Differential Interactions of the Growth Factor Receptor-bound Protein 2 N-SH3 Domain with Son of Sevenless and Dynamin

POTENTIAL ROLE IN THE Ras-DEPENDENT SIGNALING PATHWAY*

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In this paper, we show that the 36–45 surface-exposed sequence WYKAELNGKD of growth factor receptor-bound protein 2 (Grb2) N-SH3 domain inhibits the interaction between Grb2 and a 97-kDa protein identified as dynamin. Moreover, the peptide GPPQVPSRPNR from dynamin also blocks the binding of dynamin to the proline-rich recognition platform of Grb2. Mutations in the 36–45 motif show that Glu-40 is critical for dynamin recognition. These observations were confirmed by immunoprecipitation experiments, carried out using ER 22 cells. It was also observed that the proline-rich peptide from dynamin was unable to dissociate the Grb2-Sos complex, whereas the proline-rich peptide from Son of sevenless (Sos) inhibited Grb2-dynamin interaction. A time-dependent stimulation of epidermal growth factor receptor overexpressing clone 22 (ER 22) cells by epidermal growth factor resulted in an immediate increase of the Grb2-Sos complex and a concomitant decrease in Grb2-dynamin. This suggests that the recruitment of Grb2-Sos to the membrane, triggered by epidermal growth factor stimulation, activates the Ras-dependent signaling and simultaneously enhances free dynamin levels, leading to both receptor internalization and endocytotic processes.

Growth factor receptor-bound protein 2 (Grb2), 1 constituted by two Src homology 3 (SH3) domains surrounding one SH2 domain, is an example of adaptors transferring information between extracellular messages monitored by membrane-bound receptors and intracellular transducers (1). By its SH2 domain, Grb2 recognizes phosphotyrosine residues of stimulated growth factor receptors, such as the EGF receptor, either directly or through additional adaptors such as SH2 domain containing adaptor protein (Shc) (2), whereas by its SH3 domains, Grb2 interacts with several cytosolic proteins such as Sos (Son of sevenless) the exchange factor of Ras (3).

Immunoprecipitation experiments performed on stimulated and unstimulated cells have shown that Grb2-Sos exists as a preformed complex (4). Recruited to the cell membrane upon stimulation, the Grb2-Sos complex promotes Ras-GTP formation, which in turn is able to bind Raf and thus to induce the activation of transcription factors such as fos, jun, or myc, through a cascade of mitogen-activated protein kinase stimulation (5, 6). Site-directed mutagenesis experiments have shown the importance of Grb2 SH3 domains, since mutations P49L and G203R localized in the N- and C-terminal domains, respectively, were shown to block the DNA synthesis induced by activation of the Ras pathway (7, 8).

However, the mechanisms involved in the down-regulation of the Ras-activated pathway, triggered by stimulation of the receptor, remain unclear. It has been shown that the stimulation of mitogen-activated protein kinases promotes Sos phosphorylation, which in turn could uncouple the mitogenic signal through dissociation of either Grb2-Sos or Grb2 receptor complexes (9–12). The regulation of the activation and inactivation of the Ras-dependent signaling pathway could also occur directly by changes in the levels of the complexes formed between Grb2 and Sos or other ligands. Indeed, through its SH3 domains, Grb2 was reported to interact with different proteins such as dynamin, a GTPase protein involved in the endocytosis process (13, 14). However, it is not yet clear whether multiple interactions involving Grb2 proceed as concomitant or successive events in the interruption of the mitogenic signal.

The Grb2 N-SH3 domain has been shown (15–17) to interact with VPPPVPBRRR, a proline-rich peptide of the C-terminal part of Sos, which has the highest measured affinity for Grb2 (8, 18). In this complex, the side chains of Pro-2 and Val-5 in VPPPVPBRRR interact with aromatic residues that constitute a hydrophobic recognition platform, highly conserved in all the SH3 domains known to bind proline-rich peptides (19). In contrast, this aromatic hydrophobic platform has been shown by NMR to be lacking in the structure of the SH3 domain of Ras-GAP (20), a GTPase-activating protein that behaves as a negative regulator (21) or as an effector (22) of Ras. Accordingly, no proline-rich peptide has yet been found to interact with GAP SH3. However, in this SH3 domain, the peptide sequence 317–326 (WMWVTNLRTD), exposed at the surface (20), was shown to play a critical role in the binding of the GAP SH3-binding protein (23). Based on these results, the potential occurrence of two different binding sites on SH3 domains had been proposed (20), an hypothesis, supported by mutational analyses carried out on the SH3 domain of Src (24). Accord-

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1 The abbreviations used are: Grb2, growth factor receptor-bound protein 2; SH2, Src homology 2; SH3, Src homology 3; EGF, epidermal growth factor; Sos, Son of sevenless; GAP, GTPase-activating protein; mAb, monoclonal antibody; GST, glutathione S-transferase; PSH, phosphatase-buffered saline; PAGE, polyacrylamide gel electrophoresis; PVDF, polyvinylidene difluoride; ER22, epidermal growth factor receptor overexpressing clone 22.

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ingly, Schumacher et al. (25) have recently shown that the Src SH3 domain interacts with a cyclic peptide through a binding process involving both the hydrophobic platform and other exposed amino acids such as Trp-119 and Leu-120, which belong to the corresponding region on the 317–326 peptide in GAP-SH3.

A similar recognition mode, involving a motif corresponding to the 317–326 sequence of GAP, seems to occur for the binding of the Vav C-SH3 domain with the protein Ku 70 (26). All these binding motifs are located on a β-strand exposed at the surface of the SH3 domains. This is also the case for the sequences 36–45 of Grb2 N-SH3 (WYKAELNGKD) and 194–203 (WW-GACHNGQT) of Grb2 C-SH3 domains. Interestingly, whereas the 36–45 peptide is accessible, the 194–203 fragment of Grb2 was shown by crystallographic analysis to interact with the N-terminal SH3 domain (27). All these results prompted us to investigate the possible existence of a protein target interacting with the sequence 36–45 (WYKAELNGKD) of the Grb2 N-SH3 domain. We show in this paper that this peptide is able to block the interaction of Grb2 with a p97 protein, identified as dynamin, whereas the analog, where Glu is replaced by Thr, cannot block this interaction, illustrating its selectivity. Moreover, competition experiments using extracts from ER 22 cells overexpressing the EGF receptor showed that a proline-rich sequence derived from Sos displaces the Grb2-dynamin complex, whereas the proline-rich sequence of dynamin, shown to interact with Grb2, is unable to displace the Grb2-Sos complex. These results and those obtained from the stimulation of ER 22 cells by EGF suggest that the formation of the Grb2-Sos complex might occur at the membrane at the expense of the Grb2-dynamin pool. The free dynamin thus generated might interact with other SH3 domain containing proteins, such as amphiphysin, which has been shown to be involved in neuronal receptor endocytosis (28).

**EXPERIMENTAL PROCEDURES**

**Antibodies**—The anti-Sos (Sos 1 and Sos 2, IgG3 mAb) and anti-dynamin (IgG1 mAb) antibodies were purchased from Transduction Laboratories (Lexington, KY). The anti-GRB2 N-SH3 monoclonal antibody was purchased from Hybridolab Pasteur Institute (Paris, France). The polyclonal anti-Grb2 used for immunoprecipitation studies was purchased from Santa Cruz Biotechnology (Santa Cruz, CA).

**GST Fusion Proteins**—DNA sequences corresponding to Grb2 (residues 1–210) were amplified by polymerase chain reaction and cloned into the expression vector pxEXZT at BamH I and EcoRI restriction sites. Bacteria transformed with the recombinant plasmids were grown, induced with isopropyl-1-thio-β-D-galactopyranoside, and disrupted by sonication (29). The GST-SH3 fusion proteins were purified by affinity chromatography on glutathione-agarose beads (Sigma) followed by elution with 10 mM reduced glutathione.

**Peptide Synthesis and Purification**—The peptides were prepared by solid phase synthesis. The protected peptide chains were assembled according to the stepwise solid phase method of Merrifield (45) on an Applied Biosystems 431A peptide synthesizer with hydroxybenzotriazole/dicyclohexylcarbodiimide as coupling reagents. Synthetic peptides corresponding to WYKAELNGKD, WYKATLNGKD, WMWVTNLRTD, GPPQVPPSRPNL, and VYAPPYVPRRR were synthesized using 10 eq of amino acids, whereas SH3 domains were synthesized using 20 eq, as described previously (20). The peptides were purified by high pressure liquid chromatography using a C4 (for Grb2 N-SH3 domain) or a C8 (for deca- and dodecapeptides) Vydac 5-mm column diameter (220 × 10 mm) and a linear gradient of B (where A is trifluoroacetic acid 0.1% and B is CH3CN 70%, trifluoroacetic acid 0.09%) at a flow rate of 1.5 ml/min with detection at 214 nm. The identity of the peptides was checked by electrospray mass spectrometry.

**Cells and Preparation of Cell Lysates**—Adherent ER 22 cells (hamster fibroblasts overexpressing the human epidermal growth factor receptor, a kind gift from Dr. J. Pouyssegur, France) were routinely grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum containing the antibiotic G418 (200 μg/ml) and 2 mM l-glutamine (Life Technologies, Inc.) and were incubated at 37 °C in 5% CO2 (23). Cells were grown to confluence and were serum-starved for 24 h.

Cells were rapidly washed with ice-cold phosphate-buffered saline (PBS, 137 mM NaCl, 2.7 mM KCl, 9.6 mM Na2HPO4, 1.47 mM KH2PO4, pH 7.5) containing 1 mM Na3VO4, and then scraped from the plate in 1 ml HNTG lysis buffer (1% Triton, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1 mM EDTA, 1 mM MgCl2, 1 mM NaVO4, 10 mM Na3P04, 10 mM NaF, 1 μg/ml leupeptin, 1 μg/ml pepstatin A, 1 μg/ml trypsin inhibitor, 1 μg/ml chymostatin, 1 μg/ml antipain, 2 μg/ml aprotinin, 10 μg/ml benzamidine, 1 mM phenylmethylsulfonyl fluoride, pH 7.5) and solubilized for 30 min at 4 °C. Lysates were cleared by centrifugation at 15,000 g for 10 min, and the protein concentration was determined (Bio-Rad microassay).

**Cell Stimulation by EGF**—Cells were grown to confluence and then serum-starved for 24 h. They were then stimulated with EGF (50 ng/ml) for 1, 5, 15, or 30 min in Dulbecco’s modified Eagle’s medium, at room temperature (30), and immediately washed three times with ice-cold PBS containing 1 mM Na3VO4 and lysed as described above.

**Affinity Precipitated Proteins and Competition Assay—Glutathione-agarose beads (150 μl containing 60 μg of GST fusion protein) were mixed with lysates (5 μg of cellular proteins), with or without inhibitor peptide, and rocked at 4 °C overnight. Beads were washed 4 times with HNG (50 mM Hepes, 150 mM NaCl, 10% glycerol) containing 0.2% of Triton X-100. Affinity precipitated proteins were eluted by boiling in SDS sample buffer for 5 min. All these complexes were incubated with 50 μl of protein A-Sepharose for 2 h at 4 °C. The pellets were washed three times with HNTG, resuspended in SDS sample buffer, and heated at 100 °C for 10 min. The immune complexes were then resolved by SDS-PAGE and transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore Corp.). The membranes were then subjected to Western blot as described above.

**Inhibition of Grb2 N-SH3 and Purified Dynamin Complexation**—Dynamin was purified from rat brains by a novel purification procedure (31). 10 mg of the Grb2 N-SH3 domain (15) were coupled to 1 ml of CNBr-activated Sepharose 4B (Pharmacia Biotech Inc.) for 1 h at 4 °C. Grb2 was then immunoprecipitated by incubation of the supernatant with 4 μg of a Grb2 polyclonal antibody overnight at 4 °C, in the presence or absence of the peptide (1.5 μM). The resultant immune complexes were precipitated by incubation with 50 μl of protein A-Sepharose for 2 h at 4 °C. The pellets were washed three times with HNTG, resuspended in SDS sample buffer, and heated at 100 °C for 10 min. The immune complexes were then resolved by SDS-PAGE and transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore Corp.).

**RESULTS**

**Peptide-(36–45) from Grb2 Inhibits the Association of Grb2 with a p97 Protein**—To investigate the hypothesis of the presence of a second binding site on N-SH3 Grb2, the 36–45 pep-
Identification of the p97 Protein as Dynamin—
The C-terminal region of Sos contains four conserved proline-rich motifs among which VPPPVPPRRR, corresponding to amino acids 1149–1158, was shown to have the highest affinity for Grb2 and in particular for its N-SH3 domain (8, 18). Similarly, in the C-terminal domain of dynamin, the peptide GPPQVPSRPNR (amino acids 827–838) was reported to bind Grb2 SH3 domains (34, 36). The present results show that dynamin interacts with Grb2 through a dual recognition process also involving the 36–45 region of the N-SH3 domain.

Comparison of Grb2 Interactions with Dynamin and Sos—
The lysates of Chinese hamster lung fibroblasts overexpressing the human epidermal growth factor (EGF) receptor (ER 22 cells) were used for this purpose. To avoid SH2 interactions, lysates of cells in the G₀ phase were incubated with GST-Grb2 alone; lane 2 to incubation of lysate with GST alone; and lanes 3–5 to incubations of lysate with 500 μM peptides GAP-(317–326), Grb2-(36–45), and Grb2-(36–45) E40T, respectively. Detection of GST-Grb2 protein interactions by Western blot using an anti-dynamin antibody was performed. These results confirmed the identification of p97 as dynamin and show that only peptide-(36–45) from Grb2 is a competitor of the Grb2-dynamin interaction.

Peptide components involved in Grb2-Sos and Grb2-dynamin interactions. A, an ER 22 cell lysate was incubated with GST-Grb2 loaded onto glutathione-agarose beads in the absence (lane 1) or in the presence of potential inhibitor peptides at 500 μM (lane 2, GPPQVPSRPNR from dynamin; lane 3, GPPPVPPRRR from Sos; lane 4, Grb2-(36–45)). Bound proteins were resolved by 7.5% SDS-PAGE, and replicated PVDF membranes were subjected to far Western blot analysis with GST-Grb2 probe. Detection was achieved by successive incubations with the anti-GST monoclonal antibody and peroxidase-conjugated anti-mouse antibody. Peptide-(36–45) from Grb2 inhibits selectively the interaction of Grb2 with a 97-kDa protein. B, controls. Lane 1 corresponds to incubation of cell lysate with GST-Grb2 alone; lane 2 to incubation of lysate with GST alone; and lanes 3–5 to incubations of lysate with 500 μM peptides GAP-(317–326), Grb2-(36–45), and Grb2-(36–45) E40T, respectively. Detection of GST-Grb2 protein interactions by Western blot using an anti-dynamin antibody was performed. These results confirmed the identification of p97 as dynamin and show that only peptide-(36–45) from Grb2 is a competitor of the Grb2-dynamin interaction.
were immunoprecipitated using an anti-Grb2 antibody, in the presence of increasing concentrations of either the 36–45 peptide from Grb2 N-SH3 or proline-rich peptide from dynamin (PRP), in the presence of Grb2 N-SH3-Sepharose beads. Bound dynamin was then subjected to SDS-PAGE and transferred onto a PVDF membrane for an anti-dynamin Western blot (W.B.). Both 36–45 from Grb2 and proline-rich peptide from dynamin are able to inhibit Grb2 N-SH3-dynamin interaction in a dose-dependent manner. B, additive effect of proline-rich peptide from dynamin and 36–45 peptide from Grb2 to inhibit Grb2 N-SH3-dynamin interaction. A similar experiment was performed by use of a subefficient peptide concentration (lane 2, (WYKAELNGKD)300 μM; lane 3, (GPPPQVPSRPN)100 μM). Compared with the control, without any peptide (lane 1) and to the effect of each peptide (lanes 2 and 3), the association of the two peptides at subefficient concentrations (lane 4) produced a clear synergistic displacement of Grb2 N-SH3-dynamin complex.

pared with that of GPPPQVPSRPN (Kd ~300 μM), measured by fluorescence (data not shown).

These results are also in favor of an additional role for the region of Grb2 N-SH3 encompassing the sequence 36–45 in the specific recognition with dynamin. This was confirmed by the dose-dependent selective blockade of the formation of the Grb2-dynamin complex by the 36–45 peptide (Fig. 2B). To confirm the dual recognition mode of Grb2 N-SH3 with dynamin, similar experiments were performed using purified dynamin. The synthetic N-SH3 domain was loaded onto CNBr-Sepharose beads, which were further incubated in PBS buffer with purified dynamin, in the presence of increasing concentrations of inhibitory peptides. As shown in Fig. 3A, both the proline-rich peptide from dynamin and the 36–45 peptide from Grb2 were able to inhibit, in a dose-dependent manner, the Grb2 N-SH3-dynamin interaction. The occurrence of two different binding components on Grb2 N-SH3 for dynamin recognition was confirmed by competition experiments with 300 μM Grb2 36–45 peptide (Fig. 3B, lane 2) or 100 μM GPPPQVPSRPN from dynamin (Fig. 3B, lane 3) (two sub-effective doses, compared with the control lane 1). Moreover, as shown in Fig. 3B, lane 4, the association of the two peptides produced a clear synergistic inhibition of the complex.

**Immunoprecipitation of Grb2-Sos and Grb2-Dynamin Complexes from ER 22 Cells, Selective Inhibition**—To confirm the existence of a dual recognition process between Grb2 N-SH3 and dynamin at the cellular level, competition experiments were performed on ER 22 cells. Cellular lysates in G0 phase were immunoprecipitated using an anti-Grb2 antibody, in the presence or absence of inhibitory peptides at 1.5 μM. Immunoprecipitated proteins were revealed by Western blotting, using anti-Sos or anti-dynamin antibodies (Fig. 4). In the absence of competitor peptides, Grb2 clearly co-immunoprecipitated with both Sos and dynamin (lane 1). In the presence of the 36–45 peptide (lane 3), only Grb2-dynamin immunoprecipitation was partially inhibited (50% as compared with controls). As shown in lane 2, the 36–45 peptide containing the E40T mutation was unable to modify Grb2-dynamin interactions. This is in accordance with results showing that the E40T mutated N-terminal SH3 domain of Grb2 does not recognize dynamin with a high affinity. Moreover, the proline-rich peptide derived from dynamin GPPPQVPSRPN inhibited the Grb2-dynamin complexation but only very slightly the Grb2-Sos interaction (lane 4), whereas VPPPVPPRRR from Sos totally inhibited both Grb2-Sos and Grb2-dynamin interactions (lane 5).

The demonstration that the proline-rich peptide from Sos blocks the formation of the Grb2-dynamin complex, whereas the proline-rich peptide from dynamin is unable to inhibit the Grb2-Sos recognition process at the cellular level (Figs. 2 and 4), raises the question of the biological relevance of these results. Indeed, dynamin seems to play a crucial role in endocytosis and is involved in membrane-bound receptor internalization, through formation of clathrin-coated pits (37), thus constituting a possible Ras signaling regulatory pathway.

**Kinetics of Grb2-Sos and Grb2-Dynamin Complexes Induced by EGF Stimulation in ER 22 Cells**—In the ER 22 cells used in this study, preformed complexes between Grb2 and dynamin were easily demonstrated by co-immunoprecipitation with Grb2 antibodies (Figs. 4 and 5). Such preformed complexes have already been observed in unstimulated Chinese hamster ovary cells expressing the insulin receptor (38) but not in unstimulated Madin-Darby canine kidney cells expressing the EGF receptor (39). These complexes were reported to constitute potential storage forms of Grb2 (1). Grb2 immunoprecipitation experiments on ER 22 cells at different EGF stimulation times were therefore performed (Fig. 5). Interestingly, after 1 min of EGF stimulation, a large increase in the levels of the Grb2-Sos complex was observed, with a concomitant decrease of the Grb2-dynamin complex of approximately 40% (Fig. 5, A and B). A slow restoration of the initial complexes appeared to occur after 30 min of EGF stimulation. These results suggest a displacement of the Grb2-dynamin complex by Sos in vivo and concomitantly a release of free dynamin.

**DISCUSSION**

The aim of this study was to investigate the occurrence of protein target(s) able to recognize the 36–45 peptide from the Grb2 N-SH3 domain, which is located at the surface of the protein (15, 27) as are the corresponding motifs in other SH3 domains such as GAP (20) or Src (40).

We clearly show here, in addition to the hydrophobic proline-rich recognition platform, that the 36–45 sequence of Grb2 N-SH3 (WYKAELNGKD) plays a critical role in the interaction with dynamin. Indeed the 36–45 peptide alone was able to inhibit dose-dependently the formation of complexes between Grb2 and dynamin.
Differences in Grb2 N-SH3 Recognition by Sos and Dynamin

PRRR peptide from Sos, which has an affinity of around 4 proteins for SH3 domains. This is the case for the VPPPVP- shown to have lower affinities than the corresponding entire second binding component involved in their recognition with the Grb2
z
ential role played by the N-terminal SH3 domain of Grb2 in values of 20 nM), the P49L mutant, characterized by a disrup-
tion of the peptide sequence also seems to be important, since the more, illustrating the specificity of the interaction, the nature dynamin and Grb2 or its N-terminal SH3 domain. Further-
resonance have shown that while Grb2 or its mutant P206L in
terconnection between both activation and deactivation of Ras actions. Nonetheless, these results provide evidence of an in-
terconnection between both activation and deactivation of Ras pathways. Otherwise, several results suggest that dynamin might interact with the SH3 domain of amphiphysin, in connection with its role in endocytosis (28). Thus, it would be interesting to analyze whether in ER 22 cells an amphiphysin-like protein might be able to trap dynamin near the membrane and promote the receptor endocytosis (44) or whether the Grb2-dynamin complex is directly involved in endocytosis as proposed by Wang and Moran (39).

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