KLF5 Promotes Breast Cell Survival Partially through Fibroblast Growth Factor-binding Protein 1-pERK-mediated Dual Specificity MKP-1 Protein Phosphorylation and Stabilization*

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Krüpple-like transcription factor 5 (KLF5) is a zinc-finger transcription factor promoting cell survival and tumorigenesis in multiple cancers. A high expression level of KLF5 has been shown to be associated with shorter breast cancer patient survival. However, the role of KLF5 and mechanism of KLF5 actions in breast cancer remain unclear. In this study, we found that KLF5 knockdown by small interfering RNA in two breast cell lines, MCF10A and BT20, induces apoptosis. Interestingly, a pro-survival phosphatase, dual specificity mitogen-activated protein kinase phosphatase 1 (MKP-1), is down-regulated by KLF5 ablation. Consistently, KLF5 overexpression increases the MKP-1 protein expression in Hs578T and MCF7. We further found that MKP-1 is essential and sufficient for KLF5 to promote breast cell survival. However, MKP-1 is not a KLF5 direct transcription target because the MKP-1 mRNA level is not regulated by KLF5. By cycloheximide chase assays, we found that KLF5 decreases MKP-1 protein degradation via activating the ERK signaling. Inhibition of pERK by the pharmacological inhibitor U0126 specifically blocks KLF5-induced MKP-1 phosphorylation and stabilization. Additionally, constitutive activation of ERK by constitutively activated MEK1 rescues the KLF5 depletion-induced MKP-1 down-regulation. Consistently, the phosphorylation-deficient MKP-1 mutant cannot be stabilized by KLF5. Finally, the activation of ERK by KLF5 is very likely through the KLF5 direct target gene FGF-BP in breast cells. These findings suggest that KLF5 is a pro-survival factor that promotes breast cell survival partially via pERK-mediated MKP-1 phosphorylation and stabilization. The KLF5-FGF-BP-pERK-MKP-1 signaling axis may provide new therapeutic targets for invasive breast cancer.

The Krüpple-like transcription factor 5 (KLF5/KLF/BTEB2)‡ has been suggested to be an oncogene in multiple carcinomas including the intestinal (1), esophageal (2), bladder (3), and breast (4). A high level of the KLF5 mRNA has been reported to associate with a short survival time in breast cancer patients (4). In addition, KLF5 expression is induced by a number of oncogenes including ERBB2 (5), RA5 (6), and WNT (7). Consistently, KLF5 has been shown to promote cell proliferation (3), migration (8), and tumorigenesis (3) in different cell models by regulating gene transcription. KLF5 has been shown to promote cell survival through regulating Survivin (9), Pim1 (10), and PARP1 (11) in different types of cells.

Our previous study showed that KLF5 promotes the TSU-Pr1 bladder cancer cell growth in vitro and in vivo (3). Furthermore, we demonstrated that KLF5 regulates a number of downstream target genes in a microarray study. Following that, we proved that KLF5 promotes breast cell proliferation partially through directly inducing the fibroblast growth factor-binding protein 1 (FGF-BP) transcription in breast cancer. FGF-BP was confirmed to be a KLF5-induced gene in the mouse lung in an independent microarray study (13).

Besides FGF-BP, another KLF5 downstream target gene (3), dual specificity mitogen-activated protein kinase phosphatase 1 (MKP-1/DUSP1/CL-100), has been documented to promote cell survival (14). Mitogen-activated protein kinases (MAPks) are activated via phosphorylation of ERK, p38, and JNK. These MAPks are inactivated via de-phosphorylation by MKPs including MKP-1 (15). Although pERK usually contributes to cell proliferation and survival, pJNK and pp38 promote cell apoptosis in response to stress (16). The balance between MAPks and MKPs determines whether cells undergo survival or apoptosis (17). Consistently, MKP-1 has been reported to be overexpressed in many types of cancer including breast cancer (15, 18). It has been shown that MKP-1 is rapidly induced in response to multiple stress stimuli, such as the chemotherapy drugs paclitaxel (14) and cisplatin (19, 20), oxidative stress (21), and UV radiation (22), and contributes to cell survival. The MKP-1 induction by stress is at both transcriptional (23, 24) and post-translational (25, 26) levels and primarily mediated by the activation of ERK signaling. Interestingly, the pERK levels are increased by KLF5 in TSU-Pr1 (3).

Here, we studied the mechanism by which MKP-1 is induced by KLF5 in breast cancer. We showed evidence that KLF5 pro-

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3 The abbreviations used are: KLF5, Krüpple-like factor 5; ERK, extracellular signal-regulated kinase; WT, wild type; MKP-1, dual specificity mitogen-activated protein kinase phosphatase 1; FGF-BP, fibroblast growth factor-binding protein 1; PARP1, poly(ADP-ribose) polymerase 1; siRNA, small interfering RNA; MAPK, mitogen-activated protein kinase; JNK, c-Jun NH2-terminal kinase; CHX, cycloheximide.
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motors breast cell survival partially through MKP-1. The induction of MKP-1 by KLF5 in breast cells is at the protein post-translational level but not the transcriptional level. The activation of ERK signaling by KLF5 is essential and sufficient for MKP-1 protein phosphorylation and stabilization in breast cells. We further demonstrated that activation of ERK signaling is mediated by the KLF5 direct target gene FGF-BP. Taken together, the KLF5-FGF-BP-pERK-MKP-1 signaling axis may contribute to breast cancer and provide new therapeutic targets for breast cancer.

MATERIALS AND METHODS

Breast Cell Lines and Culture Conditions—The immortalized breast epithelial cell line MCF10A was maintained in Dulbecco’s modified Eagle’s medium/Ham’s F-12 50/50 medium supplemented with 5% horse serum, 0.5 μg/ml hydrocortisone, 10 μg/ml insulin, 20 ng/ml epidermal growth factor, 0.1 μg/ml cholera enterotoxin, 100 units/ml penicillin, 100 μg/ml streptomycin, and 2 mM l-glutamine. The breast cancer cell lines BT-20 and MCF7 were cultured in minimal essential medium containing 5% fetal bovine serum, 0.1 mM non-essential amino acid, 1.5 g/liter sodium bicarbonate, 1 mM sodium pyruvate, 0.01 mg/ml insulin, and 100 units/ml penicillin and 100 μg/ml streptomycin. The breast cancer cell line Hs578T was cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum, 1.5 g/liter sodium bicarbonate, 1 mM sodium pyruvate, 0.01 mg/ml insulin, and 100 units/ml penicillin and 100 μg/ml streptomycin. These cells were maintained in a humidified atmosphere with 5% CO2 at 37 °C.

Immunoblotting and Antibodies—Immunoblotting was performed with 40 μg of proteins. The anti-β-actin and anti-V5 antibodies are from Sigma. The anti-PARP, anti-cleaved caspase 3, anti-pERK, and anti-pMKP-1Ser359 antibodies are from Cell Signaling (Danvers, MA). The anti-KLF5 rabbit polyclonal antibody has been described previously (27). The anti-MKP-1 antibody was from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA).

siRNA Transfection and Adenovirus Infection—The control luciferase siRNA (Lucsi), KLF5 siRNA (KLF5si) (Dharmacon, Chicago, IL), and MKP-1 siRNA (MKP-1si) (silencer select pre-designed siRNA, Ambion, Austin, TX) were transfected by Lipofectamine 2000 (Invitrogen). The siRNA target sequences designed siRNA, Ambion, Austin, TX) were transfected by Lipofectamine 2000 (Invitrogen). The siRNA target sequences designed siRNA, Ambion, Austin, TX) were transfected by Lipofectamine 2000 (Invitrogen). The siRNA target sequences designed siRNA, Ambion, Austin, TX) were transfected by Lipofectamine 2000 (Invitrogen). Reverse Transcriptase-PCR—Total RNAs were isolated using TRIzol® reagent (Invitrogen). Reverse transcriptions were performed using the iScript™ cDNA synthesis kit (Bio-Rad). Forward primer, 5’-CATCTAGATATGCCCAGTTT-3’, and reverse primer, 5’-CAGCCTTCCAGGTACACTTTG-3’ (forward) and 5’-CTGGCCCATGAAGCTGAAGT-3’ (reverse). A total of 32 cycles were used to amplify KLF5 and MKP-1, whereas 28 cycles were used to amplify the β-actin control.

Cell Viability Assay—MCF10A and BT20 cells were transfected with KLF5si, MKP-1si, and Lucsi, respectively, for 5 days before analysis. The SRB assay was used to measure cell viability as described in our previous report (28).

Plasmids and Gene Overexpression by Lentiviruses—The human MKP-1 gene was amplified from IMAGE clone 5296005 with the pfu enzymes by PCR using primers 5’-tggattcAGTTGATCTGGAAATGGGCAC-3’ and 5’-ttctcgagTCAGCAGCGTGGAAGAGGTCG-3’. The catalytically inactive MKP-1C258S mutant was generated by PCR using primers 5’-TTTGTCCACTCCCCGAGCAGGATTTCCGG-3’ and 5’-TGCCCGTCCTGGAGTGGACAAACACCCTTC-3’. The MKP-1S359A/S364A mutant was primers 5’-ttgattcAGTTGATCTGGAAATGGGCAC-3’ and 5’-ttctcgagTCAGCAGCGTGGAAGAGGTCG-3’. The PCR products were digested by BamHI/Xhol and subcloned into the pLenti6/V5-D-TOPO vector and verified by DNA sequencing. The pLenti6/V5-GW/lacZ vector (Invitrogen) was used as a negative control.

A constitutively activated MEK1 was amplified from pMCL-MEK1-ΔED (29) (a gift from Dr. A. E. Aplin, Thomas Jefferson University, Philadelphia, PA) and subcloned into pLenti6/V5-D-TOPO vector. All plasmids were transfected into HEK 293FT packing cells using Lipofectamine 2000. Lentiviruses were collected at 72 h after transfection and used to transduce MCF10A cells in a 6-well plate. Forty-eight h after transfection, the antibiotic blasticidin (10 μg/ml) was added to select drug-resistant populations.

RESULTS

KLF5 Knockdown Induces Apoptosis and Decreases the MKP-1 Expression in Breast Cells—KLF5 has previously been shown to express in estrogen receptor α negative basal-like breast cells. To determine whether KLF5 promotes breast cell survival, we knocked down KLF5 in two KLF5 positive breast cell lines, MCF10A and BT20 (30). We examined the levels of apoptosis markers, cleaved PARP, and caspase 3, in the control luciferase siRNA (Lucsi) and well characterized KLF5 siRNA (KLF5si) (3.1) transfected cells by immunoblotting. We found that KLF5si induces the cleavage of both PARP and caspase 3 compared with Lucsi in MCF10A and BT20 (Fig. 1A). To further confirm that KLF5 knockdown decreases cell survival through inducing apoptosis, we measured cell viability by the
SRB assay and Annexin V levels by flow cytometry. Consistent with Western blot results, KLF5si significantly decreases cell viability (Fig. 1B) and increases Annexin V staining (data not shown) in both MCF10A and BT20. Interestingly, the protein expression levels of a potential KLF5 downstream gene, the pro-survival phosphatase MKP-1, are decreased by KLF5si in both cell lines (Fig. 1A).

To test if MKP-1 indeed promotes breast cell survival, we knocked down MKP-1 by a pre-designed anti-MKP-1 siRNA in both MCF10A and BT20 and examined apoptosis. As expected, knockdown of MKP-1 also induces the cleavage of both PARP and caspase 3 and the decrease of cell viability like knockdown of KLF5 in both MCF10A and BT20 (Fig. 1, C and D).

**KLF5 Promotes Cell Survival Partially through MKP-1**—Because silence of KLF5 induces apoptosis and down-regulates the expression of the pro-survival MKP-1 protein in breast cells, we wondered if KLF5 functions partially through MKP-1. We performed a rescue experiment in MCF10A to determine whether MKP-1 overexpression can block the KLF5si-induced apoptosis. The wild-type (WT) MKP-1, the catalytically inactive mutant MKP-1C258S (32), and the lacZ control genes were forced overexpressed in MCF10A populations, respectively, by lentiviruses (Fig. 2A). In line with our previous observation, KLF5si decreases the MKP-1 protein level and induces apoptosis, indicated by cleavage of PARP and caspase 3 and loss of cell viability, in the control LacZ overexpressing cells. As expected, forced overexpression of WT MKP-1 clearly decreases the pERK levels and KLF5si-induced apoptosis (Fig. 2). Similar results were obtained from two stable MKP-1 overexpressing MCF10A clones (data not shown). Unexpectedly, overexpression of the catalytically inactive mutant MKP-1C258S also blocks the KLF5si-induced apoptosis as efficiently as WT MKP-1. As a dominant negative MKP-1 mutant, MKP-1C258S increases the pERK levels (Fig. 2A). Consistently, the expression level of MKP-1C258S is higher than that of WT MKP-1 presumably because a high level of pERK stabilizes the MKP-1 protein (see below in detail). These findings suggest that overexpression of MKP-1 can partially rescue the KLF5si-induced apoptosis in MCF10A.

**MKP-1 Expression Is Positively Regulated by KLF5 at the Protein Level but Not at the mRNA Level in Breast Cells**—KLF5 is a well established transcriptional factor regulating transcription of a number of genes. To test whether MKP-1 is a KLF5 direct transcriptional target, we examined MKP-1 expression at the protein level by Western blot and the mRNA level by semiquantitative reverse transcriptase-PCR after knocking down
and overexpressing KLF5. To our surprise, KLF5si decreases MKP-1 expression at the protein level but not at the mRNA level in both MCF10A and BT20 cell lines (Fig. 3, A and B). Additionally, KLF5 overexpression increases the expression of MKP-1 at the protein level but not at the mRNA level in both Hs578T and MCF7 (Fig. 3, C and D). Finally, we found that KLF5 cannot activate the MKP-1 promoter in MCF7 by dual luciferase reporter assays (data not shown). These results suggest that MKP-1 is not a KLF5 direct transcription target gene in breast cells.

MKP-1 is a short-lived protein (the half-life is about 45 min in fibroblasts) degraded through the ubiquitin proteasome pathway (25). To investigate whether KLF5 regulates MKP-1 protein stability, we performed CHX chase assays and found that KLF5 knockdown in MCF10A cells decreases the endogenous MKP-1 protein half-life (Fig. 4, A and B). Consistently, KLF5 overexpression clearly increases the MKP-1 protein half-life in Hs578T (Fig. 4, C and D). These results suggest that KLF5 decreases MKP-1 protein degradation in breast cells.

KLF5 Increases MKP-1 Protein Stability through the pERK-mediated MKP-1 Phosphorylation—The proteasomal degradation of MKP-1 has been demonstrated to be inhibited by pERK-mediated MKP-1 phosphorylation at Ser-359 and Ser-364.

FIGURE 3. KLF5 up-regulates the MKP-1 expression at the protein level but not at the mRNA level. KLF5 siRNA decreases the MKP-1 protein levels (A) but not mRNA levels (B) in MCF10A and BT20 as measured by immunoblotting and semi-quantitative reverse transcriptase-PCR, respectively. Lucsi was used as a negative control. β-Actin served as the input control. KLF5 overexpression by adenoviruses increases the MKP-1 protein levels (C) but not mRNA levels (D) in Hs578T and MCF7 breast cancer cells. The gfp adenovirus was used as a negative control. The normalized band intensities are shown below each lane (the negative controls are defined as 1). GFP, green fluorescent protein.

FIGURE 4. KLF5 increases the MKP-1 protein stability in breast cells. A and B, knockdown of KLF5 decreases the protein half-life for MKP-1 in MCF10A as determined by the CHX (50 μg/ml) chase assay. The band intensities were quantified using densitometry. C and D, overexpression of KLF5 increases the half-life of the MKP-1 protein in Hs578T as determined by the CHX chase assay. The cells were infected with Ad-KLF5/gfp and Ad-gfp control adenoviruses, respectively. GFP, green fluorescent protein.
phosphorylation at Ser-359 by using an antibody that specifically recognizes KLF5si dramatically decrease pERK levels and MKP-1 stability. More, we demonstrated that both the MEK inhibitor U0126 and JNK inhibitors SP600125 (20 nM, a JNK inhibitor), and SB203580 (20 nM, a p38 inhibitor) were added separately 1 h before serum stimulation. A, knockdown of KLF5 decreases pERK activation and MKP-1 induction by serum. MCF10A cells transfected with KLF5 siRNA and luciferase siRNA were serum starved overnight and cultured in serum-containing media for the indicated time. B, either inhibition of pERK by U0126 or knockdown of KLF5 clearly reduce the pMKP-1 Ser-359 and total MKP-1 levels in MCF10A. C, the activation of ERK is essential for KLF5 to up-regulate the pMKP-1 Ser-359 and total MKP-1 levels in Hs578T. Hs578T cells were infected with Ad-KLF5/gfp and Ad-gfp control adenoviruses, respectively. The cells were treated with either dimethyl sulfoxide or U0126 (5 nM) as indicated. E, constitutively activated MEK1 (V5 tagged) rescues KLF5 knockdown-induced down-regulation of pMKP-1 Ser-359 and total MKP-1. The total ERK level serves as the loading control. GFP, green fluorescent protein.

**DISCUSSION**

Accumulated evidence suggests that KLF5 is a pro-survival factor. First, KLF5 has been shown to promote leukemia cell survival through directly inducing the Survivin gene expression (9). Second, KLF5 was reported to promote cell survival by directly promoting the survival kinase Pim1 expression in the HCT116 colon cancer cell line (10). In addition, KLF5 promotes HeLa and NIH-3T3 cell survival from tumor necrosis factor-α through interacting with PARP1 (11). Finally, the cardiovascular apoptosis is significantly increased in KLF5 heterozygous knock-out mice (11). High expression levels of KLF5 mRNA have been shown to be a prognostic factor for shorter disease-free survival and overall survival in patients with breast cancer (4). Our previous studies suggest that KLF5 is expressed in immortalized breast epithelial cell lines and a subset of estrogen receptor negative breast cancer cell lines (27, 30). However, the role of KLF5 and the mechanism by which KLF5 functions in the breast have not been well studied.

In this study, we showed that KLF5 promotes breast cell survival through the FGF-BP-pERK-MKP-1 signaling axis. First, we demonstrated that depletion of endogenous KLF5 or MKP-1 in two breast cell lines, MCF10A and BT20, induces apoptosis (Fig. 1). Next, we found that KLF5 maintains and stimulates MKP-1 through activation of ERK.

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increases the pro-survival phosphatase MKP-1 protein levels in breast cells (Figs. 1–3). Following that, we demonstrated that MKP-1 can partially rescue KLF5 knockdown-induced apoptosis in MCF10A (Fig. 2). Furthermore, we characterized the mechanism by which KLF5 up-regulates MKP-1 in breast cells and found that KLF5 decreases MKP-1 protein degradation via pERK-mediated MKP-1 phosphorylation (Figs. 4–6). Finally, we showed that KLF5 activates ERK signaling through its direct target gene FGF-BP (Fig. 7).

Multiple lines of evidence suggest that KLF5 up-regulates MKP-1 expression through activating the ERK signaling. First, KLF5 does not directly regulate the MKP-1 gene at the transcriptional level (Fig. 3). Second, KLF5 increases MKP-1 protein stability (Fig. 4). Third, KLF5 maintains and increases pERK levels in multiple breast cell lines, and pERK is sufficient and essential for KLF5-mediated MKP-1 stabilization (Figs. 2 and 5). Additionally, we confirmed that the pMKP-1Ser-359 is regulated by KLF5-FGF-BP-pERK signaling (Figs. 5 and 7). Furthermore, the mutation of two key pERK phosphorylation sites (S359A/S364A) in MKP-1 abrogates KLF5-mediated MKP-1 stabilization (Fig. 6). These findings strongly suggest that KLF5 up-regulates MKP-1 via pERK-mediated MKP-1 protein phosphorylation and stabilization (Fig. 7C).

As described in the Introduction, pERK can increase MKP-1 expression at both transcriptional and post-translational levels (23–26). Indeed, we found that KLF5 increases the MKP-1 mRNA levels in TSU-Pr1 (3). However, MKP-1 mRNA levels are not regulated by KLF5 in tested breast cell lines. It is possible that the signaling transduction from pERK to MKP-1 transcription is inactive in breast cells. The phosphorylation mediated...
to the lack of negative feedback control (Fig. 2). The balance between the pro-survival pERK level and the pro-apoptotic pJNK/pp38 levels determines whether cells will live or die (16). It is possible that the elevated pERK levels contribute to the pro-survival function of MKP-1 in MCF10A.

Besides MKP-1, KLF5 may promote breast cell survival through other downstream genes and pathways because MKP-1 can only partially rescue KLF5 depletion-induced apoptosis in MCF10A (Fig. 2). Other signal pathways may contribute to the function of KLF5 on cell survival as well. For example, KLF5 has been shown to increase the pAKT levels in TSU-Pr1 (3). AKT has been well documented to promote cell survival through blocking the activation of pro-apoptotic proteins (12). Indeed, we confirmed that both KLF5 and FGF-BP inhibition decreases the pAKT levels in MCF10A (data not shown). Thus, it is most likely that KLF5 promotes breast cell survival through multiple pathways, including FGF-BP-pERK-MKP-1 and FGF-BP-pAKT.

Besides FGF-BP, we cannot completely exclude that KLF5 up-regulates the pERK level and breast cell survival through other target genes such as SURVIVIN and PIM1 and other mechanisms, such as interaction with PARP1.

In summary, we showed that KLF5 is a pro-survival transcription factor in breast cells. KLF5 functions partially through pERK-mediated MKP-1 protein phosphorylation and stabilization. Finally, we found that KLF5 may up-regulate the pERK levels through the direct target gene FGF-BP in breast cells. The KLF5-FGF-BP-pERK-MKP-1 signaling axis may provide new therapeutic targets for invasive breast cancer.

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