The Intracellular Domain of the Low Density Lipoprotein Receptor-related Protein Modulates Transactivation Mediated by Amyloid Precursor Protein and Fe65*

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Low density lipoprotein-related protein (LRP) is a transmembrane receptor, localized mainly in hepatocytes, fibroblasts, and neurons. It is implicated in diverse biological processes both as an endocytic receptor and as a signaling molecule. Recent reports show that LRP undergoes sequential proteolytic cleavage in the ectodomain and transmembrane domain. The latter cleavage, mediated by the Alzheimer-related γ-secretase activity that also cleaves amyloid precursor protein (APP) and Notch, results in the release of the LRP cytoplasmic domain (LRPICD) fragment. This relatively small cytoplasmic fragment has several motifs by which LRP interacts with various intracellular adaptor and scaffold proteins. However, the function of this fragment is largely unknown. Here we show that the LRPICD is translocated to the nucleus, where it colocalizes in the nucleus with a transcription modulator, Tip60, which is known to interact with Fe65 and with the APP-derived intracellular domain. LRPICD dramatically inhibits APP-derived intracellular domain/Fe65 transactivation mediated by Tip60. LRPICD has a close interaction with Tip60 in the nucleus, as shown by a fluorescence resonance energy transfer assay. These observations suggest that LRPICD has a novel signaling function, negatively impacting transcriptional activity of the APP, Fe65, and Tip60 complex in the nucleus, and shed new light on the function of LRP in transcriptional modulation.

LRP, a member of the low density lipoprotein (LDL) receptor family, is a type I integral membrane protein that has a very large extracellular domain and a relatively small cytoplasmic tail. Cleavage by furin (1, 2) produces the mature cell membrane to liberate cytosolic fragments that enter the nucleus to control gene transcription. This mechanism, called regulated intramembranous proteolysis (Rip), adds molecular diversity in the field of signaling (for a review, see Ref. 18). APP recently has been shown to play a role in gene transcription, because the APP intracellular domain (AICD) (19), in collaboration with the adaptor protein Fe65, can transactivate a Gal4 reporter gene by interacting with the histone acetyltransferase, Tip60 (20).

Our current data show that LRPICD also may interact with Tip60, but in contrast to APP, LRPICD is a negative regulator of transactivation in this system.

EXPERIMENTAL PROCEDURES

Generation of Expression Constructs—A summary of constructs APP and LRP, which were used for this study, is shown in Fig. 1. The generation of the full-length LRP-GFP was described previously (10). The LC-Myc construct, which encodes only the light chain of LRP, tagged with Myc at its C terminus has been used and described previously (21). LRP165-Myc was generated from the LC-Myc plasmid. LC-Myc was digested with PstI, and the band containing the vector and the carboxyl terminus of LRP (coding 165 amino acids) was extracted and self-ligated to make the LRP165-Myc construct. The LRP105-Myc construct, encoding only the cytoplasmic domain of LRP, was amplified by PCR, using two sets of primers, 5′-CGCTCGAGGACCATGTTGTGTT-ATTCTGTATAAGCGG-3′ and 5′-GAAGCTTGTGGCAGAGGG-3′ and 5′-GAAGCTTGTGGCAGAGGG-3′.
LRPICD as a Transcriptional Modulator

![LRPICD as a Transcriptional Modulator](image)

**LRPICD as a Transcriptional Modulator** (41183)

**Fig. 1. Reagents used in this study.** Shown are the constructs and antibodies used in this study. LRP105 constructs contain only the cytoplasmic portion of LRP, whereas the LRP165 construct starts from the extracellular domain, containing the entire membrane-spanning and cytoplasmic region. All LRP-truncated constructs are tagged with EGFP or Myc at their C terminus (except for LRP-Gal4). In NPYX mutants, both NPYX motifs are mutated to APX. In the signalLRP105 construct, a signal peptide was added to the N terminus of LRP105.

**Mutants**, both NP

promotor vector, containing SV40 promotor upstream of the luciferase construct, a signal peptide was added to the N terminus of LRP105. Briefly, Tip60 was cut out from the pOZ-Tip60 plasmid (22) with restriction enzymes XhoI and NotI. The expression vector pEGFP-N1 (Clontech) was digested with XhoI and NotI, cutting out the GFP. The wild type Tip60 was digested and ligated into a mammalian expression vector backbone derived from the EGFP-N1 plasmid (Clontech), from which the EGFP coding sequence had been deleted.

**Antibodies and Reagents**—Mouse monoclonal antibody 11H4 against Lrp-C-terminal fragment was obtained from American Type Culture Collection (Manassas, VA). Mouse monoclonal anti-Myc antibody was purchased from Invitrogen. The antibody against amino acids 494–513 of Tip60 was purchased from Upstate Biotechnology, Inc. (Lake Placid, NY).

**Cell Culture Conditions and Transient Transfection**—H4 cells derived from human neuroglioma cells and HEK293 cells derived from human embryonic kidney cells are used in this study. Both H4 cells and HEK293 cells were cultured in OPTI-MEM 1 with 10% fetal bovine serum. Transient transfection of the cells was performed using a liposome-mediated method (FuGene 6; Roche Applied Science). For immunocytochemistry, cells were split into 4-well chambers 1 day before the transfection. For the transfection assay, HEK293 cells were split into 12-well plates 1 day before transient transfection. To see the effect of LR PICD on the transactivation induced by APP and Fe65, various LR PICD constructs were co-transfected with pMst-APP and Fe65, together with pG5E1B-Luc. pcDNA3.1 (Invitrogen) was added to make up the equal amount of DNA transfected. PGL3-SV40 was used as a positive control for firefly luciferase, and pGL2-Basic was used as a standard.

In order to assay the role of LR PICD in transactivation, LR PICD-Gal4 was co-transfected with pG5E1B-Luc with or without other plasmids encoding LRP-interacting proteins (Fe65, mDab1, Numb, and AICD).

All cells were co-transfected with pCMV-β-Gal, a constitutive β-galactosidase expression vector, to standardize for transfection efficiency. Immunocytochemistry—Immunostaining was done on the cells 24–48 h post-transfection. Cells were fixed in 4% paraformaldehyde for 10 min, washed in Tris-buffered saline (pH 7.3), and permeabilized by 0.5% Triton X-100 for 20 min and blocked with 1.5% normal goat serum for 1 h. To detect the localization of LR PICD, cells transfected with LR PICD-Myc or LR PICD-Gal4 were immunostained by mouse anti-Myc monoclonal antibody (1:1000, Invitrogen) or 1:144, respectively, for 1 h at room temperature. Cells were then washed twice in Tris-buffered saline and labeled by Cy3-conjugated anti-mouse antibody (10 μg/ml; Jackson ImmunoResearch, West Grove, PA) for 1 h at room temperature. Immunostained cells were stored in Tris-buffered saline at 4°C until imaging.

To detect the interaction of LR PICD and Tip60 in the nucleus, cells co-transfected with constructs of LR PICD-Gal4 and Tip60 were used. Co-transfected cells were fixed and permeabilized and blocked in normal goat serum and then incubated with primary antibody against Tip60, followed by anti-rabbit secondary antibodies conjugated with Cy3 (10 μg/ml; Jackson ImmunoResearch) to visualize the localization of Tip60.

**Reporter Gene Assays**—HEK293 cells were harvested for reporter gene assays 24 h after transfection. The culture medium was removed, and the cells were washed once with cold phosphate-buffered saline. After the addition of 100 μl of reporter lysis buffer (Promega) per well of the 12-well plate, cells were collected and pelleted, and the supernatant was saved. Luciferase gene expression was analyzed using the luciferase reporter assay system (Promega) in a 96-well plate. The luminescence was measured by a Wallac plate reader. β-Galactosidase assays for internal control of transcription efficiency were carried out with an aliquot of the cell lysates prepared for the luciferase assay using the β-galactosidase enzyme assay system (Promega). Luciferase activity was obtained by dividing the relative luminescence units values by those from the β-galactosidase reaction, and the values were standardized by dividing by that of pGL2-Basic-transfected cells. All transfections were done in triplicate and repeated in at least three independent experiments. Values shown are averages of transfection assays carried out in triplicate.
**RESULTS**

**Localization of LRP Cytoplasmic Domain in Various Deletion Mutants**—We asked whether the proteolytic intramembranous cleavage of LRP would affect the localization of LRPICD, as is the case for proteins that undergo Rip. H4 cells were transiently transfected with various LRP constructs, and the localization of the LRP C terminus was examined (Fig. 2). The membrane-spanning molecules, full-length LRP, LC, LRP165, and LRP105 construct with a signal peptide are localized in Golgi, endoplasmic reticulum, cell surface, and endosomes (Fig. 2). In contrast, LRP105-transfected H4 cells (tagged with either EGFP or Myc at their C termini) showed the LRP C terminus predominantly in the nucleus. LRP105-Gal4, when stained with 11H4, also showed a predominantly nuclear localization.

LRP binds to diverse cytoplasmic proteins that have been found to interact with the tail of LRP (3). The tetraamino acid motif NPYX is present in two copies in the LRP tail. One or both of the NPYX motifs might interact with other proteins in the cytoplasm, such as Fe65 (7), and mammalian Disabled-1 (mDab1) (27). The LRP105 double NPYX mutant, which has APXA substitution instead of NPYX in both copies of the LRP tail, also showed a predominantly nuclear signal, suggesting that the NPYX motifs are not necessary for LRPICD to be translocated to the nucleus and that LRPICD localization in the nucleus is independent of the interaction via NPYX with adaptor proteins, like Fe65. Thus, these results show that the intracellular domain of LRP is translocated to the nucleus.

**The Effect of LRPICD on Transcription**—As described above, the cytoplasmic domain of LRP was localized predominantly in the nucleus, suggesting that it may have some function as a transcriptional modulator, like other proteins that undergo regulated intramembranous proteolysis. We hypothesized that LRPICD might be able to modulate gene transcription. To investigate the role of LRPICD in transcription, we employed a luciferase-based reporter gene assay. We fused the cytoplasmic tail of LRP to the Gal4 DNA binding domain (Gal4) at its C terminus (LRP105-Gal4). HEK293 cells were transfected with LRP105-Gal4 along with a reporter plasmid. LRP105-Gal4 had little or no activity on the Gal4-dependent promoter (Fig. 3A), although its localization was found to be predominantly in the nucleus (confirmed by 11H4 staining). This result suggests that LRPICD alone is not sufficient to strongly activate the transcriptional response. We considered the possibility that LRPICD may require an adaptor protein to activate transcription, like AICD requiring Fe65. We transfected LRP105-Gal4 with adaptor/interacting proteins to HEK293 cells, along with a reporter plasmid. Little transactivation (4–8-fold) was observed with LRP105-Gal4 by itself or in the presence of Fe65, Numb, mDab1, or AICD compared with pGL2-Basic plasmid (Fig. 3A). Thus, the cytoplasmic tail of LRP, when overexpressed in cells as a fusion protein with a heterologous DNA binding domain, does not stimulate transcription robustly in comparison with APP-Gal4 or especially APP-Gal4 plus Fe65 (>200-fold).

We then tested whether LRPICD could have some effect on transactivation induced by APP and Fe65 (20), since LRP is known to interact with APP via its extracellular and intracellular...
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We reasoned that this inhibition could be due to inhibition of AICD generation or translocation to the nucleus, inhibition of AICD/Fe65 interaction with Tip60, or nonspecific inhibition of the luciferase reporter. In order to see whether LRPI CD non-specifically inhibited the luciferase reporter system, we co-transfected pGL2-SV40 with LRPI CD plasmid. pGL2-SV40 was used as a positive control for the firefly luciferase. Co-transfecting LRPI CD with this plasmid did not affect transactivation or the luciferase read-out.

Whether the nuclear translocation of AICD is affected by LRPI CD or not was examined by triple transfection of LRPI 05, APP, and Fe65 into H4 cells. Cells were immunostained by rabbit anti-Fe65 antibody (labeled by Cy5) and mouse 11H4 antibody (labeled by Cy3). APP770-GFP signal is localized in the cytoplasm in the absence of Fe65 (Fig. 4A); however, APP770-GFP signal was found in the nucleus as previously reported in the presence of Fe65 (28), regardless of LRPI CD co-transfection (Fig. 4B). To confirm these results, cells were transfected with pMst-APP, Fe65-Myc, and LRPI 05-GFP. Cells were immunostained by rabbit C8 antibody (labeled by Cy3) and mouse monoclonal anti-Myc antibody (labeled by Cy5). The APP C terminus was also localized in the nucleus (data not shown), confirming that the translocation of APP C terminus was not inhibited by LRPI CD.

Interaction of LRPI CD with Tip60 by FLIM Analysis—We next tested the possibility that LRPI CD may interact with Tip60, thus interfering with transactivation by APP. We first examined the localization of LRPI CD and Tip60 in co-transfected H4 cells by confocal microscopic analysis. The LRPI 05 singly transfected cells showed nuclear localization of LRPI CD, with a uniform staining pattern in the nucleus, as shown in Fig. 2. When LRPI 05 is co-transfected with Tip60, the intranuclear localization of LRPI CD changes noticeably, and it becomes localized in subnuclear compartments, showing a perfect match of localization with Tip60 (Fig. 5A).

To further test the hypothesis that LRPI CD interacts with Tip60 in the nucleus, we utilized a morphologically based new FRET technique that can reveal protein-protein interactions in intact cells, FLIM.

Fluorescence lifetime is influenced by the surrounding microenvironment and is shortened in the immediate vicinity of a FRET acceptor molecule. The degree of lifetime shortening if inherently a quantitative measure of proximity and changes in this quantity reflect alterations in proximity that can be displayed with very high spatial resolution in a pseudocolor-coded image. If the molecules are close together, the donor fluorescence lifetime will be shorter, and the color will be closer to red. Our negative control (in the absence of an acceptor molecule) showed that the lifetime of GFP alone is 2122 ± 50 ps (mean ± S.D.) (see Table I). FLIM analysis of the co-transfected H4 cells with LRPI 05-GFP (donor) and Tip60 (labeled by Cy3, acceptor) showed that the average fluorescence (GFP) lifetime decreased to 1560 ± 200 ps in the co-localized areas of the nucleus in the presence of acceptor (Table I and Fig. 5B, red-orange staining in the FLIM image), indicating that LRPI CD and Tip60 are in close proximity in some special subnuclear locations. As a negative control, FLIM analysis also revealed that there is no detectable interaction between LRPI CD and Tip60 in cytoplasmic compartments; the fluorescence lifetime of GFP in non-nuclear compartments, where it does not colocalize with Tip60, was not different from that seen in GFP alone (shown in blue-green in the FLIM image of Fig. 5B).

Taken together, the shift in nuclear localization and the FRET results both strongly suggest that LRPI CD closely interacts with Tip60.
In this study, we report a novel function of the cytoplasmic tail of LRP, the proteolytic product of LRP intramembranous cleavage (14). LRP, like the Notch family members, undergoes cleavage by furin in a late secretory compartment (1) and can be cleaved by a metalloproteinase (13). A recent report suggested that a third site cleavage in the membrane releases the cytoplasmic domain of LRP, like other members that undergo Rip. This cleavage is probably due to γ-secretase activity, because a potent γ-secretase inhibitor, DAPT, strongly inhibited this intramembranous cleavage (14). Cleavage of LRP results in the release of this domain into the cytoplasm, where it is further translocated to the nucleus and may modulate cellular signaling.

As a Rip protein, how could LRPICD modulate cellular signaling? The intracellular domain of LRP contains various binding sites for adaptor and scaffold proteins that may recruit other biologically active proteins. As we demonstrate, LRPICD is translocated to the nucleus, suggesting that LRPICD might recruit transcriptional activators that could potentially stimulate the expression of target genes. Thus, it is likely that release of LRPICD from the membrane could translocate this complex to the nucleus, where it may modulate signaling. How-
ever, we could not find a function as a potent transcriptional activator when LRPICD was used by itself. This is consistent with the report by May et al. (14). In their study, they found that transcription was moderately enhanced by LRPICD only in serum-deprived cells and not in cells growing in serum-containing media. The significance of this condition is not yet well understood.

LRP and APP both bind the scaffold protein Fe65, a transcriptional activator, via their cytoplasmic tails. Cao and Sudhof (20) recently reported that APP mediates the transcription activation in the presence of Fe65, using a luciferase reporter gene assay, and that this activation was dependent on the release of the AICD.

Therefore, we investigated whether LRPICD may have some effect on the transactivation mediated by AICD and Fe65. As shown in Fig. 3, LRPICD had a potent inhibitory effect on the transcriptional activation mediated by APP and Fe65, which was dependent on its nuclear translocation.

What mechanism underlies this phenomenon? In the report by Cao and Sudhof (20), Fe65 played a critical role in transactivation by AICD. In order to activate transcription, AICD presumably interacts with DNA-binding proteins, histone acetyltransferases, and general transcription factors. By yeast two-hybrid screening, they found that Fe65 strongly interacts with Tip60, a histone acetyltransferase, and that the interaction of AICD-Fe65 complex with Tip60 is required for the transactivation. We demonstrate that LRPICD does not affect the first few steps of this process; in the presence of LRPICD, APP-Gal4 is cleaved, interacts with Fe65, and is translocated to the nucleus.

Therefore, we hypothesized that LRPICD may interact with Tip60, interfering with the interaction between AICD and Tip60. We observed that co-transfection of LRPICD with Tip60 leads to a change in the localization of LRPICD, so that it co-localized with Tip60 in specific subnuclear compartments. To test the hypothesis that LRPICD and Tip60 interacted, we utilized a novel technique to detect protein-protein interactions in intact cells. Our FRET result demonstrated close proximity between LRPICD and Tip60 in the nucleus of cells, suggesting that the potent inhibitory effect of LRPICD on AICD-mediated transactivation may be due to interference of LRPICD with the interaction with APP-Fe65-Tip60 complex.

LRP is remarkably tightly linked to APP metabolism. Cleavage of APP by β-secretase leads to a truncated membrane-bound 99-amino acid transmembrane carboxyl terminus fragment, which is subsequently cleaved by a presenilin-dependent γ-secretase activity to release amyloid-β (which accumulates as senile plaques in Alzheimer’s disease) and AICD. These events appear to occur, at least to a great extent, in early endosomal compartments (29), and APP endocytosis is modulated by LRP (6, 8, 29, 30). Moreover, LRP also mediates endocytosis and clearance of amyloid-β when bound to apolipoprotein E or α2-macroglobulin, giving LRP a role in both generating amyloid-β (via endocytosis of APP (6, 31) and clearance of amyloid-β (via endocytosis of amyloid-β complexes (32–34)). Extensive direct interactions between APP and LRP have also been demonstrated. In the extracellular compartment, APP isoforms containing the alternatively spliced Kunitz protease inhibitor domain interact with the ligand binding domains of LRP (8–10, 30). The intracellular cytoplasmic tails of APP and LRP also interact, forming a heterotrimmeric complex with the adapter protein Fe65 (7–10). Both APP and LRP appear to undergo regulated intramembranous cleavage by γ-secretase, and the released cytoplasmic tails both translocate to the nucleus and interact with Tip60 (20, 22). However, here APP and LRP show opposite effects, with AICD demonstrating robust transactiva-

tion of a Gal4 reporter gene and LRP showing dramatic inhibition of this same assay. The function of AICD and LRPICD for other, physiological target genes remains unknown. Thus, LRP and APP share parallel, interacting metabolic pathways that lead to complementary roles in signal transduction.

Interestingly, one recent report describes the inhibition of transcriptional activity of AICD and Fe65 through the NF-κB pathway (35). The NF-κB pathway regulates transcription by activation of proinflammatory cytokines, through protein kinase cascades. AICD- and Fe65-mediated transactivation was decreased both by co-transfection of NF-κB pathway plasmids and by the treatment of cells with cytokines (35). Our current data show that LRPICD can regulate AICD/Fe65 transactivation. Thus, several pathways may regulate transcriptional activation mediated by AICD.

LRP has been reported to have two roles in modifying transcription. One role is as an endocytic receptor that internalizes the ligand, such as HIV-Tat protein (a transactivator for viral genes) (36), which leaves the endosomes after LRP-mediated endocytosis by a process that is poorly understood and enters the nucleus, where it stimulates transcription. In the second role, LRP itself is cleaved and enters the nucleus as an active transcriptional modulator. Two other members of the LDL receptor family, very low density lipoprotein receptor and ApoER2, act as co-receptors for the signaling ligand Reelin (27). It is not yet known whether LRP ligands under physiological circumstances can induce γ-secretase cleavage of LRP or initiate signal transduction in other ways, but our current results strongly support the hypothesis that LRP should be considered as a signaling molecule in addition to its role as an endocytic receptor.

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