Platelet-derived Growth Factor-induced Formation of Tensin and Phosphoinositide 3-Kinase Complexes∗

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Tensin is an SH2 domain-containing cytoskeletal protein that binds to and caps actin filaments. Investigation of signal transduction mechanisms associated with tensin revealed the presence of phosphoinositide 3-kinase (PI3-kinase) activity in tensin immunoprecipitates from platelet-derived growth factor-treated cells. Association of PI3-kinase activity with tensin was transitory, and the amount of activity was approximately 1% of the total PI3-kinase activity found in anti-phosphotyrosine (anti-pY) immunoprecipitates. In vitro, PI3-kinase activity associated with the SH2 domain of tensin in a platelet-derived growth factor-dependent manner. The optimal phosphopeptide binding specificity of the SH2 domain of tensin was determined to be phospho-Y (E or D), N, I, V, or F). Synthetic phosphopeptides containing the sequence YENI could specifically block the association of V, or F). Synthetic phosphopeptides containing the sequence YENI could specifically block the association of PI3-kinase activity with tensin in a dose-dependent manner. These results suggest that PI3-kinase interacts with the cytoskeleton via the SH2 domain of tensin and may play an important role in platelet-derived growth factor-induced cytoskeletal reorganization that is concomitant with cell migration and proliferation.

The extracellular matrix plays an important role in many cellular activities, including growth, differentiation, migration, and metastasis (1–4). The extracellular matrix and the cell interact at electron-dense regions in the plasma membrane known as focal adhesions (1). Integrins, which are heterodimeric transmembrane proteins, form a bridge at focal adhesions between the extracellular matrix and the actin filaments of the cytoskeleton (5). Other proteins found localized in focal adhesions include structural proteins (e.g. vinculin), proteins with known enzymatic activity (e.g. focal adhesion kinase, FAK), and proteins with diverse functions, such as tensin.

Of the proteins which interact with actin at focal adhesions, tensin is thought to be located closest to the ends of actin filaments because of its F-actin-binding and capping activities (6). Tensin has sequence similarity to actin-binding proteins (7) and, because it contains a well defined SH2 domain, to signal transduction molecules (8). Tensin is phosphorylated on tyrosine, serine, and threonine residues (9), suggesting that it might participate in signal transduction cascades. The presence of these characteristics in a single molecule suggests that tensin might coordinate signals involved in cytoskeletal changes.

One important signal transduction cascade stimulated by receptor protein-tyrosine kinases is the phosphatidylinositol pathway. The classical phosphatidylinositol pathway is involved in two regulatory processes. Phospholipase C cleaves phosphoinositides to yield second messengers important for cell proliferation (10, 11). Cytoskeletal architecture is maintained, in part, by actin. Polymerization of actin is directly regulated by interactions of phosphoinositides with gelsolin, profilin, and α-actinin (12–14) (reviewed in Ref. 15). The discovery of PI3-kinase revealed more of the complexity of phosphatidylinositol metabolism (16–21). The production of 3-phosphorylated polyphosphoinositides appears essential for the transformed phenotype and PDGF-induced mitogenesis (22–24).

PI3-kinase has also been implicated in actin-based cytoskeletal rearrangement. Deletion of the kinase insert domain that contains the binding site for PI3-kinase from the PDGF receptor eliminates the ability of PDGF to mediate actin reorganization (25). In addition, PI3-kinase is an important mediator of PDGF-induced membrane ruffling (26) and PDGF-induced chemotaxis (27, 28). PDGF-induced membrane ruffling and chemotaxis can be prevented if the PI3-kinase binding site on the PDGF receptor is deleted or if PI3-kinase activity is inhibited by the fungal metabolite wortmannin. The regulatory 85-kDa subunit of PI3-kinase is recruited to beads coated with fibronectin that induce the formation of focal adhesion complexes (29, 30). In platelets, thrombin induces the association of PI3-kinase and p60src (31) and the translocation of PI3-kinase and p60src to the cytoskeleton (32, 33). PI3-kinase and p60src are also recruited to the cytoskeleton by the platelet adhesion receptor glycoprotein Ib/IX when activated by von Willebrand factor (34). Additional studies have also demonstrated an interaction between PI3-kinase and FAK (35). FAK is a cytoplasmic protein-tyrosine kinase in the signal transduction cascade downstream of integrin (36). Therefore, PI3-kinase plays a role in cytoskeletal rearrangements elicited by both mitogenic and nonmitogenic stimuli.

In this paper we present evidence that tensin can form complexes with phosphoinositide kinase activities. In addition, PI3-kinase can specifically form complexes in tensin immunoprecipitates in a PDGF-dependent manner. We further investigate

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† The abbreviations used are: FAK, focal adhesion kinase; PDGF, platelet-derived growth factor; GST, glutathione S-transferase; HPLC, high performance liquid chromatography; PtdIna, phosphatidylinositol; PtdIns-4-P, phosphatidylinositol 4-phosphate; PtdIns-4,5-P2, phosphatidylinositol 4,5-bisphosphate; PtdInsP3, phosphatidylinositol 3,4,5-trisphosphate; PI 3-kinase, phosphoinositide 3-hydroxy kinase.
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the interaction of PI 3-kinase and tensin with a GST-tensin SH2 domain construct and find that PDGF stimulation is required for association of PI 3-kinase and tensin in vitro. The optimal phosphopeptide recognition specificity for the SH2 domain of tensin is p-Y(E or D/N/I, V, or F). Results of competition experiments with a synthetic peptide containing the sequence pYENI suggest that a complex containing PI 3-kinase interacts specifically with the SH2 domain of tensin. These data suggest that PI 3-kinase is involved in focal adhesion dynamics in response to growth factor stimulation, cellular signaling, and cytoskeletal rearrangement.

**Experimental Procedures**

**Tensin Clones and Cell Lines**—The full-length tensin clone was derived from chicken cardiac muscle and transfected into NIH 3T3 cells (7). This transfected cell line (designated L-1) was propagated in Dulbecco’s modified Eagle’s medium with 10% calf serum and 300 μg/ml G418. NIH 3T3, human foreskin fibroblasts (FS-2), and Balb/c 3T3 cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% CS.

**Preparation of Immune Complexes and GST-Tensin SH2 Domain Complexes**—Cells grown on 10-cm dishes were lysed in 1.0 ml of lysis buffer (1% Nonidet P-40, 20 mM Hepes, 135 mM NaCl, 5 mM EDTA, 10% glycerol, 500 μM vanadate, 1 μM aprotinin, 0.75 μg/ml leupeptin, 1 μM pepstatin) and were incubated on a platform rocker at 4°C for 5–10 min. Plates were scrape-harvested, and the lysates were triturated, collected into Eppendorf tubes, and vortexed. Lysates were cleared by centrifugation at 6000 × g for 10 min at 4°C. The appropriate antibody was added and incubated at 4°C on a rocker platform for 2 h. Protein A-Sepharose (50% suspension in phosphate-buffered saline) was added and the incubation was continued for 1 h. For GST-tensin SH2 domain association, 35 μl of purified GST-fusion protein on Sepharose beads in a 50% suspension of phosphate-buffered saline was added in place of the antibody and incubated on a rocker platform at 4°C for 1 h. The tensin SH2 domain was constructed as previously reported (8) and used without modification. All complexes were collected by centrifugation and washed twice with 1% Nonidet P-40, 1 mM EDTA, and 100 μM vanadate in phosphate-buffered saline; once with 0.5 M LiCl and 100 μM vanadate in 100 μM Tris (pH 7.25); and once with 100 mM NaCl and 1 mM EDTA in 10 mM Tris (pH 7.25).

**Phosphoinositide Kinase Assays and HPLC Analysis**—PI 3-kinase assays were performed as described previously (37) in a total volume of 50 μl. Briefly, 10 μl of sonicated lipid mix was added to the washed beads (see above) followed by 35 μl of ATP mix to initiate the reaction (final concentrations: 20 mM Heps, 5 mM MgCl₂, 20 μM ATP, 20 μM [γ-32P]ATP (3000 Ci/mmol)). Reactions were incubated for 10 min at room temperature and were stopped with 75 μl of 1 M HCl and 180 μl of methanol/chloroform (1:1). This length of time and ATP concentration was determined to be in the linear range of the assay. Samples were vortexed and then centrifuged to separate the organic and aqueous phases. Seventy-five μl of the organic phase was collected and dried by ion-exchange HPLC. Radioactivity was detected with a Radiomatic flow-through detector (Packard Instrument Co.) immediately after the anion-exchange column.

**RESULTS**

**Association of Phosphoinositide Kinase Activities with Tensin Immunoprecipitates**—To determine whether tensin is involved with phosphatidylinositol signal transduction cascades, we tested for the presence of phosphoinositide kinase activity in tensin immunoprecipitates. In addition, the effect of PDGF stimulation on phosphoinositide kinase activities in tensin immunoprecipitates was determined. L-1 cells (NIH cells expressing chicken tensin) were grown to confluence and placed in Dulbecco’s modified Eagle’s medium with 0.2% CS overnight.
lated cells is approximately 4 times greater than in unstimulated cells (Fig. 1B). The PI 3-kinase activity found in tensin immunoprecipitates represented approximately 1% of the PI 3-kinase activity recovered in anti-pY immunoprecipitations after 15 min of PDGF stimulation (data not shown and Fig. 2). The amount of tensin in the immunoprecipitate did not increase with PDGF stimulation as determined by Western blot analysis (data not shown). In addition, treatment of cells with the PI 3-kinase inhibitor wortmannin decreased the amount of PI 3-kinase activity in tensin immunoprecipitates by 71% (data not shown).

To investigate the association of PI 3-kinase with endogenous tensin, nontransfected human FS-2 fibroblast cells were quiesced as described for L-1 cells and were stimulated with PDGF-BB. Tensin was immunoprecipitated with antiserum that recognizes human tensin (R95) followed by PI 3-kinase assays. As shown in Fig. 2, endogenous tensin also forms a complex with PI 3-kinase activity, and the time course of the association of PI 3-kinase with endogenous tensin is similar to that found in NIH 3T3 cells expressing transfected chicken tensin. Thus, PI 3-kinase associates with tensin immunoprecipitates after PDGF stimulation in a transient manner, and the amount of activity recovered with tensin represents a relatively small fraction of the PI 3-kinase activity in the cell after PDGF stimulation.

Association of Phosphoinositide Kinases with the SH2 Domain of Tensin—Possible mechanisms of PDGF-induced association of phosphoinositide kinase activity with tensin were investigated. A GST-tensin SH2 domain fusion protein was used to determine whether lipid kinases can form a complex in a PDGF-dependent manner. GST-tensin SH2 domains that were affinity-purified on Sepharose beads were incubated with NIH 3T3 cell lysates from untreated cells or cells treated with PDGF-BB. As shown in Fig. 3A, PtdIns, PtdIns-4-P, and PtdIns-4,5-P2 kinase activities associated with the tensin SH2 domain if the cells had been stimulated with PDGF, indicated by the formation of PtdInsP, PtdInsP2, and PtdInsP3. Lysates from unstimulated cells had only minimal PtdIns and PtdIns-4-P lipid kinase activities. The GST alone control shows that a minor amount of nonspecific phosphoinositide kinase activity associates with the beads (Fig. 3A). HPLC analysis of the deacylated lipid products revealed that the PtdInsP was both the PtdIns-4-P and PtdIns-4,5-P2 isomers and that PtdInsP3 was also a mixture of PtdIns-4,5-P2 and PtdIns-4,5-P3 in unstimulated and PDGF-treated cells (Fig. 3B and Table I). The production of PtdInsP3 was inconsistently detected at very low levels in unstimulated cells but was consistently increased in cells exposed to PDGF, and HPLC analysis confirmed the structural identity of this phosphorylated product (data not shown). The amount of PI 3-kinase activity associated with the SH2 domain of tensin increased after PDGF stimulation (Table I). Interestingly, the amount of PtdIns-4-P 3-kinase activity increased more than that of PtdIns-4,5-P2 3-kinase activity (Table I). Thus, lipid kinase activity that phosphorylates the three classical phosphoinositides (PtdIns, PtdIns-4-P, and PtdIns-4,5-P2) forms a complex with the SH2 domain of tensin.
PDGF causes a marked increase in the amount of PI 3-kinase that associates with this complex.

**Specificity of the SH2 Domain of Tensin**—To define better the interaction of phosphoinositide kinases and tensin, we determined the phosphopeptide binding specificity of the SH2 domain of tensin using an in vitro technique that determines the recognition specificity of SH2 domains for tyrosine-phosphorylated peptides (39, 40). The results of selection are shown in Fig. 4. A strong preference for negatively charged amino acids was detected at the +1 position following the phosphorylated tyrosine residue, as indicated by the selection of E and D (Fig. 4A). The +2 position was strongly selective for N (Fig. 4B), and the +3 position had a preference for a hydrophobic residue (I, F, or V) (Fig. 4C). This selection is consistent with the SH2 domain of tensin being in the group 1B category of SH2 domains, as previously suggested from SH2 domain sequence similarities (40).

**Inhibition of Tensin-associated Lipid Kinase Activity by Peptides Specific for the SH2 Domain**—To investigate the binding of the lipid kinase activity with the SH2 domain of tensin, we tested the ability of phosphopeptides to block the association. Phosphopeptides were incubated with the GST-tensin SH2 domain and then mixed with unstimulated or PDGF-stimulated cell lysates. The optimal phosphopeptide sequence determined from the library selection was used (GDGpYENISPLLL). As shown in Fig. 5, all three products of the lipid kinase reaction (PtdInsP, PtdInsP₂, and PtdInsP₃) showed a dose-dependent decrease in association with the SH2 domain of tensin with increasing phosphopeptide concentration. The half-maximal concentration for inhibition was approximately 2 μM.

To provide additional evidence that the lipid kinase activity associates with the SH2 domain of tensin in the classical SH2 domain/phosphopeptide manner, we performed competition experiments with o-phosphotyrosine in place of the phosphopeptides. Phosphotyrosine alone blocks the association of kinases with the ability to phosphorylate PtdIns, PtdIns-4-P, and PtdIns-4,5-P₂ with equal concentration dependence (data not shown). The concentration of 50% inhibition is ~2 mM. Thus, PI 3-kinase activity associates with the SH2 domain of tensin in the traditional phosphopeptide/SH2 domain manner.

**DISCUSSION**

Tensin has been proposed to play an important role in signal transduction and cytoskeletal integrity (41). In an effort to help characterize its function and to elucidate the potential signal transduction mechanisms, we investigated the biochemistry of tensin. Data presented in this paper indicate that both PtdIns and PtdIns-4-P 5-kinase activity are present in both unstimulated and PDGF-stimulated tensin immunoprecipitates, suggesting that these enzymes are located at focal adhesions. The phosphoinositide products of these enzymes are implicated in cytoskeletal organization and have been shown to interact with a number of actin-binding proteins (15). The conventional polyphosphoinositides generally promote the polymerization of actin filaments, mainly by relieving the inhibition of polymerization caused by proteins that sequester actin monomers and cap the ends of actin filaments. Tensin may help to localize PtdIns 4-kinase and PtdIns-4-P 5-kinase to focal adhesions,
other SH2 domains. Scanning the sequences of p85
4-P 5-kinase activity binding to the SH2 domain of tensin
cause a change in the amount of PtdIns 4-kinase and PtdIns-
inositol lipids (45). In our studies, PDGF stimulation did not
in agreement with this model. Miyamoto
for PI 3-kinase at tyrosine 950 and has been shown to have a
and
preferred binding motif of tensin (Fig. 4). The SH2 domain of
3-kinase is found in tensin immunoprecipitates is based on the
biochemical mechanism for the association. This biochemical
mechanism is supported by the observation that this associa-
tion can be blocked with a phosphopeptide specific for the SH2
domain of tensin at concentrations consistent with the Kd of
other SH2 domains. Scanning the sequences of p85α, p85β,
p110α, and p110β for sequences that recognize the SH2 domain
of tensin suggest that the interaction may be indirect; thus
another protein may facilitate the interaction.

The binding specificity of the SH2 domain of tensin places it
in a family of SH2 domains with interesting characteristics,
including abl, 3BP2, and GRB2 (40), which also have a strong
preference for N at the +2 position. Because the binding char-
acteristics of these proteins are similar, their targets in vivo
may overlap. One model to explain our observation that PI
3-kinase is found in tensin immunoprecipitates is based on the
preferred binding motif of tensin (Fig. 4). The SH2 domain of
tensin could bind to the phosphorylated tyrosine 925 of FAK.
This site has recently been shown to bind GRB2 both in vitro
and in vivo (43). FAK, in turn, has an optimal binding sequence
for PI 3-kinase at tyrosine 950 and has been shown to have a
direct and PDGF-induced interaction with PI 3-kinase (35, 44).
In agreement with this model, Miyamoto et al. (30) have shown
that both tensin and FAK are recruited to a head-induced focal
adhesion complex prior to the recruitment of the 85-kDa sub-
unit of PI 3-kinase. The recruitment of the 85-kDa subunit
was also dependent on tyrosine kinase activity. Thus, FAK is
a potential bridge between PI 3-kinase and tensin.

The precise role of PI 3-kinase in the focal adhesion is cur-
rently unknown. Cells that are attached to fibronectin and
stimulated with PDGF demonstrate enhanced metabolism of
inositol lipids (45). In our studies, PDGF stimulation did not
cause a change in the amount of PtdIns 4-kinase and PtdIns-
4-P 5-kinase activity binding to the SH2 domain of tensin
(Table I), suggesting that the conventional phosphoinositide
kinase activities are probably not regulated directly by PDGF
via the SH2 domain of tensin. Recent evidence in fibroblasts
suggests that PtdIns-4-5-kinase is regulated by the small
GTP-binding protein Rho (46). In fibroblasts, Rho induces
stress fiber and focal adhesion formation (47). The 85-kDa subunit of PI 3-kinase contains a region with sequences similar
to the region of bcr that has GTPase activity for the Rho family
of proteins (48, 49). It is possible that tensin, by assisting in the
localization of PI 3-kinase activity to focal adhesions, allows PI
3-kinase to play an important role in the Rho signal transduc-
tion cascade involved in cytoskeletal rearrangements.

It is noteworthy that an optimal binding sequence for the
tensin SH2 domain is present in tensin at tyrosine 393, located
in the second actin binding domain (6). It is not known whether
this tyrosine is phosphorylated. However, dimerization or in-
tromolecular folding of tensin mediated by phosphorylation
and subsequent SH2 domain binding may lead to important
conformational and biochemical changes in the function of
tensin. For example, the recent model proposed for vinculin by
Johnson and Craig (50) is similar to a model we would propose
for tensin. Phosphorylation of tensin on tyrosine 393 would
create a binding site for the SH2 domain of tensin. This would
provide a regulated mechanism to induce a conformational
change in tensin and could produce an intramolecular head-to-
head structure. This conformation or the phosphorylation itself
could have a direct effect on the actin binding domain and thus
be important for tensin and actin interactions.

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