles in growth and metastasis of several cancer cells including hormone dependent prostate and breast cancers [2–4]. The couple CXCL12/CXCR4 has long been considered as exclusive until recently when the orphan receptor CXCR7 was identified as a second receptor for CXCL12 [5,6]. Importantly, CXCR7 was shown to bind with a higher affinity to the chemokine CXCL12 than that found with CXCR4. It is now clear that CXCR7 can relay CXCL12 signaling in the cell. However, unlike CXCR4, the activation of CXCR7 by CXCL12 does not lead to the activation of the intracellular G proteins [7,8] suggesting a differential cellular pathway. Nevertheless, CXCR7 is capable of mediating CXCL12 signalization through ligand-dependent β-arrestin recruitment, leading to CXCR7 internalization and subsequently to the activation of MAPK/Erk signaling pathway. Additionally, some authors suggest that CXCR7 could act as a decoy receptor for CXCL12 that could scavenge the ligand to limit CXCL12 signaling *via* CXCR4 [9–11]. Thus, these modes of actions of CXCR7 allow it to mediate CXCL12 signaling, but also to modulate the CXCR4 signaling.

CXCR7 is involved in various biological processes such as the control of adhesion, mobility, angiogenesis and cell survival [6]. The expression of CXCR7 was frequently associated with the invasive or more aggressive phenotype of cancer cells [5,12,13]. Moreover, overexpression of CXCR7, *in vitro*, was reported to induce the migration of bladder cancer cells [14] and resulted in markedly higher estrogen-independent growth of MCF-7 breast cancer cells [15]. Similarly, CXCR7 promotes formation and growth of mammary tumors in animal models [16].

Although the regulation of CXCR4 by estrogens (E2) in breast cancer cells is well-documented [17–19], very little is known concerning the E2-regulation of CXCR7 gene. Because our recent data showed that the expression of CXCR7 gene is robustly down-regulated when estrogen receptor (ER)-positive breast cancer cells are exposed to E2, we asked for the molecular events leading to this repression. In this study, we demonstrated that E2-mediated down-regulation of CXCR7 occurs at the transcriptional level by interfering with NFκB signaling pathways in breast cancer cells. We showed that in the presence of E2, ERα impedes the recruitment of NFκB transcription factor at the CXCR7 promoter resulting in a strong reduction of CXCR7 gene expression.

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http://dx.doi.org/10.1016/j.bbrc.2013.01.050

2. Materials and methods

2.1. Antibodies and reagents

17-β-Estradiol (E2), $ICI_{182,780}$ (ICI), 4-hydroxy tamoxifen (4-OHT), Actinomycin D, Cycloheximide, and BAY 11-7082 were purchased from Sigma–Aldrich Co. (Munich, Germany), TNFα from R&D (Minneapolis, MN USA), and 4,4′,4″-(propyl-pyrazole-triol (PPT), 3,17-dihydroxy-19-nor-17a-pregna-1,3,5(10)-triene-21,16α-lactone (16α-LE2) and diarylpropionitrile (DPN) from Tocris Bioscience (Bristol, UK).

Antibodies used for Western blot assays were rabbit polyclonal (Rp) antibody against ERα (HC-20, sc-543), NFκB p50 (NLS) (sc-114) and murine monoclonal antibody against actin-β (AC-15, sc-69879) purchased from Santa Cruz. The Rp antibody against IκB-α (#9242) and the rabbit monoclonal antibody against P-IκB-α Ser32 (14D4) (#2859) were purchased from Cell Signaling (Danvers, MA, USA).

2.2. Cell culture and treatments

MCF-7 cells were routinely maintained in DMEM (Invitrogen) supplemented with 10% fetal calf serum (FCS; Sigma, St. Louis, MO, USA) and antibiotics at 37 °C in 5% CO_2. When treatments with steroids were required, cells were maintained 48 h in DMEM-F12 (Sigma) supplemented with 2.5% dextran treated charcoal stripped FCS (dsFCS) prior to the experiments.

2.3. RT-PCR assays

Total RNA were extracted using Trizol™ reagent (Invitrogen) after treatments. cDNAs were generated by the MMLV Reverse transcriptase using random hexamers (Promega). Semi-quantitative PCR were performed with the Qiagen Taq Polymerase (Qiagen, Courtaboeuf, France). Quantitative RT-PCRs were made using the iQ SybrGreen supermix from BioRad (BioRad, Hercules, CA, USA), and were performed on a BioRad MyiQ apparatus. Sequences of primers for CXCR7 mRNA were: rev: ACGAGACTGACCACCCAGAC, fwd: ACAGGCTATGACACGCACTG and for GAPDH: rev: GAGGTCCACCACCCTGTTGC, fwd: GGGCATCCTGGGCTACACTG.

2.4. Chromatin immuno-precipitation (ChIP)

Chromatin immuno-precipitation experiments were performed as described by Métivier et al. [20] with minor modifications. Briefly, after cross-link with 1.5% formaldehyde in PBS, chromatin was purified and sonicated. About 10% of the chromatin preparation was used as input control and the remaining chromatin was submitted to a preclearing step. Immunoprecipitations were performed using the anti-NFκB p50 (NLS) (sc114X) (Santa Cruz Biotechnology). After reversion of the cross-link and DNA purification using Qiaquick PCR product Purification Kit (Qiagen), 1/25 of input and 1/10 of IP were used in PCRs performed to amplify proximal promoter fragments of the CXCR7 gene (primers rev: GGTTTGGACTTTGTGGCTTCACCA; fwd: CTGCTGGCTGCAGACTTGCATTAT).

2.5. Protein extraction/Western blot

Treatments were performed in 10 cm dishes during different time specified for each experiment. Total protein extract was prepared in RIPA buffer (NP40 1%; Na deoxycholate 0.5%; SDS 1%; in PBS) with an anti-proteases mix (Complete EDTA free Antiproteases, Roche) and measure using BioRad DC protein assay kit. Following sonication and quantification, proteins were diluted in Laemmli buffer and after 5 min of denaturation at 95 °C, 30 μg of proteins were separated on SDS polyacrylamide gels (10% or 15%), and transferred on polyvinylidene difluoride membrane (Millipore). Immunocomplexes were detected using the immune Star chemiluminescence system (BioRad).

2.6. Luciferase assay

MCF-7 cells were transfected overnight with a luciferase reporter gene containing NFκB-response elements and a CMV-β gal expression vector as internal control. Cells were then treated with vehicle, TNFα, E2 or 4-OHT for 36 h and lysed in Passive Lysis Buffer (Promega). Luciferase activity was measured using a commercially available kit (Promega). Luciferase assays were performed in triplicate, and the result presented is the mean value form three independent experiments.

2.7. Statistical analysis

Statistical analysis was performed using Student's *t*-test. The values are provided as the mean ± standard error of the mean (SEM) and were considered statistically significant with $p < 0.05$.

3. Results

3.1. E2-induced CXCR7 repression is mediated by ERα

We have previously found that the expressions of CXCR7 is down-regulated by estrogens in the MCF-7 mammary cancer cells in a dose- and time-dependent manner (Fig. 1A) [15]. To further investigate the mechanisms involved, MCF-7 cells were first treated with 10^{-8} M E2 during 6 h, in presence of either an inhibitor of the transcription, the actinomycin D, or with an inhibitor of the protein synthesis, the cycloheximide (Fig. 1B). Actinomycin D markedly repressed the basal expression of CXCR7 and abolished E2 down-regulation of CXCR7. In contrast, cycloheximide had no effect on E2 down-regulation of CXCR7 transcript, indicating that CXCR7 gene is a primary target of estrogens in the MCF-7 mammary cancer cells (Fig. 1B).

In addition, treatment of MCF-7 cells with $ICI_{182,780}$ clearly indicated that the estrogenic repression of CXCR7 was mediated by the ER [15] (and data not shown). To assay the respective role of both ER isoforms for the regulation of the CXCR7 gene, MCF-7 cells were treated with different concentrations of selective ERα agonists (PPT and 16α-LE2) or ERβ agonists (DPN) (Fig. 1C–E). The selective ERα agonists PPT and 16α-LE2, also markedly induced the repression of CXCR7 in a dose-dependent manner, whereas the ERβ agonist DPN had no effect, clearly indicating that the E2-dependent down-regulation of CXCR7 gene transcription is mediated through ERα. Altogether, these results indicate that E2 through ERα has a direct effect on CXCR7 gene transcription that does not depend on the synthesis of an intermediate factor.

3.2. Active NFκB complex is required for basal CXCR7 expression in MCF-7 cells

A recent study has shown that the NFκB transcription factor was recruited on a consensus NFκB site in the proximal promoter of CXCR7 and was necessary for the constitutive CXCR7 gene expression in rhabdomyosarcoma cells [21]. Additionally, ERα was reported to interact with the NFκB signaling pathway [22]. Together, these data suggest that the E2-dependent repression of CXCR7 expression could be mediated by the limitation of the NFκB-dependent regulation of CXCR7. To assess this possibility, we first evaluated the involvement of NFκB in the basal expression

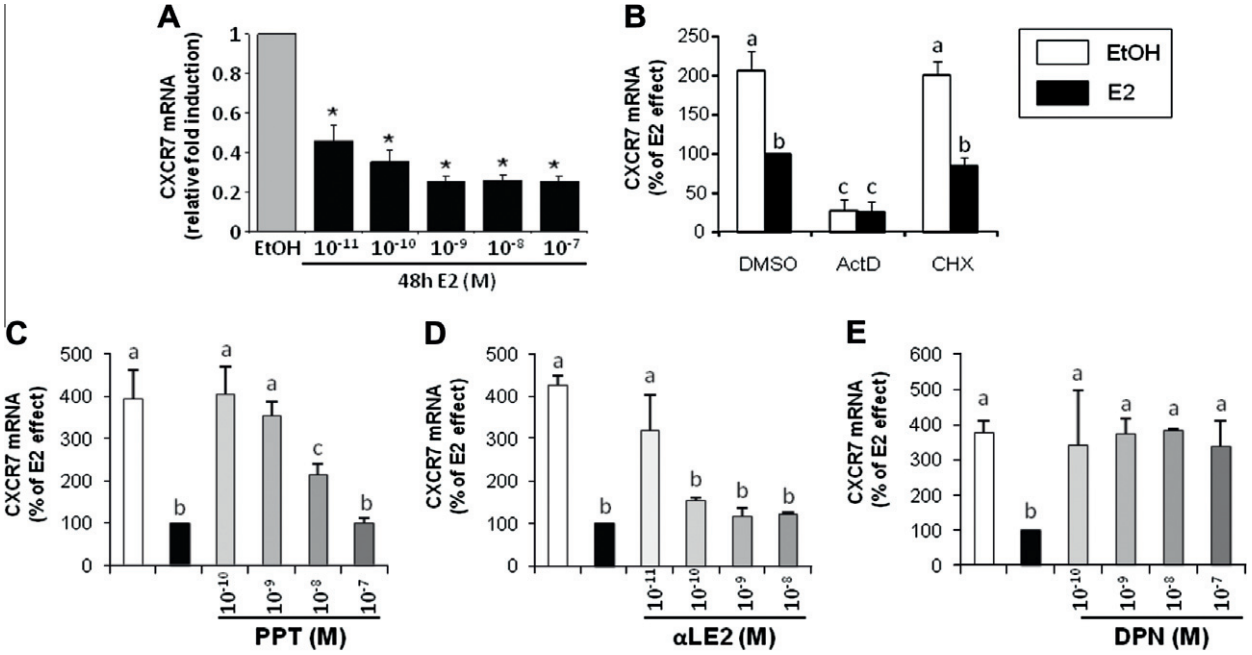

Fig. 1. Repression of CXCR7 expression by E2 in MCF-7 cells is mediated by ERα. (A) MCF-7 cells were treated with ethanol (EtOH) as vehicle or at different concentrations of E2. After 48 h, CXCR7 mRNA was quantified by real time PCR analysis. (B) MCF-7 cells were pretreated for 1 h with DMSO as vehicle, Actinomycin D (ActD), a transcription inhibitor, or cycloheximide (CHX), an inhibitor of protein synthesis, at respectively 5 μg/mL and 20 μg/mL. Cells were then treated for 6 h with ethanol or 10^{-8} M E2. The ERα specific agonists PPT (C) and αLE2 (D) and the ERβ specific agonist DPN (E) dose-reponses on CXCR7 expression were obtained after 24 h treatment. MCF-7 cells were also treated with ethanol and E2 (10^{-8} M) as a control. The real time PCR results were normalized against GAPDH mRNA as internal control and expressed as the mean CXCR7/GAPDH mRNA ratio ± SEM from at least three experiments performed on independent samples. Different lower letters indicate significant differences ($p < 0.05$) between the control and treated cells.

of CXCR7 in the MCF-7 mammary cancer cells. MCF-7 cells were treated with increasing concentrations of the NFκB inhibitor BAY 11-708, which prevents IκB phosphorylation, resulting in a decreased NFκB activity, in the absence or presence of 10^{-8} M E2. Treatment with BAY 11-708 repressed the basal expression of CXCR7 in a dose-dependent manner (Fig. 2A), confirming that NFκB is also necessary for the CXCR7 expression in the MCF-7 mammary cancer cells. Interestingly, the co-treatment of cells with E2 and BAY 11-708 does not lead to an additional repression of the gene compared to that observed with E2 alone, suggesting that the repressor effects of E2 and BAY 11-708 on the expression of this gene are governed by the same mechanisms. The ability of BAY 11-708 to block the phosphorylation of IκB was checked by Western-blot (Fig. 2B). It is also of note that MCF-7 cells treated or not to BAY 11-708 showed similar levels of IκB total protein. Moreover, E2 did not modify the phosphorylation state of IκB or the levels of expression of IκB.

3.3. E2 treatment induced a loss of p50 NFκB subunit recruitment on CXCR7 promoter

To analyze the impact of E2 on the global activity of NFκB, MCF-7 cells were transfected with a luciferase reporter gene containing NFκB-response elements and exposed to TNFα, E2 and the anti-estrogen (4-OHT). As expected, TNFα induced a strong increase of the reporter gene activity, indicating the functional NFκB signaling in MCF-7 cells (Fig. 3). Interestingly, E2 reduced about 40% of the

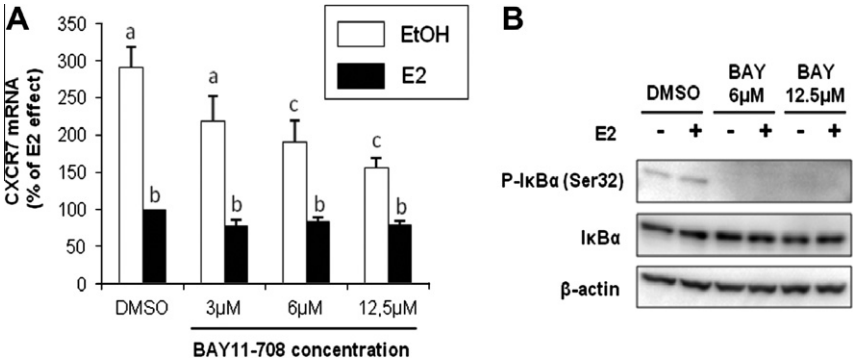

Fig. 2. Inhibition of NFκB signaling pathway represses basal expression of CXCR7. (A) MCF-7 cells were treated for 24 h with ethanol (EtOH) as vehicle, E2 in association with BAY 11-7082, a NFκB inhibitor, at different concentrations or DMSO as vehicle. CXCR7 mRNA was quantified by real time PCR analysis. Results were normalized against GAPDH as internal control and are expressed as the mean CXCR7/GAPDH mRNA ratio ± SEM of at least three independent experiments. Different lower letters indicate significant differences ($p < 0.05$) between the control and treated cells in the same conditions. (B) Total protein was extracted from MCF-7 cells and the levels of P-IκB (Ser32), IκB, and β-actin were analyzed by Western blotting.

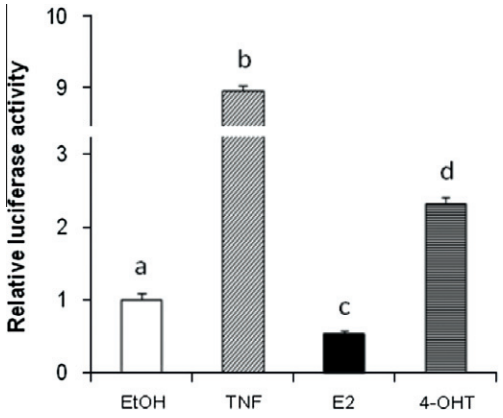

Fig. 3. Estrogenic signaling modulates global NFκB signaling in breast cancer cells. MCF-7 cells were transfected with a luciferase reporter gene containing a NFκB-responsive-element (100 ng) and the CMV-β gal expression vector (50 ng) used as an internal control. Cells were then treated for 24 h with ethanol (EtOH) as vehicle, TNFα (TNF) at 10 ng/mL, E2 10^{-9} M or 4-hydroxy tamoxifen 10^{-7} M (4-OHT). Luciferase activities were normalized to the β-galactosidase values and expressed as the relative luciferase activity ± SEM. Statistical differences ($p < 0.05$) in the absence and presence of different treatments were indicated by lower letters.

reporter gene activity while on the contrary 4-OHT induced a two-fold increased of this activity.

To assess a possible inhibition of the NFκB recruitment at the proximal promoter of CXCR7, we tested the p50 sub-unit of NFκB recruitment by ChIP experiments. Semi-quantitative (Fig. 4A and B) and quantitative PCR (Fig. 4C) were then performed to determine the relative abundance of p50 sub-unit at the CXCR7 promoter. Together, our results showed an impact of E2-treatment on the recruitment of NFκB at the promoter of CXCR7. In fact, while in the absence of E2 treatment, NFκB was robustly found at CXCR7 promoter, its recruitment was weakly detected after hormonal treatment (Fig. 4A–C). It is of note that the repressive effect of E2 is not attributable to alteration in the cellular level of the p50 sub-unit of NFκB since neither E2 nor the pure anti-estrogen $ICI_{182,780}$ modulated the expression of this protein, whereas both E2 and $ICI_{182,780}$ induced ERα degradation, as expected (Fig. 4D).

In conclusion, these results indicate that the repression of CXCR7 expression by estrogens is due to a demobilization of NFκB from the CXCR7 promoter. As NFκB is necessary for CXCR7 expression, the ERα-dependent demobilization of this factor induces a strong reduction in transcription of this gene.

4. Discussion

We have recently reported that the signalization axis of chemokine CXCL12 and its receptors, CXCR4 and CXCR7, plays a major role in E2-mediated proliferation of ER-positive breast cancer cells [15]. Indeed, we reported that the proliferative action of E2 requires up-regulation of CXCL12 and CXCR4, but conversely, down-regulation of CXCR7. More importantly, overexpression of CXCR7 in ER-positive breast cancer cells inhibits E2-enhancement of proliferation and induces E2-independent growth [15]. Recently, a study on the role of CXCR7 in bladder carcinoma showed that high CXCR7 expression is associated with bladder cancer progression and demonstrated that up-regulation of CXCR7 expression enhances the invasion of cancer cells [14]. Considering the importance of ERs and CXCL12 signaling pathways in tumor growth and metastasis of breast cancer, delineating molecular events of estrogen-regulation of CXCR7 in breast cancer cells appears critical.

In this study, we investigated the mechanisms by which E2 represses the expression of CXCR7. Our data clearly indicate that E2 and selective ER-ligands, *via* ERα, directly regulate the expression of CXCR7, resulting in a dose–dependent suppression of its expression. Because MCF-7 treatments with the translational inhibitor cycloheximide did not block E2-mediated CXCR7 repression, CXCR7 can be considered a primary ER target gene in breast cancer cells. Indeed, if the estrogenic repression of this gene involved the synthesis of an intermediate factor responsible for the repression of the transcription of CXCR7, the cycloheximide would have impaired the effect of E2. Furthermore, we demonstrated that in MCF-7 breast cancer cells, the NFκB transcription factor is an activator of CXCR7 gene transcription and it is recruited at the proximal promoter of the gene, as it was shown in rhabdomyosarcoma cells [21]. Our results clearly showed that

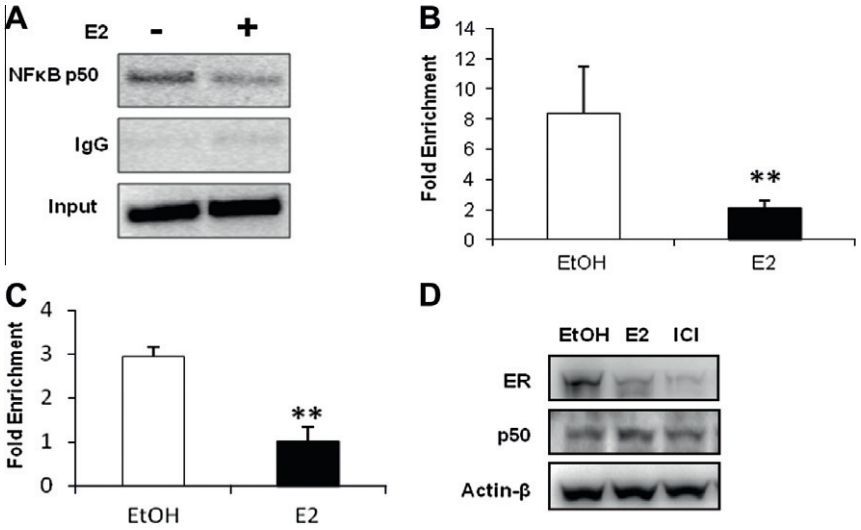

Fig. 4. E2 treatment represses p50 NFκB subunit recruitment on CXCR7 promoter. MCF-7 cells were cultivated in DMEM–F12 2.5% dsFCS, with and without 10^{-8} M E2 for 24 h. Chromatin immunoprecipitation experiments were performed on chromatin samples using antibodies raised against NFκB p50 subunit or negative control rabbit IgG. For each immunoprecipitation (IP), semi-quantitative (A) and quantitative (C) PCR were performed to determine the relative abundance of CXCR7 promoters. (B) Quantification by densitometry of signals obtained in semi-quantitative PCR. Results were normalized against IgG as background control and are expressed as the mean p50 enrichment ± SEM of at least three independent experiments. (D) Total protein was extracted from MCF-7 cells and the levels of ERα, p50 and β-actin were analyzed by western blotting.

E2-treatment impairs the recruitment of NFκB at CXCR7 promoter whereas NFκB is strikingly detected in the absence of E2-treatment. Our results are in good agreement with previously studies reported on interleukine-6 which is also down-regulated by E2 [23,24,22], indicating that E2-repression of ERα-target gene expression by preventing the recruitment of NFκB on its binding site at the proximal promoter may be a widespread mechanisms by which estrogens mediate negative regulations.

Despite the numerous publications describing the role of CXCR7 in the progression of many cancers [12,14,16], we were so far the only group exploring the repressive effect of E2 on CXCR7 expression and the involvement of this regulation in breast cancer cell growth [15]. This regulation could contribute to the braking action that ER exerts on breast cancer cell migration and to the control of hormonal growth [9,16,15]. On the other hand, an enhancement of CXCR7 expression during cancer progression may cause the loss of E2 responsiveness favoring the aggressiveness of the tumor. As a consequence, an improved knowledge of the mechanisms involved in the CXCR7 down-regulation by E2 could lead to the discovery of new therapeutic targets or protocols.

Altogether, our data demonstrated that E2, through ERα, represses CXCR7 in a dose-dependent manner in MCF-7 cells, by abolishing NFκB recruitment at the CXCR7 promoter and NFκB-dependent expression of CXCR7. In the light of these observations, inhibition of NFκB signaling could be used in association with hormonotherapies to inhibit CXCR7 expression in breast cancer cells, thus limiting the proliferative and the pro-migrative effects of this receptor.

Acknowledgment

This work was supported by fellowships from the Brittany Region (to G.K.) and funds from The INSERM and CNRS, The French League against Cancer (La Ligue Contre le Cancer, Grand-ouest, comités 35, 22 et 56), IFR140 Biosit, The University of Rennes 1, and The European University of Brittany. We also thank Dr. Valérie Lecureur for providing the IκB antibodies and the NFκBRE-Luc reporter gene.

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