Interaction of Cytosolic Adaptor Proteins with Neuronal Apolipoprotein E Receptors and the Amyloid Precursor Protein*

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Apolipoprotein E, α₂-macroglobulin, and amyloid precursor protein (APP) are involved in the development of Alzheimer's disease. All three proteins are ligands for the low density lipoprotein (LDL) receptor-related protein (LRP), an abundant neuronal surface receptor that has also been genetically linked to Alzheimer's disease. The cytoplasmic tails of LRP and other members of the LDL receptor gene family contain NPxY motifs that are required for receptor endocytosis. To investigate whether these receptors may have functions that go beyond ligand internalization, e.g. possible roles in cellular signaling, we searched for proteins that might interact with the cytoplasmic tails of the receptors. A family of adaptor proteins containing protein interaction domains that can interact with NPxY motifs has previously been described. Using yeast 2-hybrid and protein coprecipitation approaches in vitro, we show that the neuronal adaptor proteins FE65 and mammalian Disabled bind to the cytoplasmic tails of LRP, LDL receptor, and APP, where they can potentially serve as molecular scaffolds for the assembly of cytosolic multiprotein complexes. FE65 contains two distinct protein interaction domains that interact with LRP and APP, respectively, raising the possibility that LRP can modulate the intracellular trafficking of APP. Tyrosine-phosphorylated mammalian Disabled can recruit nonreceptor tyrosine kinases, such as src and abl, to the cytoplasmic tails of the receptors to which it binds, suggesting a molecular pathway by which receptor/ligand interaction on the cell surface could generate an intracellular signal.

Increasing evidence points toward a role for the multifunctional endocytic receptor LRP† and possibly also for other members of the LDL receptor gene family in the development of Alzheimer's disease. All members of this expanding family of endocytic receptors bind apoE, a lipid transport protein (1), and LRP also binds and internalizes numerous other ligands including APP (2) and α₂-macroglobulin (3, 4). The apoE4 isofrom has been found to be genetically associated with late-onset Alzheimer's disease (5), and several mutations in the APP gene have been shown to cause a familial early-onset form of the disease (6). Recently, LRP (7) and α₂-macroglobulin (8) have also been found to be linked to the development of Alzheimer's disease by genetic association. However, the biochemical mechanisms by which LRP and its ligands could affect the onset of the disease are unknown and are difficult to explain on the basis of ligand internalization functions alone.

To investigate the potential biological functions of the receptors other than endocytosis, in particular, possible mechanisms by which ligand binding to LRP or other members of the gene family might transduce a cellular signal, we scanned the amino acid sequence of their cytoplasmic tails for sequence motifs commonly found in other signaling pathways. A conserved sequence motif that is present in two copies in the LRP tail and is also found in the cytoplasmic tails of the other LDL receptor gene family members is the NPxY motif. It was first recognized in LRP (9) and subsequently recognized in numerous other cell surface receptors (10). The single NPxY motif in the LDL receptor is required for endocytosis, presumably through interaction with coated pit adaptor proteins. In other receptors, e.g. the epidermal growth factor receptor, a tyrosine-phosphorylated NPxY motif binds the adaptor protein Shc, which participates in the transmission of the epidermal growth factor signal to the ras signaling pathway (11). The Shc-epidermal growth factor receptor interaction is mediated by a protein interaction domain (PID) (12, 13) that has recently also been found in a number of other cytoplasmic proteins (14–17). Although tyrosine phosphorylation of the NPxY motif is required for Shc binding, this is not required for other PID proteins, which interact with different NPxY-containing proteins. Binding specificity is determined by the amino acids flanking the NPxY sequence (18, 19).

In this study we have identified two specific PID-containing adaptor proteins, mDb and FE65, that are primarily expressed in neurons and interact with sequences containing NPxY motifs in the cytoplasmic tails of the LDL receptor and LRP. This previously unrecognized interaction of LDL receptor gene family members with components of the cytosolic signal transduction machinery suggests a potential general biochemical mechanism by which ligands for these receptors could modulate the cellular processes leading to neurodegeneration.

**EXPERIMENTAL PROCEDURES**

Materials—Glutathione-agarose was purchased from Sigma. Antibodies against LRP (9), LDL receptor (20), and asialoglycoprotein receptor (21) have been described previously. Antibodies against SR-BI were a gift from Helen Hobbs (University of Texas Southwestern). Monoclonal antibodies against the myc-epitope and APP were purchased from Invitrogen (Carlsbad, CA) and Boehringer Mannheim, respectively.
The Two-Hybrid Assay—pBTM116 was used as a bait vector (22). Of the bait sequences were amplified by PCR and sequenced after cloning. The following baits were tested: LDLR (nt 2430–2583), the APP tail (nt 1946–2085), LRP 1–5 (nt 13808–14102), LRP 3–4 (nt 13900–14035), and LRP 1–2 (nt 13808–13922), pGAD424 (CLONTECH, Palo Alto, CA) was used as prey vector. Murine Disabled (nt 1–1667), protein interaction domains of murine Disabled (nt 1–542), FE65C (nt 1602–1984), and p96 (nt 127–531) were amplified by PCR and verified by sequencing. All bait vectors were tested for self-activation. Bait and prey vectors were cotransfected into yeast L40 strain following standard procedures. Cells were spread on selective plates (His−:Leu−:Trp−) and grown for 3 days. Single clones were grown in selective liquid media for 2 days and harvested by centrifugation. Cells were resuspended in 500 μl of breaking buffer (100 mM Tris-HCl, pH 8, 1 mM dithiothreitol, and 20% glycerol). Glass beads were added, and the cells were vortexed vigorously. Cells were incubated with 50 μl of reaction buffer (CLONTECH) for 1 h at 22 °C. Light emission was measured in a luminometer. All values were corrected for protein concentration.

The Generation of GST-Fusion Proteins and the Construction of mDab Expression Plasmid—GST-fusion plasmids of the PID domains of p96, X11, FE65, and Numb have been described previously (19). The mDab and FE65 P1 domains and the LDL receptor and LRP tail sequences were amplified by PCR, cloned into pGEX-2T vector (Phar- macia), and verified by sequencing. GST-fusion proteins were expressed in BL21 bacteria (Stratagene). mDab was isolated by PCR from a murine brain cDNA library using published sequence information (23). A myc epitope was fused in-frame to the carboxyl-terminal end by inserting the cDNA into the pCDNA3.1 expression vector (Stratagene).

Coprecipitation Experiments—Liver, brain, and cellular membrane extracts were prepared as described previously (24). 293 cells were transfected using the MBS kit from Stratagene. Cells were harvested and lysed in Buffer A (20 mM Tris-HCl, pH 7.5, 2 mM CaCl₂, 2 mM MgCl₂, 150 mM NaCl, and 1% Triton X-100) in the presence of a protease inhibitor mixture (Boehringer Mannheim) by forcing them through a 22-gauge needle 10 times. Lysates were incubated with 50 μl of glutathione-agarose and 10 μg of the respective purified GST-fusion protein for 6 h at 4 °C. Glutathione beads were washed rapidly three times in 150 mM NaCl and 10 mM Tris-HCl, pH 7.5, for 5 min. SDS sample buffer was added to the supernatant and beads. Proteins were separated by electrophoresis on 4–15% SDS-polyacrylamide gel electrophoresis under nonreducing conditions and analyzed by immunoblotting using specific antibodies and ECL detection.

RESULTS

We used two independent approaches, the yeast two-hybrid system and coprecipitation in vitro, to determine whether any of the previously published PID-containing proteins bind specifically to the NPxY motifs in the cytoplasmic tails of LRP and the LDL receptor. To test interactions with the yeast two-hybrid system, the complete tails of LRP and LDL receptor as well as parts of the LRP tail containing only one of the two NPxY motifs were used as bait. Conversely, mouse or human PIDs were cloned by PCR and used as prey. To test PID-tail interactions by coprecipitation in vitro, PID and cytoplasmic tail sequences were expressed either as GST-fusion proteins in Escherichia coli or in transfected cells. Preliminary experiments did not reveal a detectable interaction of She, Numb, or X11 with the LRP or LDL tails. However, in a two-hybrid assay, both the full-length mDab555 (25) and the mDab PID strongly interacted with the LDLR tail (Table I). We were unable to determine the binding of the mDab PID to the LRP tail using this method because the complete LRP-bait (LRP) was strongly self-activating under all conditions. A truncated bait construct containing only the amino-terminal PID domains of P96, mDab, and Fe65 was used to recognize the three of the protein constructs, and a construct containing only the carboxyl-terminal NPxY motif (LRP-2) was also self-activating. To control for specificity, we included the APP tail and the carboxyl-terminal FE65 (FE65C) protein interaction domain for which a specific and strong interaction had been previously reported (19, 25, 26). Neither the APP nor the LRP1 or LDLR baits bound to the PID from p96, a protein of unknown function that is most closely related to mDab (14), but a combination of the APP tail and both mDab preys showed weak activation (Table I).

To verify that the interaction between the LDLR and mDab had a biochemically meaningful activity, we performed a coprecipitation experiment. 293 cells were either mock-transfected (Fig. 1A, lanes 1, 2, 5, and 6) or transfected with LDLR expression plasmid (pLDLR17; Ref. 10; lanes 3, 4, 7, and 8) and incubated with GST-mDab PID fusion protein or with GST for 6 h at 4 °C. Bound proteins were coprecipitated by the addition of glutathione-agarose. LDLR in the supernatant (lanes 1–4) and bound to beads (lanes 5–8) was detected by immunoblotting. B, membrane extracts of rat liver and brain were incubated with GST-mDab PID fusion protein or GST. The LRP 55-kDa LRP fragment was coprecipitated and detected by immunoblotting as described in A. The size difference of LRP in the liver and the LRP in brain is due to differential glycosylation.

![Fig. 1. GST-mDab PID binds LDLR and LRP.](http://www.jbc.org/)
cells were either mock-transfected (Fig. 2A and B, lanes 1, 2, 5, and 6) or transfected (lanes 3, 4, 7, and 8) with an expression construct encoding the full-length mDab (mDab555). Lysates were then incubated with either a GST-fusion protein containing the LDLR tail (Fig. 2A) or the LRP tail (Fig. 2B), and coprecipitated mDab was detected by immunoblotting. The results from this experiment were consistent with those shown in Fig. 2. mDab bound strongly to the recombinant LDLR (Fig. 2A, lane 7) and LRP (Fig. 2B, lane 7) tails, but not to GST (Fig. 2, A and B, lanes 8). We also sought to determine to which of the two NPxY motifs in the LRP tail mDab binds. Cell lysates were incubated with GST-fusion proteins containing either the complete LRP tail (GST-LRP) and the amino-terminal (GST-LRP-1) or carboxyl-terminal (GST-LRP-2) motif. As shown in Fig. 2C, mDab bound specifically to the complete tail (lane 2) and to sequences containing the second NPxY motif (lane 3), but not to those containing the first motif (lane 4) or to GST alone (lane 5).

To demonstrate that the mDab protein interaction domain did not nondiscriminately bind to the cytoplasmic tail of any membrane protein, we performed a control experiment in which we incubated the GST-mDab PID fusion protein with rat liver membrane extracts. After adsorption to glutathione-agarose, proteins bound to the beads were separated on SDS gels and analyzed by immunoblotting with antibodies directed against the SR-BI (Fig. 3A) or the asialoglycoprotein receptor (Fig. 3B, ASGPR). Neither SR-BI nor asialoglycoprotein receptor bound to GST-mDab PID (A and B, lanes 3) or GST (A and B, lanes 4). In addition, GST-fusion proteins containing cytoplasmic sequences from various synaptic vesicle proteins that do not contain NPxY motifs did not interact with transfected mDab (data not shown).

It had previously been reported that the carboxyl-terminal protein interaction domain of FE65 (FE65C) interacts with the APP tail, whereas the amino-terminal domain (FE65N) does not (19). This finding raised the possibility that FE65 might link APP to another membrane protein through a heterotypic interaction. Because the Kunitz domain that is present in some cell surface, we sought to determine whether both proteins might also be linked through their cytoplasmic tails. Membrane lysates from LRP-expressing wild-type murine embry-
onic fibroblasts (MEF-1), LRP-deficient fibroblasts (MEF-4; Ref. 27), and 293 cells transfected with an expression construct encoding the human APP695 isoform (Fig. 4, lane 1) were incubated with GST-fusion proteins containing the mDab PID, FE65N, or FE65C. The mDab protein interaction domain bound strongly to LRP and also to APP (Fig. 4, lane 3). In contrast, FE65N (lane 4) interacted exclusively with LRP, not APP, whereas FE65C (lane 5) recognized APP, but not LRP.

**DISCUSSION**

The present results have shown that the cytosolic adaptor protein mDab binds to the cytoplasmic tails of the multifunctional receptor LRP, the LDL receptor, and APP, presumably by interacting with the NPxY motifs present in the tails. Another adaptor protein, FE65, contains two protein interaction domains that interact with the LRP and APP tails, respectively. Thus, FE65 is capable in principle of linking APP and LRP, raising the possibility that LRP can modulate the intracellular trafficking of APP. mDab specifically interacts with LRP tail sequences containing the carboxyl-terminal NPxY motif and also with the LDL receptor tail. Six of seven amino acids are identical between these two motifs, whereas the amino-terminal motif in LRP shares a lower degree of homology (Fig. 5). Other apoE-binding members of the gene family, namely the very low density lipoprotein receptor (28) and the neuronal apoE receptor 2 or LR8B (29, 30), share the same highly conserved NPxY motif with the LDL receptor and LRP, making it likely that they also interact with mDab.

In contrast to FE65, mDab contains only a single protein interaction domain; however, when mDab becomes tyrosine-phosphorylated, it is able to bind to LRP and APP, suggesting that mDab can function as a bivalent linker that connects LRP and APP. The WW domain in FE65 binds Mena, the mammalian homologue of enabled (34), suggesting the possibility that a multiprotein complex with important functions in neuronal development assembles on the LRP tail. The downstream targets of tyrosine kinases or other enzymes that may be part of this complex are currently unknown. Isoforms of APP that contain the Kunitz-type protease inhibitor domain can directly interact with the extracellular domain of LRP (2). However, our results show that at least in principle, regardless of the presence of a Kunitz domain, LRP and APP can also be connected through the bivalent binding of FE65 to their cytoplasmic tails, suggesting that LRP and FE65 can modulate the intracellular trafficking of APP.

**FIG. 5.** Alignment of the NPxY motifs found in the cytoplasmic tails of the LDL receptor gene family. NPxY motifs are conserved to different degrees among the members of the LDL receptor gene family. GST-fusion constructs containing the LDLR and LRP-2 motif bind mDab tightly, whereas a construct containing the first NPxY motif (LRP-1) did not interact with mDab (see Fig. 2C). The very low density lipoprotein receptor and LR8B motifs are most similar to the LDLR motif, raising the possibility that they also interact with mDab. Sequences shown are human, with the exception of megalin sequences (MEG1, MEG2, and MEG3), which are from rat.

**FIG. 6.** Hypothetical model for the assembly of multiprotein complexes on the cytoplasmic tails of the LDL receptor gene family members. As shown in Figs. 1, 2, and 4, mDab can directly bind to the cytoplasmic tails of the LDL receptor (A) and those of LRP and APP (B). The interaction of nonreceptor tyrosine kinases of the abl and src families has been described previously (23). We have shown specific interaction of the multivalent adaptor protein FE65 with the LRP tail through its amino-terminal protein interaction domain (Fig. 4), whereas the carboxyl-terminal protein interaction domain selectively interacts with the NPxY motif in the APP tail (Fig. 4; Ref. 25). The interaction of mDab and FE65 with APP presumably would be mutually exclusive. The WW domain in FE65 binds Mena, the mammalian homologue of enabled (34), suggesting the possibility that a multiprotein complex with important functions in neuronal development assembles on the LRP tail. The downstream targets of tyrosine kinases or other enzymes that may be part of this complex are currently unknown. Isoforms of APP that contain the Kunitz-type protease inhibitor domain can directly interact with the extracellular domain of LRP (2). However, these APP isoforms are expressed only at low levels in neurons in which LRP and FE65 are predominantly expressed. Our results show that at least in principle, regardless of the presence of a Kunitz domain, LRP and APP can also be connected through the bivalent binding of FE65 to their cytoplasmic tails, suggesting that LRP and FE65 can modulate the intracellular trafficking of APP. KD, Kunitz domain; KIN, nonreceptor tyrosine kinase; Y*, phosphotyrosine.
phosphorylated, it can bind several nonreceptor tyrosine kinases, including src, fyn, and abl, through an interaction with their SH2 domains (23). FE65 and mDab are almost exclusively expressed in neurons (23, 31). mDab is required for the organelles. Adaptor proteins might induce receptor dimerization and through which the binding of mDab and FE65 to cytoplasmic tails may modulate receptor endocytosis. However, the molecular mechanism by which apoE affects the onset of this neurodegenerative disease is unclear. The interaction of mDab with the LRP and the LDL receptor tails now reveals a possible pathway through which the binding of multivalent apoE-containing lipoprotein particles might induce receptor dimerization and thus alter the phosphorylation state of cellular signaling molecules. ApoE3 is the most abundant isoform in the general population. A deficiency in apoE protects APP transgenic mice from forming amyloid plaques (37), and the apoE2 isoform, which binds poorly to the LDL receptor or to LRP, is protective against neurite outgrowth and branching (40). This difference in physicochemical properties of the apoE molecules. ApoE3 is the most abundant isoform in the general population (23). The interaction of Adaptor Proteins with the LDLR Gene Family

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