PRL-3 Promotes the Malignant Progression of Melanoma via Triggering Dephosphorylation and Cytoplasmic Localization of NHERF1

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Phosphatase of regenerating liver-3 (PRL-3) has been reported to have a critical role in metastatic progression of cancers. Here, we investigate how PRL-3 increases the malignant degree of melanoma cells. The expression of PRL-3 increased gradually during the malignant progression of melanoma. The phosphorylation of Akt was elevated in highly malignant melanoma cells, which was accompanied by a decrease in nuclear phosphatase and tensin homolog (PTEN). The phosphorylation of NHERF1 in the serine site was regulated by PRL-3 and showed cytoplasmic translocation upon dephosphorylation, which resulted in a decrease in nuclear PTEN. The co-translocation of NHERF1 and PTEN from the nucleus to the cytoplasm was observed during the malignant progression of melanoma cells. Tumor growth was inhibited significantly, and the survival was prolonged upon knockdown of cytoplasmic NHERF1 in B16BL6 cells prior to the inoculation into mice. Taken together, to our knowledge previously unreported, we have identified NHERF1 as a potential substrate of PRL-3. Its phosphorylation status as well as its change in cellular localization and association with PTEN correlated with the malignant progression of melanoma. Our data provide an explanation for how PRL-3 promotes the malignant progression of melanoma, as well as a diagnostic marker or therapeutic target for malignant melanoma.

INTRODUCTION

Melanoma, a malignant tumor of melanocytes, can be very serious if not diagnosed early (Nikolaou et al., 2012). The elevated expression of phosphatase of regenerating liver-3 (PRL-3) was shown to be associated with the increased metastatic potential and the poor prognosis of human cancers (Al-Aidaroos and Zeng, 2010; Wang and Lazo, 2012). Our previous studies have indicated that highly metastatic B16BL6 melanoma cells express more PRL-3 than poorly metastatic B16F1 cells (Wu et al., 2004). Furthermore, the downregulation of PRL-3 inhibits the growth and metastasis of melanoma (Qian et al., 2007; Wang et al., 2009). However, the underlying mechanisms of PRL-3-promoted metastasis remain unclear.

Ezrin, Keratin 8, and integrin β1 are reported to be dephosphorylated by PRL-3 (Forte et al., 2008; Mizuuchi et al., 2009; Tian et al., 2012). Recent research shows that PRL-3 serves as a regulator of H3K9 methylation during the progression of colorectal carcinoma (Liu et al., 2013). In addition, several studies have revealed that PRL-3 seems to activate the PI3K/Akt signaling pathway (Wang et al., 2007; Wang et al., 2010; Jiang et al., 2011), which is usually hyperactivated in tumor cells (Fang et al., 2013). However, phosphatase and tensin homolog (PTEN), another important phosphatase, functions as a tumor suppressor by negatively regulating the PI3K/Akt signaling pathway (Parapurm et al., 2011). Over the last few years, a variety of proteins have been identified to interact with PTEN and to regulate its function, including controlling its localization (Feng et al., 2008; van Diepen et al., 2009; Zhang and Yu, 2010). Nuclear-cytoplasmic compartmentalization may be an important mechanism in the regulation of PTEN’s biological function (Ming and He, 2009).

NHERF1/EBP50 (Na+/H+ exchanger regulating factor 1; ezrin-radixin-moesin binding phosphoprotein of 50 kDa) is a PDZ domain–containing protein (Georgescu et al., 2008). NHERF1 seems to act as a tumor suppressor when localized at the apical level of the cell membrane but as an oncogenic protein when localized in the cytoplasm or the nucleus (Shibata et al., 2003; Mangia et al., 2009; Hayashi et al., 2010; Malfettone et al., 2012; Mangia et al., 2012). It has been both predicted and experimentally verified that NHERF1 function is determined by the residues on which it is...
phosphorylated (Chen et al., 2012; Sun et al., 2013). However, little is known about the relationship between the phosphorylation of NHERF1 and the malignant progression of tumor cells.

Comparative studies are often used to identify key regulatory molecules in tumor growth and progression (Yang et al., 2004). Here, we performed a systematic study to investigate the relationship between PRL-3 and NHERF1 in the malignant progression of melanoma by using a series of melanoma cell lines with different degrees of malignancy and human melanoma samples of different stages. The phosphorylation status, change in cell translocation, and association of NHERF1 with PTEN were kinetically examined to provide a deeper explanation for how PRL-3 promotes the malignant progression of melanoma.

RESULTS

Metastatic generation–related increases in proliferation, adhesion, migration, invasion, spontaneous metastasis, as well as PRL-3 expression of murine B16 melanoma cells during malignant progression

To examine the malignant progression of melanoma cells, we established a series of sub-cell lines, B16F2-F10, with a successively progressed malignancy from low-metastatic murine melanoma B16F1 cells by an in vivo repeated inoculation approach. As expected, the cell growth rate increased in a malignancy-dependent manner from B16F1 to F10, and highly metastatic B16BL6 grew fastest in vitro (Supplementary Figure S1a online). We selected three cell lines B16F1, B16F10, and B16BL6 to evaluate their adhesive capabilities and their migratory and invasive capabilities. Both B16F10 and B16BL6 cells exhibited a significant increase in their ability to adhere to fibronectin compared with B16F1 cells (Supplementary Figure S1b online). Similar to the results of the adhesion assay, 2.23 and 3.76 times more B16F10 and B16BL6 cells, respectively, migrated to the undersurface in the migration assay compared with B16F1 cells. B16F10 and B16BL6 cells were 1.29 and 1.97 times more invasive, respectively, compared with B16F1 cells, as measured by the proportion of cells traversing the matrigel in the invasion assay (Supplementary Figure S1c and f online).

As shown in Figure 1a, the expression of PRL-3 was gradually elevated along with the increase in B16 cell generations. To confirm the impact of PRL-3 on melanoma metastasis in vivo, we constructed a spontaneous metastasis model using B16F10-luc cells stably transfected with luciferase. B16F10-luc cells were transfected with a PRL-3 expressing plasmid or PRL-3 siRNA and then injected subcutaneously into the footpad of C57BL/6 mice (Figure 1b). Live bioluminescence imaging revealed that tumor metastasis from footpad to draining lymph nodes was greatly promoted by PRL-3 overexpression, whereas reduced by PRL-3 knockdown compared with controls (Figure 1c). Accordingly, the draining popliteal lymph nodes from the mice implanted with PRL-3 overexpressing B16F10-luc cells showed higher ratios of visible metastasis than controls, whereas those from the mice implanted with PRL-3 knockeddown cells were opposite (Figure 1d). Taken together, the results suggest that progressively elevated PRL-3 levels could drive the malignant development of melanoma.

To rule out off-target effects, a second nonoverlapping siRNA special for human PRL-3 was used in the cell invasion assay and inhibited the metastasis of human melanoma cells (Supplementary Figure S1g online).

The difference in malignancy between B16F1 and B16BL6 is relative to the level of Akt phosphorylation and the phosphatase activity of PTEN

We selected B16F1 and B16BL6 cells and examined the status of their Akt signaling pathway. The phosphorylation level of Akt was higher in B16BL6 cells than that in B16F1 cells, but there was no difference in the expression of total Akt (Supplementary Figure S2a online). Treatment with Akt inhibitor abrogated the difference in the growth rate between the two cell lines, suggesting the possible involvement of Akt signaling in the malignant progression from B16F1 to B16BL6 cells (Supplementary Figure S2b online). When the upstream molecules of the Akt signaling pathway were examined, no significant difference was found in the levels of either total or phosphorylated PDK1, mTOR, PI3K subunit p110, or PTEN between the two cell lines (Supplementary Figure S2c online).

To exclude the possibility of PTEN mutation, PTEN mRNA was extracted for sequencing analyses. The PTEN sequence in the two cell lines was identical to NCBI Data Base (data not shown). Three siRNAs for PTEN were designed, and the most effective of them, PTEN-siRNA-1, was used in the following experiments (Supplementary Figure S3a online). When PTEN expression was knocked down by PTEN siRNA, the level of phosphorylated Akt (pAkt) specially in the nucleus was increased markedly in B16F1 cells but slightly in B16BL6 cells (Figure 2a). Treatment with PTEN inhibitor, bpV (Hopic), also caused the elevation of pAkt (Supplementary Figure S2d online), suggesting that PTEN negatively regulated Akt phosphorylation more actively in B16F1 cells than in B16BL6 cells.

PTEN accompanied with NHERF1 translocates from nucleus to the cytoplasm in melanoma cells during malignant progression

NHERF-1 has been reported to interact with PTEN in normal cells (Takahashi et al., 2006). B16BL6 cells were co-transfected with HA-NHERF1 and Flag-PTEN-WT (wild type/Flag-PTEN-ΔPDZ (PDZ-domain deletion mutation) vectors) and then injected subcutaneously into the footpads of C57BL/6 mice (Figure 2b). Interestingly, IF colocalization experiments revealed that the endogenous NHERF1 and PTEN accumulated mostly in the nucleus of B16F1 cells (Figure 2c). By contrast, NHERF1 and PTEN were diffuse in both the nucleus and cytoplasm of B16F10 cells and accumulated mostly in the cytoplasm of B16BL6 cells. The expression of cytoplasmic or nuclear NHERF1 and PTEN as determined by WB confirmed the trafficking direction of NHERF1 and PTEN from the nucleus to the cytoplasm during the malignant progression of melanoma cells (Supplementary Figure S4a and c online).

Similar results were obtained from the 231 human malignant melanoma samples (Figure 2d). NHERF1 localized
to the nucleus of 60, 22.3, and 27.3% of stage I, II, and III melanoma, respectively. NHERF1 could not be detected in the nucleus of stage IV or lymph node metastatic melanoma.

By contrast, NHERF1 was present in the cytoplasm of 10.6, 18.2, 57.1, and 60.6% of stage II, III, IV, and lymph node metastatic melanoma, respectively. No NHERF1 was found in the cytoplasm in stage I melanoma. By an analysis of human melanoma tissues from patients in stage I and lymph node metastasis, we found that NHERF1 and PTEN colocalized in the nucleus in stage I melanoma. However, such colocalization shifted to the cytoplasm in lymph node metastatic melanoma (Supplementary Figure S4d online). The results reflect a consistency in the trafficking direction of NHERF1 and PTEN between the successively progressed melanoma cell lines and human malignant melanoma with progressive clinical stages.

**Cytoplasmic NHERF1 promotes Akt activation dependently on the phosphatase activity of PTEN**

To address the question of whether the change of NHERF1 localization has any effect on the phosphorylation of Akt, we examined the effect of NHERF1 knockdown on PTEN localization in B16BL6 cells transfected with NHERF1 siRNA. The most effective and specific NHERF1-siRNA-1 was used (Supplementary Figures S3b and c online). As shown in Figure 4a, the expression of NHERF1 siRNA resulted in the translocation of PTEN from the cytoplasm to the nucleus. With the accumulation of nuclear PTEN, the level of pAkt in

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**Figure 1. Phosphatase of regenerating liver-3 (PRL-3) promotes the metastasis of melanoma cells.** (a) The protein levels of PRL-3 were compared among a series of B16 melanoma cells by WB. (b) The PRL-3 levels in B16F10-luc cells were detected 48 hours after PRL-3 overexpression (pTARGET-Myc-PRL-3) or interference (pRNA-U6.1/Neo-Luc-PRL-3-siRNA). (c) Treated B16F10-luc cells (5 × 10⁵ cells) were injected subcutaneously into the right footpads of C57BL/6 mice (n = 6), respectively. In vivo fluorescent imaging of all mice was taken 20 days after injection, and the luminescence statistics of the near-end lymph node metastasis were shown. (d) The draining popliteal lymph nodes from the injected footpads. In all WB, the relative band density was analyzed using Image J. Data are the mean+/− SEM of three independent experiments. *P<0.05 and **P<0.01.

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the nucleus decreased significantly (Figure 3b). Furthermore, the decrease in pAkt caused by NHERF1 siRNA was nearly reversed by the pretreatment of B16BL6 cells with the PTEN inhibitor, bpV (Figure 3c). Similarly, the phosphorylation of Akt, which was stimulated by FBS after serum-deprivation, was reduced by NHERF1 siRNA, and it was reversed by treatment of B16BL6 cells with bpV (Figure 3d). These results suggest that the amount of PTEN in the nucleus, which can be regulated by NHERF1, determines the activation of Akt.

**PRL-3 regulates the phosphorylation of NHERF1 at Ser residue and promotes the translocation of NHERF1 from the nucleus to the cytoplasm**

On the basis of the findings described above, we reasoned that progressively elevated PRL-3 levels might account for the trafficking direction of NHERF1 and PTEN from the nucleus to the cytoplasm during the malignant progression of melanoma cells. Thus, we transfected B16F1 cells with a PRL-3-expressing plasmid, or we transfected B16BL6 cells with PRL-3 siRNA. If colocalization experiments revealed that PRL-3 overexpression promoted the translocation of NHERF1 and PTEN from the nucleus to the cytoplasm, whereas PRL-3 interference led to the nuclear retention of NHERF1 (Figure 4a). WB results confirmed the effect of PRL-3 on the intracellular distribution of NHERF1 and PTEN (Figure 4b). The experiment in B16F10 cells showed the same results (Supplementary Figures S5a online). When human melanoma A375 (PRL-3 low) and A875 (PRL-3 high) cells were treated with PRL-3 overexpression or interference, respectively, similar results were obtained (Figure 4c and d). To further confirm the proposed PRL-3-NHERF1-PTEN circuitry, co-perturbation experiments such as siPRL-3/siNHERF1 and overexpression PRL-3/siNHERF were taken as shown in Figure 4e. When B16F1 and B16BL6 cells were co-perturbed with NHERF siRNA, the cytoplasm–nucleus translocation of NHERF1 and PTEN triggered by PRL-3 was inhibited.
Because PRL-3 is a phosphatase and NHERF1 can be phosphorylated at multiple serine and threonine residues (Chen et al., 2012), we compared the phosphorylation levels of NHERF1 in B16F1 and B16BL6 cells. The anti-p-Ser and anti-p-Thr antibodies were used to detect the phosphorylation of NHERF1 indirectly after NHERF1 was immunoprecipitated. The levels of phosphorylated NHERF1(Ser) were much higher in B16F1 cells than they were in B16BL6 cells, whereas no significant change in the phosphorylation status of NHERF1(Thr) was found in either cell line (Figure 5a). Furthermore, the levels of phosphorylated NHERF1(Ser) were detected in the nucleus of B16F1 cells, whereas it was barely detected in either the nucleus or the cytoplasm of B16BL6 cells (Figure 5b). These findings suggest that the subcellular localization of NHERF1 is dependent on its phosphorylation status.

To further determine whether the levels of phosphorylated NHERF1(Ser) were regulated by the phosphatase activity of PRL-3, we transfected B16F1 cells with a PRL-3-expressing plasmid or transfected B16BL6 cells with PRL-3 siRNA. PRL-3 overexpression led to a decrease in the levels of phosphorylated NHERF1(Ser), whereas PRL-3 interference did the reverse (Figure 5c), indicating that NHERF1 could be a substrate of PRL-3. Using IF colocalization and IP assays, we confirmed the interaction between PRL-3 and NHERF1 in the nucleus of B16F1 cells transfected with myc-PRL-3-expressing
plasmids (Supplementary Figure S6 online). In addition, B16F1 cells were transfected with PRL-3 (C104S), a loss-of-function mutant. Unlike wild-type PRL-3, PRL-3 (C104S) overexpression failed to decrease the levels of phosphorylated NHERF1(Ser) (Figure 5d). It also failed to promote the translocation of NHERF1 and PTEN from the nucleus to the
cytoplasm (Figure 5e). Taken together, PRL-3 could trigger the dephosphorylation of NHERF1 in the nucleus and promote the translocation of dephosphorylated NHERF1 from the nucleus to the cytoplasm.

Targeting NHERF1 has therapeutic significance in highly malignant melanoma

To verify the importance of NHERF1 as a mediator in highly malignant melanoma with high levels of PRL-3, we examined...
In this study, we examined the mechanism by which PRL-3 promotes melanoma malignant progression. For this purpose, a series of B16 melanoma cell lines with gradually increasing degrees of malignancy (B16F2-F9) were generated in our laboratory to be used in addition to the commercial B16F1, B16F10, and B16BL6 cells. By using these successive cell lines, we concluded that PRL-3 must be involved in the change in cellular functions including increased proliferation, adhesion, migration, and invasion.

The activation of the Akt signaling pathway has been known as an important event during the malignant progression of tumor cells (Zhang et al., 2014). Through a series of comparisons, we found that the phosphatase activity but not the expression level of PTEN in B16F1 cells was higher than B16BL6 cells, resulting in lower levels of pAkt in B16F1 cells. PTEN is an important negative regulator of the Akt activation, and the loss or mutation of PTEN usually results in tumorigenesis (Carracedo et al., 2011). However, no PTEN mutation was found in the series of B16 melanoma cell lines.

Traditional views suggest that PTEN functions at the cell membrane to inhibit PI3K-Akt signaling. The function of nuclear PTEN as tumor-suppressor has been widely reported (Baker, 2007; Planchon et al., 2008; Jang et al., 2010; Wrighton, 2011), but none of these reports suggest a relationship between PTEN and Akt activity. In this study, PTEN was observed to colocalize and translocate with NHERF1 in both melanoma cell lines and human melanoma tissues. As reported previously, PTEN can be recruited by NHERF1 to the cell membrane where it suppresses the activation of the Akt signaling pathway in glioblastoma cells (Molina et al., 2012). In the current experiment, we also confirmed that PTEN interact with NHERF1 in B16BL6 cells, but it was not recruited by NHERF1 as described in previous reports.

During the malignant progression of melanoma cells, it should be noted that co-localized NHERF1 and PTEN showed an obvious trafficking direction from the nucleus to the cytoplasm. Namely, PTEN translocated from the nucleus to the cytoplasm following NHERF1, and then it was sequestered in the cytoplasm by NHERF1. Analysis showed that phosphorylated Akt mostly accumulated in the nucleus in B16 melanoma cells, and the nuclear accumulation of PTEN decreased the level of pAkt. Therefore, the cytoplasmic translocation of PTEN contributes to the increase in pAkt. These results confirmed that the NHERF1/PTEN interaction and the nucleus–cytoplasm direction may be a key event during the malignant progression of melanoma. The next question is to determine what promotes the cytoplasmic translocation of NHERF1.

Considering that the expression of PRL-3 also increased gradually during the malignant progression of melanoma cells, we examined the relationship between PRL-3 and NHERF1. The association of PRL-3 and NHERF1 is theoretically possible as they were both reported to interact with ezrin (Reczek et al., 1997; Forte et al., 2008). Our results indicated that PRL-3 determined the cellular location of the NHERF1–PTEN interaction. The overexpression of PRL-3 greatly increased the NHERF1–PTEN interaction in the cytoplasm, whereas no interaction was observed in the...
nucleus. By contrast, the interference of PRL-3 decreased the interaction in the cytoplasm but not in the nucleus. On the basis of the existing knowledge, NHERF1 can be regulated by phosphorylation at serine and threonine sites. The results obtained in the present study show that the phosphorylation of NHERF1(Ser) is higher in B16F1 cells than in B16BL6 cells. Interestingly, we found that PRL-3 inhibited the phosphorylation of NHERF1(Ser) in melanoma cells. These data suggest that the cytoplasmic translocation of NHERF1 from the nucleus depends on the de-phosphorylation of NHERF1, which can be promoted by PRL-3.

Consistent with previous reports, cytoplasmic NHERF1 seems to act as an oncogenic protein. Upon NHERF1 interference in B16BL6 cells, tumor growth was significantly inhibited both in vitro and in vivo, and the survival rate of tumor-bearing mice increased. However, the effect of NHERF1-interference on B16F1 cells was scarcely evident. Such a different response between B16F1 and B16BL6 cells further certified the oncogenic role of cytoplasmic NHERF1. These results suggest that cytoplasmic NHERF1 may serve as a therapeutic target for malignant tumor growth and metastasis.

Taken together, our study provides a unique insight into melanoma metastasis and a diagnostic marker for malignant melanoma. PRL-3 regulates the phosphorylation of NHERF1 at its serine site and promotes its cytoplasmic translocation, which further promotes the cytoplasmic translocation of PTEN and results in the upregulation of pAkt. Cytoplasmic NHERF1 can serve as a diagnostic marker and a good therapeutic target for malignant melanoma. It further highlights the significance of rational targeted therapy.

MATERIALS AND METHODS

Reagents

DMEM, MEM, fetal bovine serum (FBS), and lipofectamine 2000 were purchased from Life Technologies (Carlsbad, CA). MTT and type IV collagenase were purchased from Sigma-Aldrich (St Louis, MO). Western blotting/immunoprecipitation lysis buffer was obtained from Beyotime (Nantong, China). D-Luciferin Firefly Potassium Salt was obtained from Xenogen (Alameda, CA). PTEN-specific inhibitor bpV (Hopic) was purchased from Merck Bioscience (Bad Soden, Germany). Antibodies to pAkt (S473) (D9E), Akt, Lamin B1 (D4Q4Z), GAPDH (14C10), HA-Tag (6E2), and Flag-Tag were obtained from Cell Signaling Technology (Beverly, MA). Protein A/G PLUS-Agarose, antibodies to β-Actin, p-Ser (16B4), and p-Thr (H-2) were obtained from Santa Cruz Biotechnology (Santa Cruz, CA). Antibodies to PRL-3, NHERF1, and PTEN (Y184) were purchased from Abcam (Cambridge, UK). Fixation buffer and 1× Phosflow Perm Buffer were from BD Biosciences (San Diego, CA). NE-PER Nuclear and Cytoplasmic Extraction Reagents were obtained from Thermo (Rockford, IL). The Real Envision Detection kit was the product of GeneTech Company (Nanjing, China). Melanoma tissue arrays were purchased from US Biomax (Rockville, MD). All other chemicals were obtained from Sigma-Aldrich (St Louis, MO).

Animals

Six-week-old female C57BL/6 mice were purchased from Academy of Military Medical Sciences (Beijing, China). They were maintained with free access to pellet food and water in plastic cages at 21 ± 2 °C and kept on a 12-h light/dark cycle. All efforts were made to minimize the animals’ suffering and to reduce the number of animals used. The medical ethical committee of Nanjing University approved all described studies. The study was conducted according to the Declaration of Helsinki Principles.

Cell culture

Mouse melanoma B16F1, B16F10, and B16BL6 cells and human melanoma A375, A875, and M14 cells were obtained from the Shanghai Institute of Cell Biology (Shanghai, China) and were maintained in DMEM supplemented with 10% FBS plus 2 mM glutamine, 100 U/ml penicillin, and 100 mg/ml streptomycin. B16F10-luc cells were obtained from Cold Spring Biotech Corp. (Taipei, Taiwan). B16F2, F3, F4, F5, F6, F7, F8, and F9 cells were generated in our laboratory by repeated i.v. injection of B16 melanoma cells as previously described (Fidler, 1975).

Small animal in vivo imaging system

B16F10-Luc cells in the exponential growth phase were harvested by trypsinization and washed twice before injection. Cells were injected into the right hind footpads of C57BL/6 mice. Twenty days after inoculation, each mouse was injected with the luciferase substrate (D-Luciferin Firefly Potassium Salt, 15 mg/ml, 100 μl). In vivo fluorescent images of all mice were taken within 1 h. Luminescence statistics were recorded.

Vector construction

HA-NHERF1, Flag-PTEN-WT, and Flag-PTEN–PDZ were generated as described in supplementary materials online. The following plasmids were constructed as previously described: pTARGET-Myc-PRL-3, pRNA-U6.1/Neo-Luc-siRNA, pRNA-U6.1/Neo-Luc-PRL-3-siRNA, pIERS2-EGFP, and pIERS2-EGFP-PRL-3 (Qian et al., 2007; Wang et al., 2009).

Statistical analysis

Data are expressed as mean±SEM. Student’s t test and the one-way ANOVA test were used for statistical analyses of the data. All statistical analyses were conducted using SPSS 10.0 statistical software (SPSS, Chicago, IL). Cases in which P values of <0.05 were considered statistically significant.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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