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The oncoprotein HBXIP promotes migration of breast cancer cells via GCN5-mediated microtubule acetylation

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ABSTRACT

We have documented that the oncoprotein hepatitis B X-interacting protein (HBXIP) is able to promote migration of breast cancer cells. A subset of acetylated microtubules that accumulates in the cell leading edge is necessary for cell polarization and directional migration. In this study, we explored the hypothesis that HBXIP contributes to migration of breast cancer cells by supporting microtubule acetylation in breast cancer cells. We found that HBXIP could induce acetylated microtubules accumulating into the leading protrusion in wound-induced directional migration in breast cancer cells by immunofluorescence staining analysis. Interestingly, HBXIP was able to increase the acetylation of α-tubulin in the cells by immunofluorescence staining and Western blot analysis. Furthermore, we observed that acetyltransferase GCN5 was involved in the event that HBXIP induced increase of acetylated microtubules and their expansion in protrusions in breast cancer cells by Western blot analysis and immunofluorescence staining. Moreover, GCN5 was required for the HBXIP-enhanced migration of breast cancer cells by wound healing assay. Thus, we conclude that HBXIP promotes the migration of breast cancer cells through modulating microtubule acetylation mediated by GCN5. Therapeutically, HBXIP may serve as a novel target in breast cancer.

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1. Introduction

Mammalian hepatitis B X-interacting protein (HBXIP) is originally identified due to its interaction with the C terminus of the hepatitis B virus X protein [1]. It can bind to survivin to control cell apoptosis and division, and modulates centrosome dynamics and cytokinesis in cell growth [2,3]. In addition, HBXIP functions as a Ragulator component in amino acids-induced activation of mTORC1 [4]. Our group has reported that HBXIP functions as an oncoprotein and acts as a coactivator of transcription factors, such as CREB, TF II D and Sp1, in facilitation of cancer cell proliferation [5–7]. HBXIP is highly expressed in lymph node tissues with breast cancer metastasis, and promotes the migration of breast cancer cells though up-regulating IL-8 and S100A4 [8,9]. Recently, we have reported that HBXIP enhances migration of breast cancer cells through increasing filopodia formation involving MEKK2/ERK1/2/Capn4 signaling [10]. However, the underlying mechanism by which HBXIP promotes the migration of breast cancer cells is not well documented.

Cell migration plays a fundamental role in numbers of biological processes, including embryonic development and organogenesis, wound healing, as well as cancer cell metastasis [11–13]. Cytoskeleton system based on the microtubules regulates cell migration and undergoes dynamic remodeling in cell locomotion [14]. In mammalian cells, microtubules frequently undergo post-translational modifications such as acetylation of α-tubulin on lysine 40 (K40), a widespread modification closely associated with the stabilization of microtubules [15,16]. In cell migration, this subset of acetylated microtubules extends into protrusions [17], regulates cell polarization [18], and is required for persistent directional movement [19,20]. GCN5 (general control non-derepressible 5) is the first identified transcription-related histone acetyltransferase and has been implicated in diverse cellular processes including transcription [21,22], DNA repair [23], nucleosome assembly [24], cell cycle regulation [25], and cancer cell growth [26]. Additionally, it has been reported that GCN5 acts as α-

Abbreviations: HBXIP, hepatitis B X-interacting protein; GCN5, general control non-derepressible 5; αTAT, α-tubulin acetyltransferase.

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tubulin acetyltransferase (αTAT) in muscle cell differentiation [27,28]. However, whether GCN5 is involved in cell migration is poorly understood.

In this study, we elucidated the mechanism by which HBXIP promotes migration of breast cancer cells, involving cellular microtubule system. Interestingly, we show that HBXIP is able to induce acetylation of microtubules via acetyltransferase GCN5, resulting in promotion of migration of breast cancer cells. Our finding provides new insights into the mechanism by which HBXIP accelerates the migration of breast cancer cells.

2. Materials and methods

2.1. Cell culture, plasmids and SiRNAs

The breast cancer cell line MCF-7 and LM-MCF-7 (a metastatic subclone from MCF-7 cell line [29]), were cultured in RPMI Medium 1640 (Gibco, Grand Island, NY, USA) with 10% fetal calf serum (FCS). MDA-MB-231 cells were cultured in DMEM (Gibco) supplemented with 10% FCS (Gibco), 100 U/ml penicillin, 100 U/ml streptomycin and 1% glutamine. Stable cell lines were constructed as previously described [9], including the engineered cell lines named MCF-7-pCMV (stably transfected pCMV-Tag2B empty vector), MCF-7-HBXIP (stably transfected with pCMV-Tag2B-HBXIP plasmid), MDA-MB-231-psi-control (stably transfected pSilencer vector containing a random fragment), and MDA-MB-231-psi-HBXIP (stably transfected pSilencer vector containing the HBXIP RNAi fragment), respectively. These cell lines were cultured at 37 °C in a humidified atmosphere with 5% CO_2. For the transfections, cells were grown to 30%~50% confluence and transfected with plasmids or siRNAs using Lipofectamine2000 (Invitrogen, USA) according to the manufacturer's instructions. The small interfering RNAs (siRNAs) targeting human HBXIP (siHBXIP, 5′-CGGAAGCGCAGUGAUGUUUdTdT-3′) and GCN5 (siGCN5, 5′-GGAAAUGCAUCCUGCAGAUdTdT-3′) were described previously [25,30].

2.2. Immunofluorescence staining

Cells were processed for indirect immunofluorescence staining as described previously [31]. Primary antibodies used were rabbit anti-acetylated α-tubulin (lysine 40) (Proteintech Group, Chicago, IL, USA) and mouse anti-α-tubulin (Sigma–Aldrich, St Louis, MO, USA). The secondary antibodies used were Alexa Fluor 488 goat anti-rabbit IgG (Invitrogen, Life Technologies, Grand Island, NY), Alexa Fluor 594 goat anti-rabbit and anti-mouse IgG (Invitrogen). Stained cells were observed with Nikon TE200 inverted microscope. The fluorescence intensity was quantified by Image J software.

2.3. Western blot analysis

Western blot analysis was carried out with standard protocols. Primary antibodies used were rabbit anti-HBXIP (Abcam, Cambridge, UK), rabbit anti-acetylated α-tubulin (lysine 40) (Proteintech Group, Chicago, IL, USA), mouse anti-α-tubulin (Sigma–Aldrich, St Louis, MO, USA), rabbit anti-GCN5 (Proteintech), and mouse anti-β-actin (Sigma–Aldrich).

2.4. Wound healing assays

A wound on confluent cell monolayers was created by dragging a pipette tip through the monolayer. After cell debris were washed using PBS, cells were further cultured in serum-free medium. Wound images were photographed when the scrape wound was introduced (0 h) and 48 h after wounding. The wound gaps were measured at each time point. For immunofluorescence staining, cells were fixed at 12 h after wounded and migrating cells within wound front were imaged.

2.5. Statistical analysis

Each experiment was repeated at least three times. Statistical significance was assessed by comparing mean values (±SD) using a Student's *t*-test for independent groups and was assumed for $P < 0.05$ (*), $P < 0.01$ (**) and $P < 0.001$ (***).

3. Results

3.1. HBXIP is associated with acetylated microtubules extending into cell protrusion

Given that the stabilized microtubules accumulating in the leading protrusion play crucial roles in persistent directional movement [19,20], we supposed that HBXIP might promote cell migration through modulating this stable subset of microtubules. Acetylation of α-tubulin on K40 is closely associated with microtubule stabilization [25]. Therefore, we are interested in the effect of HBXIP on acetylated microtubules in directed migration. A scratch-wounding monolayer of breast cancer cells migrated into a wound gap in the wound healing assay. Immunofluorescence staining revealed that MCF-7-HBXIP cells at the edge of wound showed robust polarization and elongated membrane extension, accompanied with strongly increased accumulation of acetylated α-tubulin oriented towards in the leading protrusion. Conversely, the control MCF-7-pCMV cells at the edge of wound displayed weak acetylation of α-tubulin in cell protrusions. The percentage of wound-edge cells with acetylated α-tubulin extending into protrusions was increased from ~10% to ~70% (Fig. 1A). Moreover, MDA-MB-231 cells with stable knockdown of HBXIP (termed MDA-MB-231-psi-HBXIP) exhibited a dramatically decreased accumulation of acetylated α-tubulin in the leading edge in the system, relative to the control cells, in which the percentage of wound-edge cells with acetylated α-tubulin accumulating into protrusions was decreased from ~90% to ~20% (Fig. 1B), suggesting that HBXIP-overexpressed migrating cells display an increased accumulation of acetylated microtubules into the leading protrusion. Thus, we conclude that HBXIP is associated with acetylated microtubules extending into cell protrusion in the process of migration of breast cancer cells.

3.2. HBXIP increases α-tubulin acetylation

It is documented that increased stability of microtubules could result in their accumulation in protrusions in the process of cell migration [14]. Next, we examined whether HBXIP increases the stability of microtubules which induced their extension into cell protrusion. Then, we investigated the effect of HBXIP on overall α-tubulin acetylation in breast cancer cells. Interestingly, immunofluorescence staining showed that MCF-7-HBXIP cells possessed a stronger fluorescence intensity of acetyl-K40 α-tubulin relative to control cells, in which the relative average fluorescence intensity of acetyl-α-tubulin (normalized to α-tubulin) was quantified (Fig. 2A). Western blot analysis further validated that ectopically expressed HBXIP significantly increased the levels of acetylated α-tubulin in MCF-7 cells using the specific anti-acetyllysine 40 (acetyl-K40) α-tubulin antibody (Fig. 2B). Conversely, depletion of HBXIP by siRNA dramatically decreased the levels of acetyl-K40 α-tubulin in LM-MCF-7 or MDA-MB-231 cells, but the total α-tubulin levels were not altered in the cells (Fig. 2C), suggesting that HBXIP can increase acetylation of α-tubulin, resulting in stabilization of microtubules,

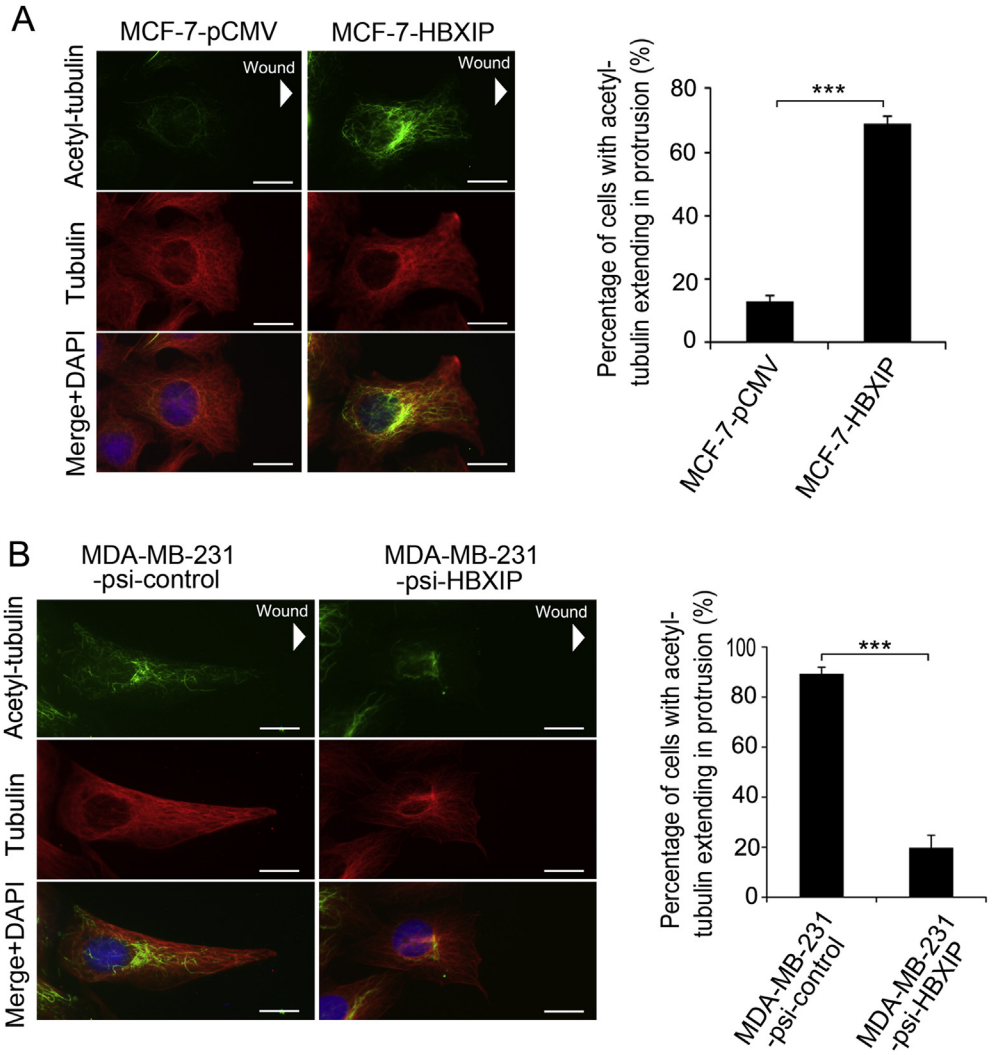

Fig. 1. HBXIP is associated with acetylated microtubules extending into cell protrusion. (A, B) Acetylated α-tubulin (green) and α-tubulin (red) were visualized by immunofluorescence staining in wound-edge cells. Nuclei were stained by DAPI. Scale bars: 20 μm. The percentage of cells in the wound edge with acetylated α-tubulin extending into protrusion was calculated against overall wound-edge cells. Five randomly selected fields were used to quantify in each group (mean ± SD, $^{***}P < 0.001$, Student's *t*-test). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in breast cancer cells. We conclude that HBXIP increases α-tubulin acetylation in breast cancer cells.

3.3. Depletion of acetyltransferase GCN5 blocks HBXIP-increased α-tubulin acetylation

Next, we investigated the mechanism by which HBXIP increases acetylation of α-tubulin in breast cancer cells. It is reported that GCN5 serves as an αTAT in muscle cell differentiation and plays a crucial role in the cell mitosis through acetylation of α-tubulin [25,27,28]. Accordingly, we concerned whether GCN5 is involved in HBXIP-induced α-tubulin acetylation in breast cancer cells. Interestingly, we found that depletion of GCN5 by siRNA abolished the HBXIP-induced increase of acetylated α-tubulin in MCF-7 cells (Fig. 3A). The RNA interference efficiency of siGCN5 was validated in the cells (Fig. 3B). Moreover, we validated that knockdown of GCN5 by siGCN5 abolished the HBXIP-enhanced microtubule acetylation in MCF-7 cells by immunofluorescence staining (Fig. 3C), suggesting that GCN5 is required for the HBXIP-induced increase of acetylated α-tubulin in the cells. We conclude that depletion of acetyltransferase GCN5 blocks HBXIP-increased α-tubulin acetylation in breast cancer cells.

3.4. HBXIP induces cell migration through GCN5-mediated acetylated microtubule extension

Then, we accessed the effect of HBXIP-induced expansion of acetylated microtubules on cell migration. Wound healing assays showed that MCF-7-HBXIP cells exhibited increased migratory distance compared with the control cells, but the treatment with GCN5 siRNA dramatically blocked the enhancement (Fig. 4A). Moreover, we validated that knockdown of GCN5 by siGCN5 could block the HBXIP-induced accumulation of acetylated microtubules in the leading protrusion in the system by immunofluorescence staining, in which the percentage of wound-edge cells with acetylated α-tubulin extending into protrusion was decreased from ~70% to ~20% (Fig. 4B). Collectively, we conclude that HBXIP induces cell migration through GCN5-mediated acetylated microtubule extension in breast cancer cells.

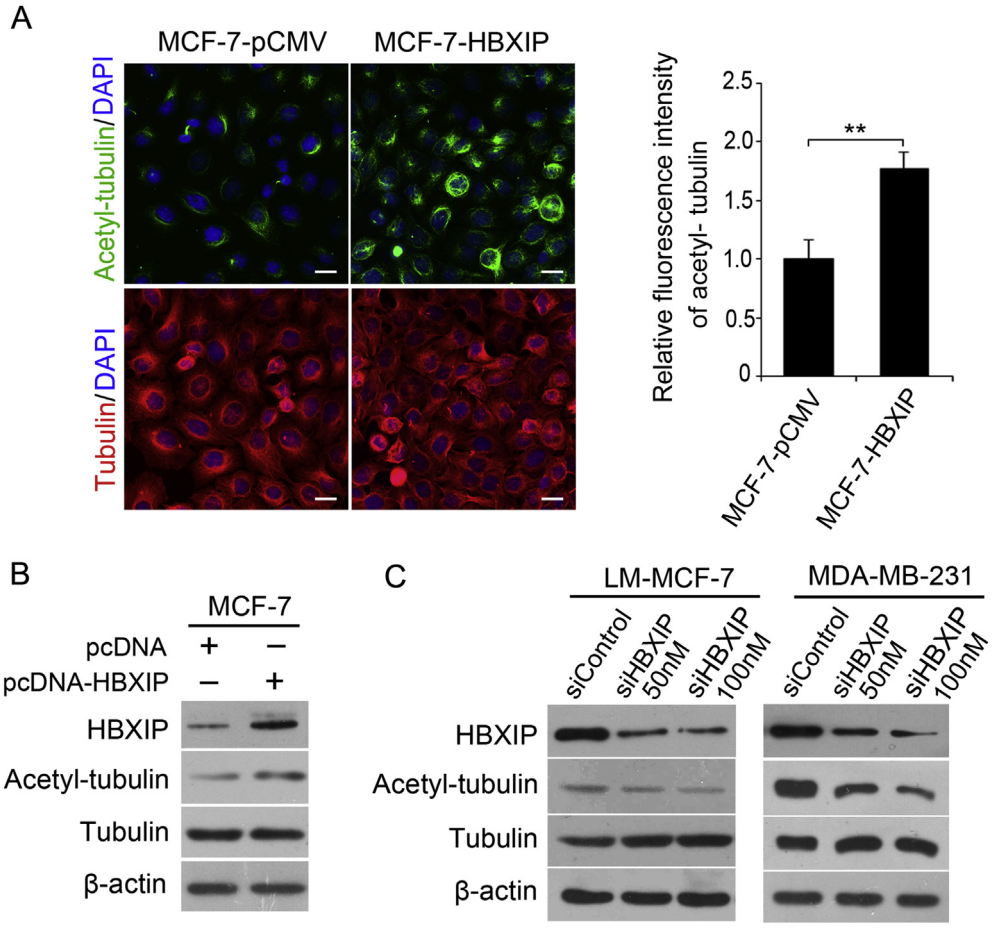

Fig. 2. HBXIP increases α-tubulin acetylation. (A) Acetylated α-tubulin (green) and α-tubulin (red) were visualized by immunofluorescence staining in indicated cells. DNA was visualized by DAPI (blue). Scale bars: 20 μm. The relative average fluorescence intensity of acetyl-α-tubulin (normalized to α-tubulin) was quantified. Five randomly selected fields were used to quantify in each group (mean ± SD, $^{**}P < 0.01$, Student's *t*-test). (B) Acetylated K40 of α-tubulin was detected by Western blot analysis in MCF-7 cells transfected with indicated plasmids. (C) Acetylated K40 of α-tubulin was examined by Western blot analysis in indicated cells transfected with corresponding siRNAs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

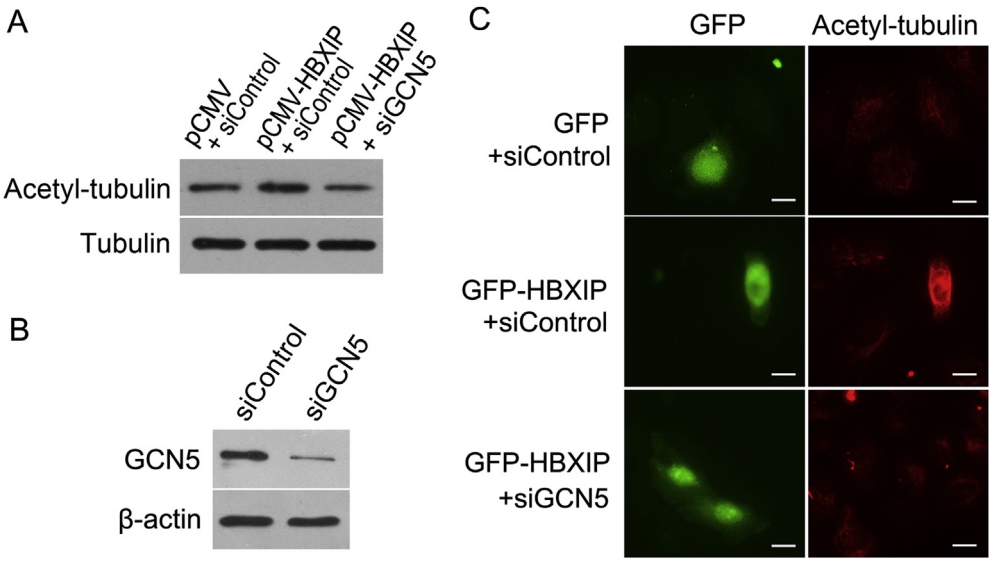

Fig. 3. Depletion of acetyltransferase GCN5 blocks HBXIP-increased α-tubulin acetylation. (A) The levels of acetyl-K40 α-tubulin were detected by Western blot analysis in MCF-7 cells with indicated transfections. (B) The expression levels of GCN5 were accessed by Western blot analysis in MCF-7 cells treated with 50 nM GCN5 siRNAs. (C) The fluorescence of GFP or acetyl-K40 α-tubulin staining was shown in MCF-7 cells transfected with indicated constructs or siRNAs. Scale bars: 20 μm.

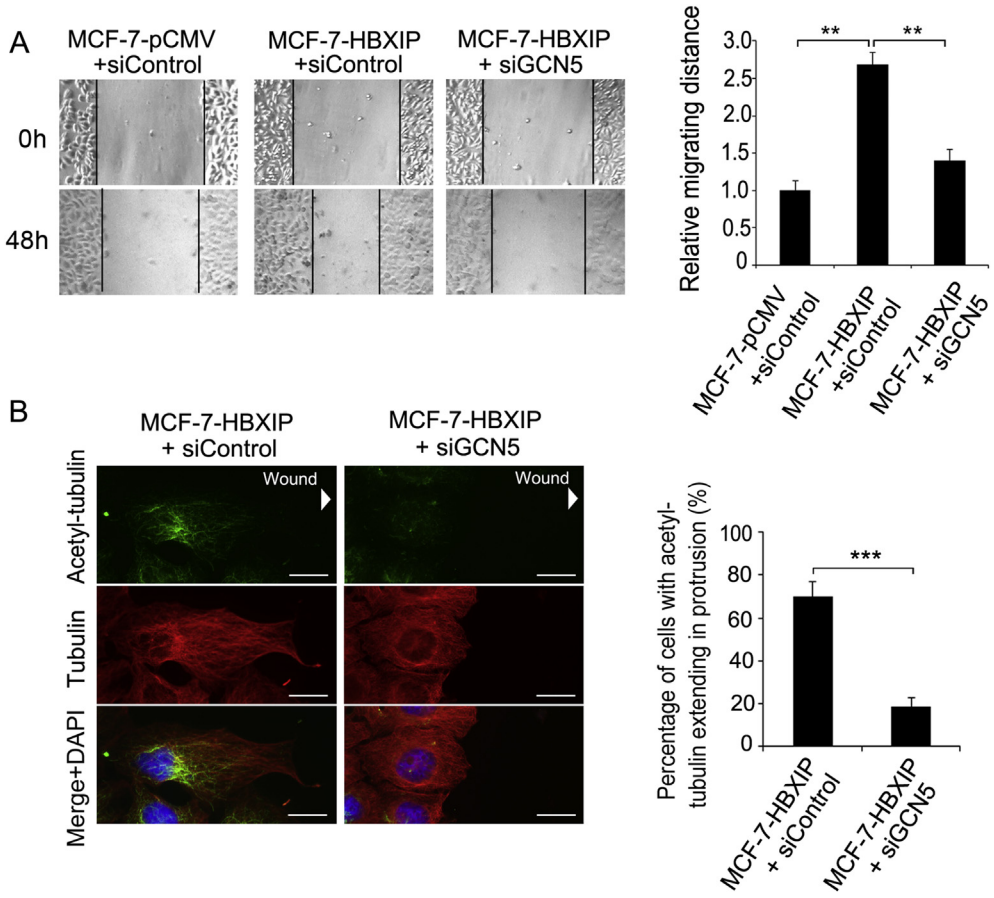

Fig. 4. HBXIP induces cell migration through GCN5-mediated acetylated microtubule extension. (A) The locomotion of MCF-7 cells with indicated transfections was determined by wound healing assays (mean ± SD, $^{**}P < 0.01$, Student's *t*-test). (B) Acetylated α-tubulin (green) and α-tubulin (red) were imaged by immunoflurescence staining in wound-edge cells. Nuclei were stained by DAPI. Scale bars: 20 μm. The percentage of cells in the wound edge with acetylated α-tubulin extending into protrusion was calculated against overall wound-edge cells. Five randomly selected fields were used to quantify in each group (mean ± SD, $^{***}P < 0.001$, Student's *t*-test). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

Cell migration exerts a fundamental function in a variety of biological processes, including cancer cell metastasis [11]. Cellular microtubule system plays crucial roles in the regulation of cell migration [14,32]. In migrating cells, a stable subset of microtubules that accumulates in the leading edge [16] is necessary for cell polarity establishment [18] and directional locomotion [19,20]. The oncoprotein HBXIP is able to promote migration of breast cancer cells [5,8], but the underlying mechanism remains poorly understood. In the present study, we are interested in whether HBXIP affects microtubule stabilization in promotion of migration of breast cancer cells.

Given that α-tubulin acetylation acts as a post-translational modification which is closely related to microtubule stabilization, we evaluated the effect of HBXIP on acetylated microtubule extension in directed cell migration. Interestingly, we observed that HBXIP induced acetylated microtubules accumulating in the protrusion in wound-induced directional migration of breast cancer cells. Further, we found that HBXIP elevated acetylation level of α-tubulin in breast cancer cells. Sharona Even-Ram et al. reported that the increased stability of microtubules could be considered as an explanation of their accumulation in protrusions [14], due to that stabilized microtubules could drive the excessive ruffling either by exerting force against the membrane [33] or particularly by enhancing actin polymerization at the leading edge [34]. According to this notion, we emphasized that HBXIP-caused overall increase of α-tubulin acetylation might account for HBXIP-induced accumulation of stabilized microtubules into the leading protrusion in wound-induced directional migration. More importantly, we identified that an αTAT GCN5 is required for HBXIP-increased microtubule acetylation and expansion, resulting in the migration of breast cancer cells. GCN5 have been documented for its functions in transcription [21] and cell cycle regulation [25], as well as cellular transformation and cancer cell survival [35,36]. Recently, it has been reported that GCN5 is able to potentiate cell growth in the development of non-small cell lung cancer [26]. Interestingly, in this study we found a novel role of GCN5 in modulation of breast cancer cell migration mediated by HBXIP. Then, we examined the effect of HBXIP on the expression of GCN5 by RT-PCR and Western blot analysis in breast cancer cells. However, we failed to observe the positive data (data not shown), suggesting that HBXIP may not regulate GCN5 expression in breast cancer cells. It has been reported that Myc-Nick, a cytoplasmic cleavage product of c-Myc, can induce α-tubulin acetylation and cell protrusion extension by recruiting GCN5 to microtubules in Rat1 fibroblasts [28]. We previously reported that HBXIP was able to up-regulate c-Myc expression in breast cancer cells [37], therefore, we speculated that HBXIP might recruit GCN5 to microtubules through up-regulating c-Myc in α-tubulin acetylation in breast cancer cells.

Taken together, in this study we report that HBXIP serves as a pivotal regulator in cellular cytoskeleton-mediated migration of

breast cancer cells. HBXIP induces acetylation of α-tubulin via GCN5 to increase accumulation of acetylated microtubules in leading protrusion, resulting in promotion of directional migration of cells. Thus, HBXIP might serve as a potential therapeutic target in breast cancer.

Conflict of interest

Leilei Li designed the research methods, performed the experiments, analyzed the data, and prepared the manuscript. Bowen Liu participated in the experiments. Lihong Ye and Xiaodong Zhang designed and revised the manuscript. All authors declare that there is no competing financial interest exists.

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