Platelet-derived Growth Factor (PDGF) Receptor-α Activates c-Jun NH2-terminal Kinase-1 and Antagonizes PDGF Receptor-β-induced Phenotypic Transformation*

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Platelet-derived growth factor (PDGF) is a potent mitogen for mesenchymal cells. The PDGF B-chain (c-sis proto-oncogene) homodimer (PDGF BB) and v-sis, its viral counterpart, activate both α- and β-receptor sub-units (α-PDGFR and β-PDGFR) and mediate anchorage-independent growth in NIH3T3 cells. In contrast, the PDGF A chain homodimer (PDGF AA) activates α-PDGFR only and fails to induce phenotypic transformation. In the present study, we investigated α- and β-PDGFR specific signaling pathways that are responsible for the differences between the transforming ability of PDGF AA and BB. To study PDGF BB activation of β-PDGFR, we established NIH3T3 clones in which α-PDGFR signaling is inhibited by a dominant-negative α-PDGFR, or an antisense construct of α-PDGFR. Here, we demonstrate that β-PDGFR activation alone is sufficient for PDGF BB-mediated anchorage-independent cell growth. More importantly, inhibition of α-PDGFR signaling enhanced PDGF BB-mediated phenotypic transformation, suggesting that α-PDGFR antagonizes β-PDGFR-induced transformation. While both α- and β-receptors effectively activate ERKs, α-PDGFR, but not β-PDGFR, activates stress-activated protein kinase kinase (MEKK) and JNK-1 activation. Inhibition of JNK-1 activity using a dominant-negative JNK-1 mutant markedly enhanced PDGF BB-mediated anchorage-independent cell growth, demonstrating an antagonistic role for JNK-1 in PDGF-induced transformation. Consistently, overexpression of wild-type JNK-1 reduced PDGF BB-mediated transformation. Taken together, the present study showed that α- and β-PDGFRs differentially regulate Ras-mitogen-activated protein kinase pathways critical for regulation of cell transformation, and transformation suppressing activity of α-PDGFR involves JNK-1 activation.

Platelet-derived growth factor (PDGF)

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‡The abbreviations used are: PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; MAPK, mitogen-activated protein kinase; Ab, antibody; mAb, monoclonal antibody; ERK, extracellular signal-regulated kinase; PAGE, polyacrylamide gel electrophoresis; JNK, c-Jun NH2-terminal kinase; kb, kilobase pair(s); hPGF, basic fibroblast growth factor; RIPA, radiimmune precipitation buffer; DN, dominant negative; AS, antisense; TTBS, Tris-buffered saline with Tween 20; MEKK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK) kinase.
transforming ability of PDGF AA and BB. First, is β-PDGFR alone sufficient for PDGF BB-mediated anchorage-independent cell growth, or is activation of both receptors required? Second, what signaling molecules are differentially regulated by α- and β-PDGFRs that cause distinct α- and β-PDGFRs-induced cellular responses? To address these questions, we have established NIH3T3 clones in which α-PDGFR activation is inhibited by its dominant-negative mutant, or α-PDGFR expression is down-regulated using an antisense construct. Using these clones, PDGF BB activation of β-PDGFR was investigated. PDGF AA activation of α-PDGFR and PDGF BB activation of both receptors was studied in control NIH 3T3 cells.

EXPERIMENTAL PROCEDURES

Cell Culture and Antibodies—NIH3T3 cells were cultured in a humidified 5% CO2 incubator with Dulbecco’s modified Eagle’s medium/F-12 nutrient media containing 10% bovine calf serum, 2 mM glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, 250 μg/ml amphotericin B, and 205 μg/ml sodium deoxycholate (Life Technologies, Inc.). Anti-active MAPK (ERK) and anti-active JNK antibodies were from Promega (Madison, WI). Anti-Erk2 antibody was from Calbiochem (La Jolla, CA), anti-β-actin antibody from Sigma, and anti-phosphotyrosine antibody from Oncogene Research Products (Cambridge, MA). Monoclonal Ab against α- or β-PDGFR was purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Polyclonal Ab against α-PDGFR was provided from the manufacturer’s instruction. Immunoblot Analysis—Cells were lysed in lysis buffer (RIPA buffer: 0.1% SDS, 0.5% sodium deoxycholate acid, 0.5% Nonidet P-40, 10 mM Tris, pH 7.4, 1 mM EDTA, 2 mM sodium vanadate, 1 mM phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin, and 10 μg/ml aprotinin). Protein concentrations were determined with BCA protein assay kit. The lysates were centrifuged for 15 min at 12,000 × g to remove debris, and immunoprecipitated using anti-PDGF receptor Ab, and protein G-agarose beads (Roche Molecular Biochemicals). Immunoprecipitates were washed five times with RIPA buffer and resolved by reducing SDS-PAGE. Tyrosine-phosphorylated PDGFs were detected by immunoblotting using the anti-phosphotyrosine antibody.

Inhibition of α-PDGFR Signaling in NIH3T3 Cells—In order to examine the effect of β-PDGFR activation alone in PDGF-mediated anchorage-independent cell growth, we established NIH3T3 cell clones in which α-PDGFR signaling is inhibited. One approach was to prevent autoactivation of α-PDGFR using a dominant-negative mutant of α-PDGFR (DN α-PDGFR) that contains the extracellular and transmembrane domains, but lacks the cytoplasmic kinase domains (Fig. 1). The DN α-PDGFR protein was expected to dimerize with wild-type α-PDGFR upon PDGF AA binding, but be unable to autophosphorylate the wild-type α-PDGFR, and therefore prevent α-PDGFR-mediated signal transduction. We selected DN α-PDGFR-transfected NIH3T3 clones (DN clones) that express truncated α-PDGFR mRNA (~2 kb) by Northern blot analysis (data not shown). To identify the DN clones in which α-PDGFR autoactivation is inhibited, the α-PDGFR protein was immunoprecipitated with an anti-α-PDGFR Ab and the active form was detected by immunoblot analysis using an anti-phosphotyrosine Ab. While α-PDGFR was autophosphorylated in the control cells following PDGF AA treatment, the active form of α-PDGFR was undetectable in DN clones 9 and 16 (Fig. 2). This showed that DN α-PDGFR successfully prevented PDGF AA-mediated dimerization and activation of wild-type α-PDGFR in DN9 and DN16. Of note, the truncated DN α-PDGFR protein was not detected by immunoblot analysis, since anti-α-PDGFR Ab recognized the COOH terminus of α-PDGFR. The second approach to inhibit the α-PDGFR signaling was to down-regu-

**RESULTS**

**Immunoprecipitation**—Cells were lysed in lysis buffer (RIPA buffer: 0.1% SDS, 0.5% sodium deoxycholate acid, 0.5% Nonidet P-40, 10 mM Tris, pH 7.4, 1 mM EDTA, 2 mM sodium vanadate, 1 mM phenylmethylsulfonyl fluoride, 10 μg/ml leupeptin, and 10 μg/ml aprotinin). Protein concentrations were determined with BCA protein assay kit. The lysates were centrifuged for 15 min at 12,000 × g to remove debris, and immunoprecipitated using anti-PDGF receptor Ab, and protein G-agarose beads (Roche Molecular Biochemicals). Immunoprecipitates were washed five times with RIPA buffer and resolved by reducing SDS-PAGE. Tyrosine-phosphorylated PDGFs were detected by immunoblotting using the anti-phosphotyrosine antibody.

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late α-PDGFR expression using an antisense construct of α-PDGFR (AS α-PDGFR) (Fig. 1). The level of α-PDGFR expression was significantly down-regulated in AS clones 4 and 6, as determined by immunoblot analysis (Fig. 2). Hereafter, we present data obtained mostly using DN16 and AS6 to avoid redundancy.

To confirm that α-PDGFR signaling is inhibited in DN and AS clones, PDGF AA-activation of ERK was readily detected in the control NIH3T3 cells 7 min after exposure to 5 ng/ml PDGF AA. In contrast, PDGF AA-induced ERK-2 activation was significantly inhibited in DN and AS clones, showing that α-PDGFR signaling is down-regulated in these cells (Fig. 3).

To ensure that β-PDGFR signaling is not significantly altered in DN and AS clones, the expression level and activation of β-PDGFR was examined. While PDGF AA induces α-PDGFR homodimerization only, PDGF BB induces homodimerization of αα- and ββ-PDGFRs and heterodimerization of αβ-PDGFR. Thus, if DN α-β-PDGFR levels are too high, β-PDGFR activation can also be disturbed by DN α-PDGFR. The efficiency of PDGF BB-induced tyrosine phosphorylation of β-PDGFR in DN and AS clones was similar to that in control NIH3T3 cells (Fig. 4A). In contrast, PDGF BB-induced α-PDGFR phosphorylation occurred only in the control NIH3T3 cells, but not in DN or AS cells (Fig. 4B). This showed that DN α-PDGFR inhibited dimerization and activation of α-PDGFR without significant alteration of β-PDGFR activation.

An antisense α-PDGFR construct contained cDNA encoding extracellular, transmembrane, and juxtamembrane domains of α-PDGFR in reverse orientation. Although α- and β-PDGFRs are closely related molecules, the antisense transcript of α-PDGFR should not interfere with β-PDGFR expression, since the nucleotide sequence homology is relatively low, especially in the extracellular domain. Indeed, Fig. 4A showed that β-PDGFR expression was not altered by AS α-PDGFR. The β-PDGFR protein and activation levels were comparable in the control NIH3T3, DN, and AS clones as determined by immunoblot analysis (Fig. 4A). To further ensure that β-PDGFR signaling is intact in DN and AS clones, PDGF BB activation of ERK-2 was examined. As shown in Fig. 4C, 5 ng/ml PDGF BB activated ERK-2 in DN and AS clones as efficiently as in the control NIH3T3 cells.

Inhibition of α-PDGFR Signaling Enhances PDGF BB-mediated Phenotypic Transformation of NIH3T3 Cells—We examined whether PDGF BB-mediated anchorage-independent cell growth requires activation of both α- and β-PDGFR, or if β-PDGFR alone is sufficient. Soft agar assay was performed to compare the efficiencies of PDGF BB-induced colony formation among the control NIH 3T3, DN, and AS cells. PDGF BB activation of β-PDGFR alone in DN and AS cells was sufficient to induce anchorage-independent cell growth (Fig. 5A). Surprisingly, the efficiency of PDGF BB-induced colony formation was significantly higher in DN and AS cells than in the control NIH3T3 cells (Fig. 5B), suggesting that inhibition of α-PDGFR signaling further enhanced PDGF BB-induced phenotypic transformation. This suggests that α-PDGFR may antagonize PDGF BB-induced transforming activity.

α-PDGFR Is Critical for PDGF Activation of JNK—Accumulating evidence implies that the balance between mitogenic (such as ERKs) and stress-induced (such as JNKs) signaling molecules downstream of Ras are critical for growth factor-induced cellular responses (28–32). ERK, a MAPK family member known to be critical for cell proliferation, was activated either by α- or β-PDGFR (Figs. 3 and 4C), in agreement with the previous observation that PDGF AA and BB are equally potent mitogens (7–9). In contrast to ERK, JNK activity is associated with cell cycle arrest or cell death following the loss of cell anchorage (33–35). Recent studies showed that JNK activates caspases (cysteine proteases that initiate apoptotic

![Fig. 2. Screening of dominant negative and antisense clones.](http://www.jbc.org/)

A. 50 ng/ml PDGF AA

Ctrl DN7 DN9 DN16

![Tyr-p](http://www.jbc.org/)

α--PDGFR

B. No Treatment

Ctrl AS4 AS6 AS7 AS8

α--PDGFR

![Fig. 3. PDGF AA-induced ERK2 activation is down-regulated in DN and AS clones.](http://www.jbc.org/)

A. 1 ng/ml 5 ng/ml PDGFAA

Active-Erk2

Erk2

β--actin

B. 1 ng/ml 5 ng/ml PDGFAA

Active-Erk2

Erk2

β--actin
cell death) and caspasates further activate JNK, suggesting a positive feedback loop between JNK and caspases leading to cell death (33, 34). We next asked if the ability of a-PDGFR to antagonize anchorage-independent cell growth is associated with its ability to activate the JNK pathway. To this end, we examined a- and b-PDGFR-induced activation of JNKs. Both PDGF AA and BB effectively activated JNK-1 in the control NIH3T3 cells, while they had little effect on JNK-2 (data not shown). The kinetics and dose responses of PDGF AA- or BB-induced JNK-1 activation were similar. Maximal JNK-1 induction occurred within 30 min with 50 ng/ml PDGF AA or BB (data not shown). PDGF AA-mediated JNK-1 activation was significantly inhibited in DN and AS clones as expected (Fig. 6A). Importantly, PDGF BB-induced JNK-1 activation was also drastically inhibited in these clones. This showed that b-PDGFR alone is not sufficient, and a-PDGFR signaling is critical for maximum induction of JNK-1 activity by PDGF. To ensure that lack of PDGF-induced JNK-1 activity was not due to intrinsic incapability to activate JNK-1 in these DN and AS clones, bFGF-activated JNK-1 was examined. As shown in Fig. 6B, active JNK-1 was readily detectable in DN and AS clones following bFGF treatment, as in the control cells.

JNK-1 Regulates PDGF BB-mediated Phenotypic Transformation of NIH3T3 Cells—To investigate the role of JNK-1 in PDGF BB-induced transformation, we introduced a dominant negative JNK-1 mutant (JNK1-APF, kindly provided by Dr. R. Davis, University of Massachusetts Medical School, Worcester, MA) into NIH 3T3 cells. JNK-1 is activated upon phosphorylation of Thr<sup>183</sup> and Tyr<sup>185</sup>. JNK1-APF, a catalytically inactive JNK-1 mutant, was constructed by replacing Thr<sup>183</sup> and Tyr<sup>185</sup> with Ala and Phe, respectively (36). The expression level of JNK-1 protein (sum of endogenous and mutant JNK-1) was significantly higher in JNK-APF-transfected NIH 3T3 cells than in the control vector-transfected cells (Fig. 7A). When PDGF activation of JNK-1 was examined, both PDGF AA and BB failed to activate JNK-1 in JNK1-APF-transfected NIH3T3 cells (Fig. 7B), demonstrating a dominant negative activity of mutant JNK as reported previously (36). PDGF BB-induced
phenotypic transformation was markedly enhanced in JNK1-APF-transfected cells compared with the control cells (Fig. 8), indicating that JNK-1 negatively regulates PDGF BB-induced transformation. To further confirm this, we next examined the effect of enhanced JNK-1 activity on PDGF BB-induced phenotypic transformation. To this end, we introduced wild-type JNK-1 (provided by Dr. R. Davis) into NIH 3T3 cells, and JNK-1 overexpression in these cells was confirmed by immunoblot analysis (Fig. 9A). PDGF BB activation of JNK-1 was significantly enhanced in JNK1-transfected cells (Fig. 9B), and the efficiency for PDGF BB-induced anchorage-independent cell growth was significantly reduced when JNK-1 activity was enhanced (Fig. 9C). Taken together, the present study demonstrated that JNK-1 plays a critical role for PDGF regulation of cell transformation, and lack of JNK-1 activation in the absence of α-PDGFR enhances PDGF BB-induced phenotypic transformation in NIH3T3 cells.

**DISCUSSION**

Critical functions of PDGF isoforms and their receptor subunits during embryogenesis have been well studied using knock-out mice deficient in PDGF A, PDGF B, α-receptor, or β-receptor gene (37–40). However, embryonic mortality of these knock-out mice does not allow studies of PDGF isoforms and their receptors in physiological and pathological processes in adults. Such processes include wound healing, inflammation, and proliferative diseases such as atherosclerosis, fibrosis, and tumorigenesis (reviewed in Refs. 1 and 2). In *vitro*, primarily PDGF BB has been used to study PDGF-induced signaling pathways, which binds both α- and β-receptors (reviewed in Ref. 2). The α- or β-PDGFR specific signaling pathway was investigated by introducing each receptor subunit into cells lacking endogenous PDGFRs (10, 41, 42). These studies helped identify signaling molecules that bind to each PDGFR subunit and reveal their roles in some PDGFRs-mediated cellular processes (43–49). However, it is now well recognized that PDGF-mediated cellular responses vary among cell types. These variations are most likely due to innate differences in available signaling molecules, making it critical to investigate PDGF-mediated pathways in cell types that express PDGFRs and contain the requisite signaling molecules for diverse PDGF-induced cellular responses.

Using NIH3T3 cells that are highly responsive to PDGF, we studied the differential roles of α- and β-PDGFRs in PDGF BB-induced anchorage-independent cell growth and activation of signaling molecules. Here, we report a transformation-suppressing activity of α-PDGFR in PDGF BB-induced transformation through JNK-1 induction. Both PDGF AA and BB activated JNK-1 in NIH 3T3 cells without noticeable JNK-2 activation. JNKs are often constitutively activated in apoptotic cells (34) and also during transformation processes induced by growth factors, virus, or oncogene products (50–54). JNK isoforms appear to mediate different cellular responses. The JNK-2 isoform mediates EGF-induced transformation of human A549 lung carcinoma cells (53). In contrast to the transforming activity of JNK-2, suppression of JNK-1 activity by dominant negative JNK-1 (JNK1-APF) enhanced arsenite-induced cell transformation of mouse epithelium (54), suggesting that JNK-1 transduces transformation-suppressing activity. JNK-1-mediated negative regulation of cell growth/survival was also suggested in another study (34). Following loss of cell-substrata interactions, JNK activity increases, followed by cell cycle arrest or apoptosis (34). Consistently, we found that JNK-1 down-regulation by either inhibition of α-PDGFR signaling or using a dominant negative JNK-1 mutant drastically increased anchorage-independent growth efficiency in NIH 3T3 cells in response to PDGF BB.

PDGF activation of α-PDGFR does not induce phenotypic transformation in murine fibroblasts (9). Interestingly, however, we previously showed that PDGF AA induces anchorage-independent cell growth of normal rat kidney (NRK) fibroblast cells that overexpress Bcl-2, an anti-apoptotic gene product (9). Bcl-2 was shown to inhibit JNK-1 activation and to prevent cell death following loss of cell anchorage (34). These studies (9, 34), together with our present results, provided the basis for our working model for PDGF regulation of transformation pathway as diagrammed in Fig. 10. Activation of α-PDGFR may transduce both positive and negative signaling for cell transformation, while β-PDGFR mainly induces positive signaling for cell...
transformation. PDGF BB activation of both receptors shifts the balance of signaling to favor the transformation pathway, while PDGF AA activation of \( \alpha \)-PDGFR alone does not. When \( \alpha \)-PDGFR-mediated negative signaling is inhibited (e.g. by Bcl-2), \( \alpha \)-PDGFR activation can result in phenotypic transformation. The present study clearly demonstrated that \( \beta \)-PDGFR activation alone is sufficient to induce phenotypic transformation of murine fibroblasts, and that \( \alpha \)-PDGFR signaling downregulates \( \beta \)-PDGFR-induced transformation through JNK-1 activation. However, it should be noted that PDGF BB activates JNK-1 as effectively as PDGF AA, and that PDGF BB induces phenotypic transformation in the presence of active JNK-1. In our working model (Fig. 10), we hypothesize that \( \alpha \)-PDGFR, through activation of JNK-1, serves as a negative regulator for PDGF BB-induced phenotypic transformation.

At present, it is unclear how \( \alpha \) - and \( \beta \) -PDGFRs differen-
tially activate JNK-1, a member of MAPK family. Tyrosine kinase growth factor receptors activate a protein kinase cascade that leads to MAPK activation by a complex mechanism involving the SH2/3 proteins, Grb2, Sos, and Ras (55). Several MAPK kinase kinases have been identified including c-Raf, c-Mos, and MEKK (56). Among them, MEKK-1 was shown to activate the JNK pathway (33, 57). While active Ras is sufficient for ERKs activation, phosphatidylinositol 3-kinase and Rac1 are apparently required for maximum induction of JNK activity (58–60). Both \( \alpha \) - and \( \beta \)-PDGFRs can activate Ras and phosphatidylinositol 3-kinase pathways, yet the level and duration of the activation may differ between \( \alpha \) - and \( \beta \)-PDGFR. This is suggested by the observation that the GTPase-activating protein of Ras, a negative regulator of Ras, preferentially binds to the \( \beta \)-PDGFR (61, 62). The subtle differences in the activities of the initial signaling molecules are likely to trigger different biochemical cascades leading to different cellular responses. Consistently, it was shown that prolonged activation of ERK induces PC12 cell differentiation (63) and constitutive activation of Raf-1 at the cytoplasmic membrane induces apoptotic cell death (64), whereas transient activation of these signaling molecules results in cell growth (63). The cell lines that we have generated should provide powerful tools to investigate the Ras-MAPK pathways differentially regulated by \( \alpha \) - and \( \beta \)-PDGFRs.

![Fig. 9. Enhanced JNK-1 activation reduced PDGF BB-induced transformation. A, more than 150 NIH 3T3 clones transfected with control vector (pcDNA3) (Ctrl) or with wild-type JNK-1 expression vector (wt-JNK-1) were pooled together. Lysates (20 \( \mu \)g/lane) of control and wt-JNK-1-transfected cells were subjected to immunoblot analysis with anti-JNK-1 antibody. B, serum-starved (48 h) cells (control, JNK1-APF, and wt-JNK-1) were treated with 25 ng/ml PDGF BB for 30 min and lysed in RIPA buffer. Lysates (20 \( \mu \)g/lane) were then subjected to immunoblot analysis with anti-active JNK antibody (top panel). The same blot was reprobed with an anti-\( \beta \)-actin mAb (bottom panel). C, control and wt-JNK-1-transfected NIH 3T3 cells were assayed for their ability to grow in soft agar in the presence of 25 ng/ml PDGF BB. After 16 days, colonies (>0.2 mm diameter) were counted. The mean values of triplicates and standard deviation of the mean of triplicate are shown.](http://www.jbc.org/)

![Fig. 10. A working model for PDGF regulation of transformation pathways. PDGF AA or BB activation of \( \alpha \)-PDGFR induces both pro- and anti-transformation pathways, while PDGF BB activation of \( \beta \)-PDGFR promotes transformation pathway. PDGFRs-activation of signaling molecules (such as JNK, ERK, phosphatidylinositol 3-kinase, and Src) critical for transformation regulation (14, 54, 65) are depicted.](http://www.jbc.org/)
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