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Protein tyrosine phosphatase-1B and T-cell protein tyrosine phosphatase regulate IGF-2-induced MCF-7 cell migration

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ABSTRACT

The protein tyrosine phosphatase-1B (PTP1B) and the T-cell protein tyrosine phosphatase (TC-PTP) have been implicated in down-regulation of tyrosine kinase receptors, conferring anti-oncogenic functions to these PTPases. However, recent work has shown that PTP1B is positively implicated in oncogenic properties of breast cancer cells by regulating the ERK pathway. Here, we studied the function of PTP1B and TC-PTP in IGF-2-induced growth, survival and migration of MCF-7 breast cancer cells. Using siRNA, we showed that reduction in the expression of these PTPases decreased cell growth and ERK phosphorylation. Reduction in the expression of these PTPases did not impair IGF-2 effects on cell survival to acute treatment with 4-OH Tamoxifen. In contrast, IGF-2-induced MCF-7 cell migration was markedly impaired by reduction of PTP1B or TC-PTP expression, independently of the ERK pathway. This novel finding reinforces the potential role of these PTPases as therapeutic targets for treatment of breast cancer.

Introduction

Protein tyrosine phosphatases are keys regulators of tyrosine kinase receptor activity. Among them, PTP1B is of particular interest due to its function in the regulation of insulin signaling [1,2]. Moreover, PTP1B and its closely related PTPase, the T-cell protein tyrosine phosphatase (TC-PTP), have been implicated in inhibition of oncogenic tyrosine kinases [3]. This function initially conferred anti-oncogenic properties to these PTPases. However, recent data have demonstrated a positive role of PTP1B in cancer, notably in a mouse model of ErbB2-induced breast cancer, by regulating ERK signaling pathway [4–6]. We previously showed that PTP1B and TC-PTP are also positively implicated in growth of human MCF-7 breast cancer cells by regulating ERK pathway [7]. In addition, we demonstrated that PTP1B, but not TC-PTP, is necessary for MCF-7 cell resistance to 4-OH Tamoxifen (4-OHT).

IGF-2 is a growth factor acting through binding to IGF1R and IR tyrosine kinase receptors. IGF-2 is highly expressed during embryonic development and its levels decreases after birth. In some cancers, and particularly in breast cancers, IGF-2 is over-expressed and participates in proliferation, migration and resistance of cancer cells to apoptosis [8–10].

In the present work, we have evaluated the role of PTP1B and TC-PTP in IGF-2-induced cellular processes such as growth, survival and migration of the human breast cancer MCF-7 cell line. Using siRNA, we showed that basal and IGF-2 stimulated cell growth were markedly reduced by PTP1B or TC-PTP inhibition. Importantly, decreased expression of these PTPases abolished IGF-2-induced MCF-7 cell migration, reinforcing the notion that PTP1B and TC-PTP may constitute interesting therapeutic targets for breast cancer treatment.

Materials and methods

Drugs and antibodies. IGF-2 was from Peprotech (Neuilly-Sur-Seine, France). 4-OH Tamoxifen was from VWR (Strasbourg, France). Anti-pERK, was from Cell Signaling (Ozyme, Saint-Quentin en Yvelines, France); anti-TC-PTP and anti-PTP1B were from VWR and anti-ERK2 was from Santa Cruz (Tebu-Bio, Le Perray en Yvelines, France). PD98059 was from Sigma–Aldrich (Saint-Quentin Fallavier, France).

Cell culture. MCF-7 cells were grown in Dulbecco's Modified Eagles's Medium (DMEM)/F12 medium (Invitrogen, Cergy-Pontoise, France) supplemented with 4.5 g/l glucose and 5% fetal bovine serum (FBS) (Eurobio, Les Ulis, France).

Abbreviations: DMEM, Dulbecco's Modified Eagle's Medium; ER, estrogen receptor; ERK, extracellular regulated kinase; FBS, fetal bovine serum; FITC, fluoresceine iso thio cyanate; IGF-2, insulin-like growth factor-2; KO, knock out; PTP1B, protein tyrosine phosphatase-1B; PTPase, protein tyrosine phosphatase; RNA, ribo nucleic acid; RTK, tyrosine kinase receptor; siRNA, small interfering RNA; TC-PTP, T-cell protein tyrosine phosphatase.

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Transfections. MCF-7 cells seeded at a density of 2.5×10^5 cells per 35 mm dish were transfected with siRNA specific for TC-PTP (50 pmol/well; 5′-CUG-AAG-ACC-UCC-ACA-UUA-A-3′) or PTP1B (125 pmol/well; 5′-CUG-AAG-ACC-UCC-ACA-UUA-A-3′), or with negative control siRNA (Eurogentec, Angers, France). Transfections were performed using Lipofectamine-2000 (Invitrogen) according to the manufacturer's protocol.

Determination of cell growth. Cell growth was monitored using Uptiblue (Interchim, Montluçon, France). Reduction of this compound by the cell results in the formation of a fluorescent compound quantified by measuring fluorescence at 595 nm after excitation at 532 nm using a Typhoon apparatus (GE Healthcare, Aulnay-sous-Bois, France). One day after siRNA transfection, MCF-7 cells were seeded in 96-well plate at a density of 2×10^3 cells/well in DMEM/F12 containing 5% FBS. Twenty-four hours later, Uptiblue (10%, w/v) was added to the culture medium for 2h30 at 37 °C. Fluorescence was then measured and reflected the number of cells at day 0. To measure IGF-2-induced cell growth, medium containing Uptiblue was replaced by DMEM/F12 supplemented with 0.5 mg/ml BSA (Sigma–aldrich) containing or not IGF-2 (100 nM) for 72 h. To measure the effect of IGF-2 on 4-OH Tamoxifen-induced inhibition of cell growth, medium containing Uptiblue was replaced by DMEM/F12 supplemented with 0.5 mg/ml BSA containing or not the different agents for 72 h. Uptiblue was then added to culture medium for 2h30 at 37 °C. Fluorescence was measured as described above and reflected the number of cells at day 3. Cell growth was defined as the ratio of fluorescence intensity at day 0 to fluorescence intensity at day 3.

Migration experiments. One day after siRNA transfection, MCF-7 cells were seeded in 96-well plate at a density of 7×10^5 cells per culture-insert chamber (Ibidi, Biovalley, Marne La Vallée, France), in DMEM/F12 containing 5% FBS. One day later, medium was replaced by DMEM/F12 supplemented with 0.5 mg/ml BSA. After 24 h, culture-inserts were removed and medium was changed by DMEM/F12 supplemented with 0.5 mg/ml BSA containing or not IGF-2 (100 nM). Pictures were taken at time 0 and 8 h after IGF-2 addition and analyzed using Image J software.

Western blot analysis. Proteins were extracted as described [11] subjected to Western blotting [12] and detected using chemiluminescence.

Statistical analysis. Statistical comparisons were made using one-way Anova following by a Newman–Keuls multiple comparison test.

Results

TC-PTP and PTP1B si RNA inhibit basal MCF-7 cell growth but do not impair IGF-2 stimulatory effect on cell growth and survival

Previous studies have shown that PTP1B and TC-PTP are implicated in negative regulation of several tyrosine kinase receptors. Among them, two receptors for IGF-2, IGFIR and IRA, which are dephosphorylated by these PTPases, have been implicated in numerous cancers [13,14]. To evaluate the role of PTP1B and TC-PTP in IGF-2-induced MCF-7 cell growth, survival and migration, we have used siRNAs specifically directed against TC-PTP or PTP1B. As shown in Fig. 1A, transfection of MCF-7 cells with these siRNAs markedly decreased PTPases expression. The growth of MCF-7 cells, measured using Uptiblue, was significantly decreased in cells transfected with siRNAs against PTP1B or TC-PTP compared to cells transfected with control siRNA (Fig. 1B). As observed previously [7], inhibition of MCF-7 cell growth by PTP1B and TC-PTP siRNA was not due to an increase in apoptosis (Supplementary Fig. 1). Although siRNA treatment inhibited cell growth both in absence and presence of IGF-2, the IGF-2 stimulatory effect on cells growth was preserved (Fig. 1C). IGF-2 is also implicated in the activation of survival pathways [15]. To determine whether TC-PTP and PTP1B are involved in the regulation of IGF-2-induced survival, we treated MCF-7 cells with 4-OH Tamoxifen (4-OHT), a pro-apoptotic drug that has been largely used in the treatment of breast cancer. Fig. 1D shows that 4-OHT strongly decreased the growth of MCF-7 cells transfected with control siRNA as well as with TC-PTP and PTP1B siRNA. Treatment of cells with IGF-2 markedly reduced the cytotoxic effect of 4-OHT in cells transfected with control siRNA. This effect of IGF-2 was also observed in cells transfected with TC-PTP or PTP1B siRNA. This result indicates that, in MCF-7 cells, TC-PTP or PTP1B depletion does not impair the protective effect of IGF-2 against the cytotoxic effect of 4-OHT.

TC-PTP and PTP1B are implicated in IGF-2-induced MCF-7 cell migration

IGF-2, through IGF1R and IR activation, can induce migration of cancer cells. We have studied whether PTP1B and TC-PTP could be implicated in the regulation of MCF-7 cell migration (Fig. 2). In the absence of IGF-2, reduction of TC-PTP and PTP1B expression in MCF-7 cells did not change significantly cell velocity (Fig. 2A). Treatment of cells with IGF-2 increases MCF-7 cell velocity by 2-fold (Fig. 2A). However, whereas IGF-2 significantly increased velocity of cells transfected with control siRNA, this effect was abolished in cells transfected with TC-PTP or PTP1B siRNA (Fig. 2A and B). This result suggests that these PTPases are positively implicated in IGF-2-induced cell migration.

TC-PTP and PTP1B control ERK but do not Akt phosphorylation

In order to correlate the effects of reduction of the expression of the PTPases on growth and migration with changes in intracellular signaling, we have studied Akt and ERK1/2 phosphorylation in MCF-7 cells. As observed in Fig. 3A, basal Akt phosphorylation on Ser 473 was not changed by PTP1B or TC-PTP siRNA transfection. Treatment of cells with IGF-2 induced the phosphorylation of Akt on serine 473 and this phosphorylation was not affected by PTP1B or TC-PTP siRNAs. As observed previously [7], basal phosphorylation of ERK 1/2 was strongly decreased by transfection of cells with TC-PTP or PTP1B siRNA (Fig. 3B). In the presence of IGF-2, phosphorylation of Erk1/2 was also markedly reduced in cells transfected with TC-PTP or PTP1B siRNAs. However, the stimulatory effect of IGF-2 was preserved in these cells. This result suggests that TC-PTP and PTP1B regulate basal ERK phosphorylation but not the induction of ERK1/2 phosphorylation by IGF-2.

In order to determine whether inhibition of ERK1/2 pathway played a role in the effect of PTP1B and TC-PTP siRNA on cell growth and migration, we have treated MCF-7 cells with the MAPK pathway inhibitor PD98059 as described previously [7]. We observed that treatment with the MAPK pathway inhibitor decreased basal and IGF-2 stimulated cell growth without inhibiting the fold-stimulatory effect of IGF-2 (Fig. 4A and B). In contrast, MCF-7 cell migration was not affected by PD98059, neither in absence nor in presence of IGF-2 (Fig. 4C). This suggests that the MAPK pathway regulates growth but not migration of MCF-7 cells.

Discussion

Recent data including ours have shown that PTP1B and TC-PTP are positively implicated in tumorigenesis and oncogenic properties of breast cancer cell [4–7]. In the present work, we have studied the role of these PTPases in IGF-2 signaling. This growth factor, which is known to be over-expressed in breast cancers [8], acts through binding to IGF1R and IRA tyrosine kinase receptors (also

known to be over-expressed in breast cancers [16]). Activation of these RTK increases growth, survival and migration of breast cancer cells [10,17]. As observed in our previous work [7], inhibition of PTP1B or TC-PTP expression by siRNA transfection reduced MCF-7 cell growth (Fig. 1B and D) and basal ERK phosphorylation (Fig. 3B), but did not modified cell apoptosis (Supplementary Fig. 1). Moreover, growth (Fig. 1B) and ERK phosphorylation (Fig. 3B) in the presence of IGF-2 were also reduced by the transfection with PTPases siRNA, although the IGF-2-fold-effect was not affected (Figs. 1C and 3B). As observed previously [7], the inhibitory effect of PTPases siRNA on MCF-7 cell growth (Fig. 1B) correlated with inhibition of ERK phosphorylation (Fig. 3B). In agreement with this notion, the MAPK inhibitor PD98059 mimicked the effects of PTPases siRNA on cell growth (Fig. 4A). These observations are also in agreement with studies realized using an *in vivo* model of ErbB2-induced breast cancer [4,5], which have shown that PTP1B is positively implicated in breast cancer tumorigenesis by regulating ERK activity.

IGF-2-induced survival to acute 4-OHT treatment was not modified by the reduction of PTPases expression (Fig. 1D). RTK-induced signaling pathway implicated in cell survival generally involves Akt stimulation. In agreement with preservation of IGF-2 induced survival effects in siRNA treated cells, IGF-2-induced phosphorylation of Akt on serine 473 was not inhibited by transfection with PTPases siRNA (Fig. 3A). This result could also be related to previous work realized on the *in vivo* model of ErbB2-induced breast cancer [5], which showed that Akt phosphorylation on serine 473 was not changed in PTP1B knockout mice.

Migration of cancer cells is an important factor for the issue of the disease. The growth factor IGF-2 is known to be over-expressed in several breast cancers and to induce cell motility [8,13,15,18]. Here, we showed that transfection of MCF-7 cells with PTP1B or TC-PTP siRNA had no significant effect on basal cell migration. However, whereas IGF-2 stimulated the migration of MCF-7 cells transfected with control siRNA, reduction of PTPases expression completely abolished IGF-2-induced migration. This effect seems to be independent of ERK activity since the MAPK inhibitor PD98059 did not affected migration of MCF-7 cells (Fig. 4C), whereas it markedly reduced basal and IGF-2 stimulated cell growth (Fig. 4A). This result is in agreement with a previous study

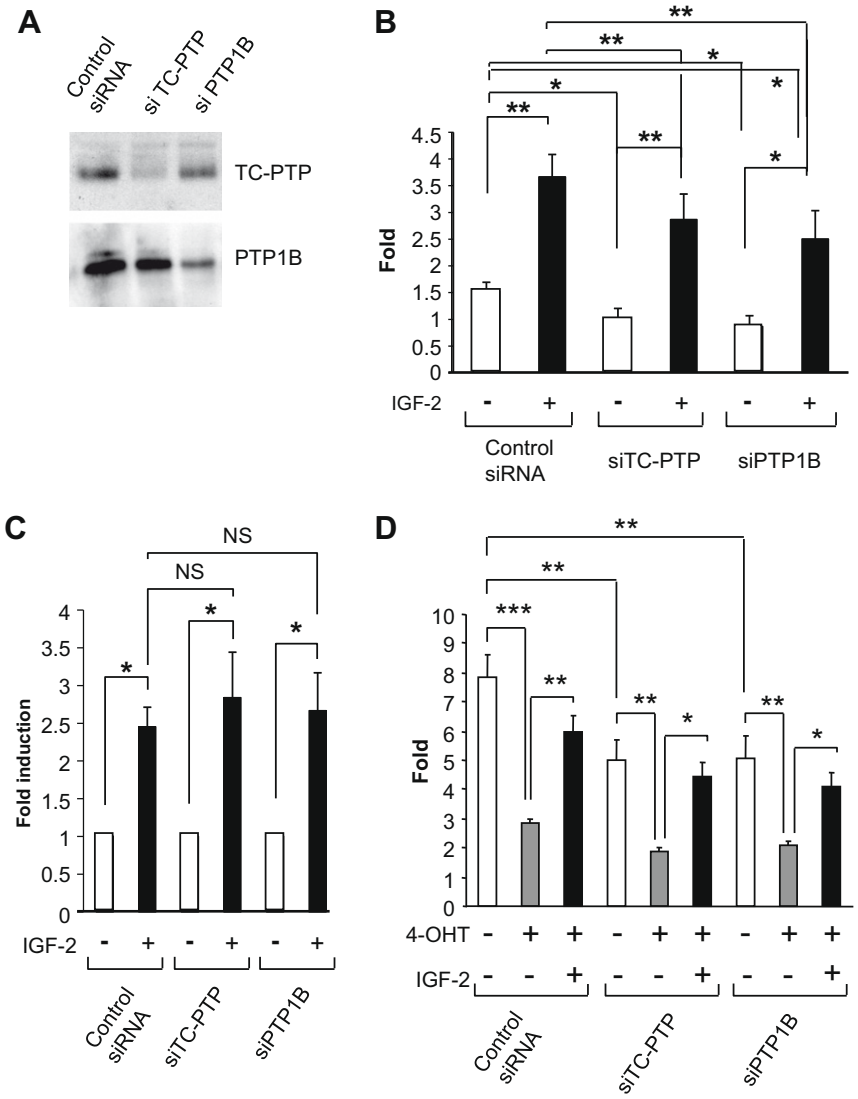

Fig. 1. PTP1B and TC-PTP control the growth of MCF-7 cells. (A) PTP1B and TC-PTP expression were markedly decreased by siRNA transfection. (B) The growth of MCF-7 cells during 72 h, in medium containing 0.5% BSA in absence or presence of 100 nM IGF-2, was evaluated using Uptiblue. (C) IGF-2-fold-effect on growth of siRNA-transfected MCF-7 cells. (D) The survival of MCF-7 cells to acute 4-OH Tamoxifen treatment (5 μM) during 72 h, in absence or presence of 100 nM IGF-2, was measured using Uptiblue. Data are represented as means ± SEM of three determinations.

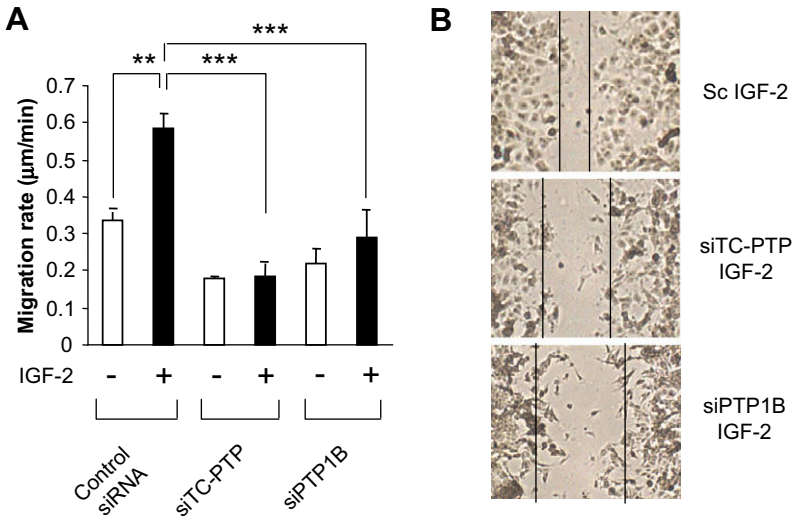

Fig. 2. PTP1B and TC-PTP are necessary for IGF-2-induced migration of MCF-7 cells. (A) Graphic representation of MCF-7 cell migration velocity determined after 8 h in the absence or presence of 100 nM IGF-2 in medium containing 0.5% BSA. (B) Microphotography of migrating MCF-7 cells 8 h after treatment with 100 nM IGF-2 in medium containing 0.5% BSA. Data are represented as means ± SEM of three determinations.

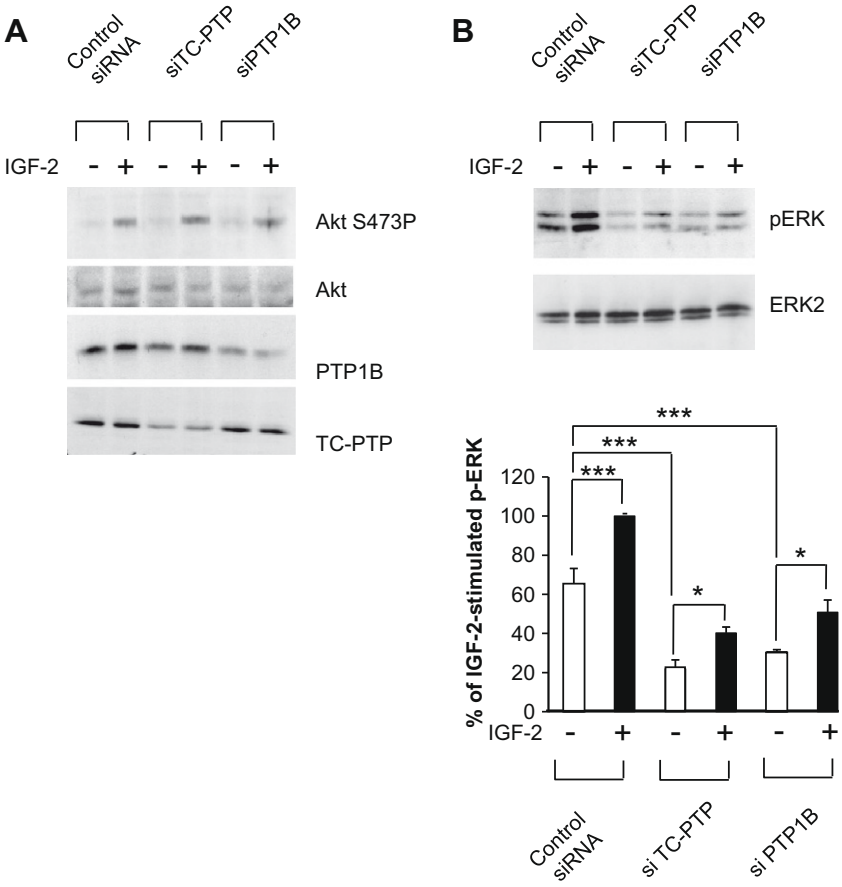

Fig. 3. PTP1B and TC-PTP regulate ERK phosphorylation but not Akt phosphorylation. Forty-eight hours after siRNA transfection, MCF-7 cells were treated with 100 nM IGF-2 during 5 min at 37 °C. Cells were extracted and proteins were analyzed by Western blotting. (A) Evaluation of Akt phosphorylation on serine 473 using specific antibody. (B) Evaluation of ERK phosphorylation using specific antibody. Quantifications of ERK phosphorylation autoradiograms are represented as means ± SEM of three determinations.

showing that ERK1/2 activity was not required for MCF-7 cell motility [19].

Some studies have shown that PTP1B can modulate cell migration, although contradictory results were obtained [20–24]. IGF-1-mediated motility is increased in PTP1B deficient transformed fibroblasts, suggesting a negative role of PTP1B on fibroblast migration [20]. Moroever, overexpression of PTP1B was found to inhibit 3Y1 cell migration [21]. However, co-expression of PTP1B with the CrkII adaptor protein promoted migration of HT 1080 cells, through regulation of p130Cas phosphorylation [24]. In

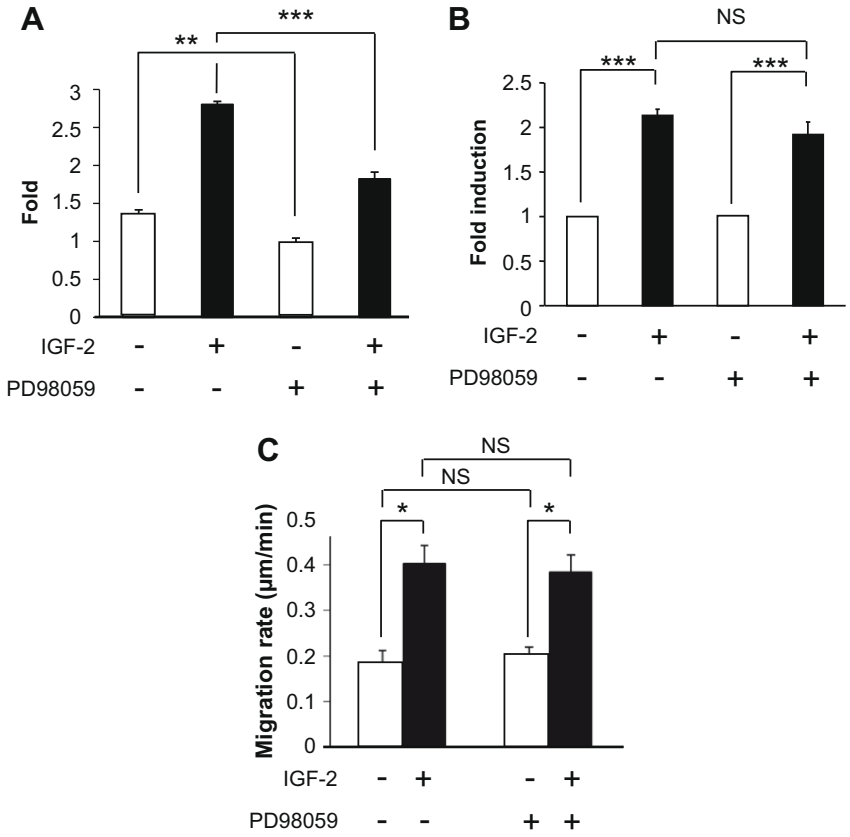

Fig. 4. PTP1B and TC-PTP control IGF-2-induced migration of MCF-7 cells independently of the ERK pathway. (A) MCF-7 cells were pretreated with PD98059 (40 μM) for 1 h and cultured during 72 h in absence or presence of 100 nM IGF-2 and 40 μM PD98059. Cell growth of was evaluated using Uptiblue. (B) IGF-2-fold effect on the growth of MCF-7 cells treated or not with 40 μM PD98059. (C) Effect of IGF-2 (100 nM IGF-2) on migration of MCF-7 cells treated or not with 40 μM PD98059. MCF-7 cells were pretreated with PD98059 (40 μM) for 1 h and migration was performed during 8 h hours in absence or presence of 100 nM IGF-2 and 40 μM PD98059.

agreement with a positive role of PTP1B in cell migration, small molecules PTP1B inhibitors significantly reduced L cells migration [23]. The implication of PTP1B in cell migration has been explained by the regulation of p130cas pathway [21–24]. Since p130cas is activated by tyrosine phosphorylation upon IGF1R stimulation [25], our results suggest that in MCF-7 cells transfected with PTP1B siRNA, inhibition of IGF-2-induced migration could result from deregulation of p130cas pathway. The involvement of TC-PTP in cell migration was not documented in the above-mentioned studies [21–24] and, to the best of our knowledge, our work constitutes the first evidence for a role of TC-PTP in cell migration.

In conclusion, we and others have shown previously that PTP1B [4–7] and TC-PTP [7] are positively implicated in oncogenic properties of breast cancer cells by regulating ERK1/2 signaling pathway. In the present work, we demonstrate that PTP1B and TC-PTP are also positively implicated in IGF-2-induced migration of MCF-7 cells, suggesting that they could play a role in metastasis development. Altogether, our results further confirm the potential of these enzymes as a new therapeutic target for the treatment of breast cancer.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bbrc.2009.12.176.

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