The RUNX Transcriptional Coregulator, CBFβ, Suppresses Migration of ER⁺ Breast Cancer Cells by Repressing ERα-Mediated Expression of the Migratory Factor TFF1

Henry J Pegg, Hannah Harrison, Connor Rogerson, and Paul Shore

Abstract

Core binding factor β (CBFβ), the essential coregulator of RUNX transcription factors, is one of the most frequently mutated genes in estrogen receptor–positive (ER⁺) breast cancer. Many of these mutations are nonsense mutations and are predicted to result in loss of function, suggesting a tumor suppressor role for CBFβ. However, the impact of missense mutations and the loss of CBFβ in ER⁺ breast cancer cells have not been determined. Here we demonstrate that missense mutations in CBFβ accumulate near the Runx domain–binding region. These mutations inhibit the ability of CBFβ to form CBFβ–Runx–DNA complexes. We further show that deletion of CBFβ, using CRISPR-Cas9, in ER⁺ MCF7 cells results in an increase in cell migration. This increase in migration is dependent on the presence of ERα. Analysis of the potential mechanism revealed that the increase in migration is driven by the coregulation of Trefoil factor 1 (TFF1) by CBFβ and ERα. RUNX1–CBFβ acts to repress ERα-activated expression of TFF1. TFF1 is a motogen that stimulates migration and we show that knockdown of TFF1 in CBFβ⁻/⁻ cells inhibits the migratory phenotype. Our findings reveal a new mechanism by which RUNX1–CBFβ and ERα combine to regulate gene expression and a new role for RUNX1–CBFβ in the prevention of cell migration by suppressing the expression of the motogen TFF1.

Implications: Mutations in CBFβ contribute to the development of breast cancer by inducing a metastatic phenotype that is dependent on ER.

Introduction

Core binding factor β (CBFβ) is the obligate binding partner of all three mammalian Runx transcription factors, Runx1, 2, and 3 (1). Knockout of CBFβ in mouse phenocopies Runx-loss and is embryonic lethal (2, 3). CBFβ binding to Runx proteins protects Runx from proteasomal degradation and causes a conformational change in the runt domain, the DNA-binding domain, which increases its affinity for DNA binding (4, 5).

We have previously shown that CBFβ has a proinvasive role in triple-negative breast cancer cells (6). More recently, mutations in CBFβ (and RUNX1) were reported in breast tumors and are among the most frequently reported for breast cancer tumors (7–9). Many of these mutations are nonsense mutations predicted to result in loss of function, suggesting a tumor suppressor role for CBFβ. In addition, numerous missense mutations have also been reported. However, the effects of these mutations have not been established. All CBFβ mutations reported appear to be in estrogen receptor–positive (ER⁺) breast cancer, with CBFβ mutations estimated to occur in approximately 2.6%–4.7% of all ER⁺ breast cancers (7–9). ERα is a key driver of cell proliferation in ER⁺ breast cancer, and it has recently been shown that RUNX1 prevents ERα-mediated repression of the Wnt pathway repressor, AXIN1, suggesting one explanation for the role of RUNX1 and CBFβ in this context (10).

Trefoil factor 1 (TFF1) is a well-established ERα target gene and is often used as a robust marker of activated ERα. TFF1 is essential for normal function of the gastric mucosa; it is a small, secreted protein that has been described as a “motogen” needed for repair of the gastric epithelia following damage (11). In breast cancer, it has been demonstrated to play a role in cell migration (12) and chemotaxis (13).

To investigate the role of CBFβ in ER⁺ breast cancer, we initially evaluated the mechanistic function of CBFβ missense mutations that occur in patients with breast cancer. All of the missense mutations we studied suppress the formation of the CBFβ–Runx–DNA complex. We then used CRISPR-Cas9 to delete CBFβ in ER⁺ MCF7 cells and we show that loss of CBFβ leads to an increase in cell migration. Subsequent analysis revealed that the increased migration is mediated, at least in part, by the derepression of TFF1 and we demonstrate that the increased TFF1 expression is mediated by loss of ERα repression by CBFβ. Importantly, this mechanism is distinct from the coactivator role of Runx1 previously reported for AXIN1 regulation and reflects a novel explanation for the occurrence of CBFβ mutations in ER⁺ breast cancer.

Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom.

Note: Supplementary data for this article are available at Molecular Cancer Research Online (http://mcr.aacrjournals.org/).

Corresponding Author: Paul Shore, University of Manchester, Michael Smith Building, Oxford Road, Manchester M13 9PT, United Kingdom. Phone: 44-0161-2755978; Fax: 44-0161-2745978; E-mail: paul.shore@manchester.ac.uk

doi: 10.1158/1541-7786.MCR-18-1039

©2019 American Association for Cancer Research.

www.aacrjournals.org
Materials and Methods

Cells and culture conditions

Human HeLa, MCF7, MDA-MB-231, and T47D cell lines were obtained from LGC Standards and were maintained in DMEM (Sigma-Aldrich) supplemented with 10% FBS (Biowest), 1% l-glutamine (Sigma-Aldrich), and 1% penicillin-streptomycin (Sigma). Charcoal-stripped FBS (cs-FBS) was generated by incubation of FBS with 3% (m/v) dextran-coated charcoal (Sigma-Aldrich) at 4°C for 72 hours before filter (0.22 μm) sterilization. For estrogen stimulation experiments, cells were grown in phenol red-free DMEM (Life Technologies), supplemented with 5% cs-FBS, 1% l-glutamine (Sigma-Aldrich), and 1% penicillin-streptomycin (Sigma-Aldrich) for 4 days prior to 10 nmol/L β-estradiol stimulation (4–24 hours depending on the experiment).

Preparation of conditioned media

A total of 1 × 10^6 cells were plated in a 10-cm² dish and grown in complete media supplemented with 10 nmol/L estrogen (17β-Estradiol, Sigma-Aldrich) for 3 days. Media were removed from cells, spun at 4,000 g for 15 minutes to remove dead cells, and stored at −20°C.

CBFβ plasmid mutagenesis

To introduce specific mutations into the CBFβ sequence, a QuikChange II XL Site-Directed Mutagenesis Kit (Agilent Technologies) was used with primers designed using the complementary QuikChange Primer Design Program (Agilent Technologies, 2017). All plasmids were DNA sequenced by Manchester University DNA Sequencing Facility to confirm the presence of the mutation.

Cell lysis and Western blotting

Briefly, cells were twice washed in ice-cold PBS and lysed in RIPA buffer (Sigma-Aldrich) supplemented with protease inhibitor cocktail (Roche) for 15 minutes on ice. Lysates were cold spun for 15 minutes at 16,000 × g and cleared supernatant was transferred to new tubes. Protein concentration was determined using the DC Protein Assay (Bio-Rad) and equal amounts of protein run on 12% tris-glycine gels. Protein was transferred to nitrocellulose membrane (GE Healthcare) and protein complexes were washed and stained with 0.1% crystal violet. Cells were then imaged and cells/view counted.

Cotransfection communoprecipitation assay

HeLa cells were plated and transfected for 48 hours with CBFβ-myc-Flag (OriGene), wild-type (WT) or mutant, alongside RUNX1-Flag or RUNX2-Flag (generated in house) using Lipofectamine 2000 (Thermo Fisher Scientific). Cells were lysed as above and 1 mg of cell lysate was incubated per immunoprecipitate with 3 μg myc tag antibody- ab19312 (Abcam) and 30-μL PBS-Tween washed protein G Dynabeads (Life Technologies) for 3 hours. Beads–protein complexes were washed five times with RIPA buffer, prior to elution in 2× SDS loading buffer (95°C for 10 minutes), followed by Western blotting.

Fluorescent electrophoretic mobility shift assays

CBFβ (WT and mutant) and Runx domain were expressed and purified from Bl21-gold DE3 Cells (Agilent Technologies) using a GST tag that was cleaved off during purification. Electrophoretic mobility shift assays (EMSA) performed using the Odyssey Infrared EMSA Kit (LI-COR Biosciences) using a double-stranded fluorescently labeled DNA probe 5'-ATT0700-TC1GAAACCCACAGCCGCA-3'. CBFβ (5 μg; WT or mutant) was used per well alongside 0.6-mg Runx domain per protein. An SDS-PAGE gel was also run and stained with InstandBlue (Expedeon) to confirm equal loading of each protein.

CRISPR-Cas9–mediated gene knockout

CBFβ gene knockout was performed using a double nickase CRISPR-Cas9 strategy as described previously (14). Guide RNA sequences were designed using E-CRISP (15) to minimize off-target effects. Cells were fluorescence-activated cell sorted for GFP-Cas9 expression 48 hours after transfection and grown up from single colonies prior to genomic DNA PCR and Western blotting screening.

Genomic DNA PCR

Genomic DNA was isolated using a Purelink gDNA Extraction Kit (Invitrogen) as per the manufacturer’s protocol. The genomic region around the CRISPR-Cas9 target site was amplified using nested PCR. Initially, a larger fragment was amplified using external-F: GAATGGTGCGTCTTGTTTGC; external-R: AAGACGGCCCGAAAATCAGG. DNA was purified and PCR repeated using primers inside the previously amplified piece; internal-F: GCCGGCGACGGCAACCGGTAG and internal-R: CCTCACACTCGCGGGCTACG.

Quantitative reverse transcription PCR

RNA was extracted using RNeasy Mini Kit (Qiagen) as per the manufacturer’s protocol. RNA was quantified using a Nanodrop 2000 (Thermo Fisher Scientific) and 50 ng used per reaction using Quantitect RT-PCR SYBR Green Kit (Qiagen). Primer sequences used: TFF1-F GTGTCACGCCCTCCCAGT; TFF1-R GGACCCCACCGG. DNA was purified and PCR repeated using primers inside the previously amplified piece; internal-F: GCCGGCGACGGCAACCGGTAG and internal-R: CCTCACACTCGCGGGCTACG.

Migration assay

Briefly, 5 × 10^4 cells in serum-free media were placed in a Boyden chamber insert (Corning) and allowed to migrate for 24 hours at 37°C. Nonmigrating cells were removed from the top of the filter by scrubbing with a cotton swab. Cells that migrated were fixed and stained with 0.1% crystal violet. Cells were then imaged and cells/view counted.

Proliferation assay

Proliferation rate was assessed using the thiazolyl blue tetrazolium bromide (MTT) assay. Briefly, 1,000 cells were plated (in octuplicate) in a 96-well plate harvested after 24 hours growth. At which time, the cells were washed with PBS and incubated with 0.4 mg/mL MTT solution in complete media for 3 hours at 37°C/5% CO₂. The cells were then washed twice with PBS and the formazan crystals were dissolved in 200 μL absolute DMSO per well. The absorbance was read at 560 nm using a microplate reader.
siRNA transfections

Dharmacon smartpool siRNA (CBFβ, RUNX1, TFF1, and non-targeting, Horizon Discovery) was transfected using RNAiMax (Thermo Fisher Scientific) as per the manufacturer’s instructions for 72 hours prior to Western blot analysis and migration assay. When conditioned media was to be isolated following siRNA transfection, the siRNA was transfected as above for 48 hours prior to media change and further 48 hours incubation before isolation of conditioned media as mentioned previously.

Fulvestrant treatment

Cells were treated with 100 nmol/L fulvestrant (Sigma) for the time specified in the figure legend.

Statistical analysis

All bar graph data are presented as the mean ± SEM and all statistical analysis was done using Graphpad Prism 7.0 using unpaired or paired t tests depending on the experimental set up; *, *P < 0.05; **, *P < 0.01; and ***, *P < 0.001.

Results

Missense CBFβ mutations occur more frequently near the Runt domain–binding site

CBFβ mutations that occur in patients with breast cancer are found along the whole-protein sequence (Fig. 1A). Approximately 60% of the mutations are truncating and are therefore likely to result in a loss of functional CBFβ in these patients (Fig. 1B). However, the functional effect of the missense mutations has not been reported. To analyze the effect of missense mutations, we first mapped them onto the crystal structure of the CBFβ–Runt–DNA complex (16). This analysis revealed that there are “hot-spots” where mutations occur with greater frequency (Fig. 1C). A χ² test performed on a frequency distribution of the mutations along the primary structure determined that the mutations are not randomly distributed along the protein [χ² (8, N = 52) = 40.892, *P < 0.001; Fig. 1D]. One region in particular, between amino acids 100 and 120 harbors a large number of the most commonly mutated amino acids. This region makes a significant contribution to the interaction with the Runt domain suggesting that the majority of mutations may directly affect the interaction of CBFβ with Runx proteins.

Missense mutations in CBFβ inhibit the formation of a CBFβ–Runt–DNA complex

To determine whether missense mutations in CBFβ affect its ability to bind the Runt domain, six missense mutations found near the Runt–CBFβ binding interface were chosen for analysis (Fig. 2A). A cotransfection communoprecipitation assay was used to assess the impact of the mutations on the ability of CBFβ to bind to RUNX1 and RUNX2. Surprisingly, only one of the mutations, N104S, robustly abrogated the binding of CBFβ to RUNX1 and RUNX2 in comparison with WT CBFβ (Fig. 2B and C). To determine the effect of the mutations on DNA complex formation, we performed EMSAs using purified recombinant proteins. CBFβ and Runt domain proteins were expressed and purified from bacterial extracts (Supplementary Fig. S1). EMSAs were performed using a fluorescently labeled RUNX-binding site and the Runt domain with either WT or mutant CBFβ proteins. All six mutations significantly abrogated the formation of the DNA–RUNX–CBFβ ternary complex (Fig. 2D). This demonstrates that the defect in binding is only observable when CBFβ–Runx is in complex with DNA. These data suggest that missense mutations, like the truncating mutations, are loss of function, supporting the notion that CBFβ is acting as a tumor suppressor gene.

Loss of CBFβ in MCF7 cells leads to an increase in ERα-driven cell migration

All of the CBFβ mutations that have been discovered are in ER⁺ patients. Given that CBFβ appears to act as a tumor suppressor, we decided to study the function of CBFβ by deleting the gene in an ER⁺ context. To this end, a CRISPR-Cas9 double nickase strategy was used to target the start of CBFβ exon1 in MCF7 cells (Fig. 3A; Supplementary Fig. S2A; ref. 14). Two clones were generated that had changes in the genomic locus and complete loss of CBFβ protein (Supplementary Figs. S2B and S3B). To determine whether the loss of CBFβ prevented the function of the Runx transcriptional
complexes, the expression level of MMP13, a well-characterized target gene of Runx–CBFb was measured (Fig. 3C). MMP13 expression level was decreased by approximately 80% in CBFb/C0/C0/MCF7 cells, demonstrating that loss of CBFb resulted in a decrease in Runx protein–mediated gene transcription.

Previously, knockdown of CBFb in a triple-negative model of breast cancer led to a dramatic decrease in cell migration (6). With this in mind, the migratory capacity of CBFb/C0/C0/C0 cells was determined using a transwell migration assay. Surprisingly, CBFb/C0/C0/C0 cells were found to be significantly more migratory (Fig. 3D). This is in contrast to what is observed in CBFb-depleted ERα models. As MCF7 cells are dependent on the function of ERα, the role of ERα in this observed increase in cell migration was determined. This was determined by treating CBFb−/− MCF7 cells with fulvestrant, a drug that targets ERα for degradation, or 72 hours prior to a migration assay. The increased migratory capacity of the CBFb−/− cells was attenuated following fulvestrant treatment, suggesting that this phenotype is dependent on ERα activity (Fig. 3E).

Runx–CBFb acts as an activator or a repressor of ERα target genes in a gene-specific manner

Interplay between RUNX1 and ERα has been studied previously (10). Analysis of RUNX1 in MCF7 cells has established RUNX1 as an inhibitor of ERα-driven cell proliferation. RUNX1 was shown to relieve the repression of AXIN1, a Wnt pathway repressor, by ERα (10).

To assess whether CBFb is required for this function of RUNX1 in MCF7 cells, AXIN1 expression level was measured in CBFb−/− cells. AXIN1 was found to be decreased at both mRNA (Fig. 4A) and protein level (Fig. 4B) showing that CBFb is essential for this RUNX1-mediated gene activation. The regulation of AXIN1 does not explain the increase in migration observed in CBFb−/− cells, however, and we therefore sought to determine the molecular mechanism by which loss of CBFb increases migration. To this end, public datasets were reanalyzed. Two previously reported RUNX1 ChIP-seq datasets, which had used different RUNX1 antibodies, were merged to...
generate high-confidence RUNX1-binding peaks (Supplementary Fig. S4; refs. 10, 17). These peaks and an ERα dataset were then interrogated (10, 17, 18). From this meta-analysis, we ascertained that TFF1 was bound by both ERα and RUNX1 at both the gene promoter and an enhancer region (Fig. 4C; refs. 19, 20). To establish the role of CBFb in the regulation of TFF1, TFF1 mRNA was then quantified in CBFb/C0/C0 cells in the absence and presence of estrogen. TFF1 was found to be upregulated in the presence of estrogen in comparison with the MCF7 control cells (Fig. 4D). These data suggest that Runx1–CBFb complexes antagonize ERα function by repressing the expression of TFF1. Importantly, this is in contrast to the role of Runx1–CBFb as an activator of AXIN1.

CBFβ suppresses ERα-mediated expression of TFF1

To establish the effects of CBFβ loss on TFF1 protein expression, Western blot analysis of TFF1 was performed. TFF1 was significantly increased in MCF7 CBFβ−/− cells in comparison with control cells (Fig. 5A). Depletion of CBFβ in ERα−/− MDA-MB-231 cells did not lead to an increase in TFF1, indicating that CBFβ loss alone is not sufficient to induce TFF1 upregulation if Erα is not present (Fig. 5A). siRNA was used to knockdown CBFβ and RUNX1 in T47D cells, another ERα+ cell line, and elicited the same TFF1 upregulation as seen in CBFβ−/− MCF7 cells (Fig. 5B). Furthermore, reexpression of GFP-CBFβ in CBFβ−/− MCF7 cells rescued the repression of TFF1, confirming that this is a specific effect (Fig. 5C). GFP-CBFβ is known to be functional as it has been shown to rescue fetal liver hematopoiesis in CBFβ−/− mice (21).

Depletion of ERα with fulvestrant for 24 hours prior to estrogen stimulation for 24 hours led to a decrease in the amount of TFF1, thus confirming ERα is required for the observed increase in TFF1 following loss of CBFβ (Fig. 5D).

Upregulation of TFF1 contributes to the migratory phenotype of CBFβ−/− cells

Because TFF1 has previously been linked to cell migration, TFF1 knockdown was performed in CBFβ−/− and control MCF7 cells to investigate the role of TFF1 in the context of CBFβ loss. Seventy-two–hour siRNA-mediated TFF1 knockdown was effective and led to a decrease in the migration of the MCF7 CBFβ−/− cells to a level comparable with the control cells (Fig. 6A and B). This demonstrated that TFF1 is indeed required for the increased migration of the cells following loss of CBFβ. Furthermore, as TFF1 is a secreted protein and has previously...
been shown to initiate chemotaxis of breast cancer cells, this possibility was investigated (Fig. 6C; ref. 12). Conditioned media from control or CBFβ−/− cells was used as a chemoattractant for a migration assay. When conditioned media derived from CBFβ−/− cells was used as the attractant in a migration assay, an increase in cell migration occurred (Fig. 6D).
Furthermore, when TFF1 was knocked down, prior to the generation of conditioned media, the migration was inhibited (Fig. 6E and F). Taken together, these data demonstrate that CBFβ represses ERα-mediated activation of TFF1, thereby suppressing the migratory phenotype of ER⁺ MCF7 cells (Fig. 6G).

Discussion

Because most CBFβ mutations in patients with breast cancer appear to result in loss of function, we set out to determine the role of CBFβ in ER⁺ breast cancer cells. We initially showed that missense mutations in CBFβ abrogate binding to the runt domain
and are therefore likely to result in loss of function. We subsequently modeled the loss of CBFβ in a well-characterized estrogen-dependent ERα breast cancer cell line, MCF7. Our findings revealed an alternate mechanism by which Runx–CBFβ and ERα combine to regulate gene expression. We also demonstrated a new role for Runx–CBFβ in the prevention of cell migration by suppressing the motogen TFF1.

The first part of this study focused on the mechanistic function of CBFβ missense mutations found in patients with breast cancer. It was evident that while missense and truncating mutations were found along the CBFβ primary sequence, a large number of missense mutations clustered in the 100–120 amino acid region. N104S was the joint highest occurring missense mutation and caused an almost total abrogation of CBFβ–binding to RUNX1 and RUNX2 and a complete failure to form a CBFβ–RUNX–DNA heterocomplex. This was not altogether surprising as it has previously been shown that mutating N104 to alanine prevented the binding of CBFβ to the Run domain (22).

The other five mutations, while not as severe as N104S, all exhibited a reduced binding affinity for the Run–DNA complex. This suggests that a reduction in affinity of CBFβ for Run–DNA is sufficient to contribute to development of breast cancer in ERα patients.

Previous analysis of AXIN1 regulation has shown that RUNX1 activates this gene by counteracting the repressive effect of ERα. Loss of RUNX1 function therefore leads to decrease in AXIN1 expression. In contrast, we have shown that loss of CBFβ (and hence RUNX1 function) leads to an increase in the expression of TFF1 (Fig. 6G). In this case, CBFβ acts to repress the activator function of ERα. Therefore, the mechanism by which Runx–CBFβ and ERα combine to regulate gene expression is gene specific (Fig. 6G).

Another important observation was that loss of CBFβ in ERα cells leads to an increase in cell migration and that this was due to an increase in TFF1 expression, because knockdown of TFF1 blocked this effect. TFF1 is an archetypal ERα-activated gene, frequently used as a readout of ERα activity (23–25). However, surprisingly little is known about the role of TFF1 in breast cancer, but it has previously been shown to be a chemotherapeutant for ERα breast cancer cells (12). In the stomach, TFF1 has been characterized as a "motogenic factor", leading to the disruption of cell–cell and cell–matrix contacts and wound healing (11, 26).

RUNX1 is known to repress transcription by recruitment of the corepressor, TLE1 via the VWRPY peptide located at its C-terminus (27). Interestingly, TLE3 has been implicated in the repression of a subset of ERα target genes, including TFF1 in MCF7 cells (28). In this case, TLE3 is recruited by FOXA1 to both the TFF1 promoter and enhancer, where it recruits HDACs to repress gene expression. It is therefore possible that repression of TFF1 by RUNX1–CBFβ is also mediated by recruitment of TLE proteins. However, what determines whether RUNX1–CBFβ activates or represses a specific gene is not presently understood. To date, no specific combination or organization of RUNX-binding sites within the promoters and enhancers, that predict whether a gene is repressed by RUNX1–CBFβ, have been identified. It will therefore be important to characterize other RUNX-repressed genes to establish whether there are sequence-specific determinants of RUNX-mediated transcriptional repression.

Finally, our findings suggest that therapies designed to inhibit formation of the RUNX1–CBFβ complex in ERα breast cancer could actually contribute to disease progression, by relieving the repression on ERα (29, 30). Therefore, because the primary treatment for ERα patients is to inhibit ERα activity, it would be important not to use inhibitors of the RUNX1–CBFβ complex in these patients. Indeed, future work on therapies that stimulate the repressive activity of RUNX1–CBFβ might provide effective treatment in some ERα patients.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: H.J. Pegg, P. Shore
Development of methodology: H.J. Pegg, H. Harrison
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.J. Pegg, H. Harrison, P. Shore
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.J. Pegg, C. Rogerson, P. Shore
Writing, review, and/or revision of the manuscript: H.J. Pegg, H. Harrison, C. Rogerson, P. Shore
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.J. Pegg
Study supervision: H. Harrison, P. Shore

Acknowledgments
The Bioimaging Facility microscopes used in this study were purchased with grants from BBSRC, Wellcome Trust, and the University of Manchester Strategic Fund. The FACS Aria within the flow cytometry core was purchased with funding from the MRC. Thanks to Michael Jackson for guidance and assistance with sorting. The work was funded by a Cancer Research UK PhD Studentship (to H.J. Pegg and C. Rogerson), Breast Cancer Now (to P. Shora and H. Harrison), and the University of Manchester (to P. Shore).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received September 26, 2018; revised November 13, 2018; accepted January 8, 2019; published first January 17, 2019.

References


The RUNX Transcriptional Coregulator, CBFβ, Suppresses Migration of ER+ Breast Cancer Cells by Repressing ERα-Mediated Expression of the Migratory Factor TFF1


Mol Cancer Res  Published OnlineFirst January 17, 2019.

Updated version
Access the most recent version of this article at:
doi:10.1158/1541-7786.MCR-18-1039

Supplementary Material
Access the most recent supplemental material at:
http://mcr.aacrjournals.org/content/suppl/2019/01/17/1541-7786.MCR-18-1039.DC1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://mcr.aacrjournals.org/content/early/2019/02/12/1541-7786.MCR-18-1039.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.