37-kDa Laminin Receptor Precursor Modulates Cytotoxic Necrotizing Factor 1-mediated RhoA Activation and Bacterial Uptake*

Jin Woong Chung‡, Suk Jin Hong§, Kee Jun Kim‡, Daniel Goti‡, Monique F. Stins‡, Sooan Shin‡, Valina L. Dawson§¶**, Ted M. Dawson§¶**, and Kwang Sik Kim‡ ‡‡

From the Departments of ‡Pediatrics, §Neurology, ¶Neuroscience, ¶¶Physiology, and **Institute for Cell Engineering, Johns Hopkins University, School of Medicine, Baltimore, Maryland 21287

Cytotoxic necrotizing factor 1 (CNF1) is a bacterial toxin known to activate Rho GTPases and induce host cell cytoskeleton rearrangements. The constitutive activation of Rho GTPases by CNF1 is shown to enhance bacterial uptake in epithelial cells and human brain microvascular endothelial cells. However, it is unknown how exogenous CNF1 exhibits such phenotypes in eukaryotic cells. Here, we identified 37-kDa laminin receptor precursor (LRP) as the receptor for CNF1 from screening the cDNA library of human brain microvascular endothelial cells by the yeast two-hybrid system using the N-terminal domain of CNF1 as bait. CNF1-mediated RhoA activation and bacterial uptake were inhibited by exogenous LRP or LRP antisense oligodeoxynucleotides, whereas they were increased in LRP overexpressing cells. These findings indicate that the CNF1 interaction with LRP is the initial step required for CNF1-mediated RhoA activation and bacterial uptake in eukaryotic cells.

Escherichia coli K1 is a major cause of neonatal Gram-negative bacillary meningitis. Despite advances in antimicrobial chemotherapy and supportive care, the mortality and morbidity associated with E. coli meningitis remain significant because of incomplete understanding of the pathogenesis of this disease. We have previously shown that E. coli invasion of human brain microvascular endothelial cells (HBMEC) is a prerequisite for penetration into the central nervous system in vivo, and identified several E. coli determinants contributing to invasion of HBMEC, including the proteins, AsLA, TraJ, and CNF1 (1–6). We have also demonstrated that E. coli invasion of HBMEC requires host cell actin cytoskeleton rearrangements and activations of RhoA (7, 8). CNF1, a bacterial toxin known to induce host cell cytoskeleton rearrangements, activates Rho GTPases such as RhoA, Cdc42, and Rac1 (9, 10), which regulate various cellular processes involving actin filaments. The constitutive activation of Rho GTPases by CNF1 has been shown to induce stress fiber formation, membrane ruffling, and phagocytosis in epithelial cells (11–13). We have shown that CNF1 contributes to E. coli invasion into HBMEC, in part through activation of RhoA (8).

CNF1 is a 113-kDa single chain toxin molecule that consists of a N-terminal cell surface receptor binding domain, a C-terminal catalytic domain, and a transmembrane domain in the middle (14). After translocation into the cytosol, the enzymatic domain of CNF1 activates Rho GTPases by deamidation of glutamine 63 of RhoA (9, 10), or glutamine 61 in Rac1 and Cdc42 into glutamic acid (11). The glutamine residue is essential for GTP hydrolysis, and its modification results in constitutive activation of Rho GTPases by CNF1. How exogenous CNF1 exhibits such phenotypes in epithelial cells (11–13) is unclear how CNF1 enters the eukaryotic cells and activates Rho GTPases. CNF1 has been suggested to be internalized via receptor-mediated endocytosis upon binding to a cell surface receptor (15, 16), but the identity and characteristics of the CNF1 receptor are not known.

In this study, for the purpose of identifying CNF1 receptor, the cDNA library of HBMEC was constructed and screened by the yeast two-hybrid system using the N terminus of CNF1 (nCNF1) as bait. We identified for the first time that 37-kDa laminin receptor precursor (LRP) functions as the receptor for CNF1. Exogenous LRP or LRP antisense oligodeoxynucleotides (ODN) inhibited CNF1-mediated RhoA activation and bacterial uptake, whereas overexpression of LRP increased binding and effects of CNF1.

EXPERIMENTAL PROCEDURES

Bacterial Strains, Plasmids, and Antibodies—E. coli K1 strain E44 is a spontaneous rifampin-resistant mutant derived from the cerebrospinal fluid isolate of a neonate with meningitis, strain RS218 (serotype O18:K1:H7). The isogenic cnf1 deletion mutant of strain E44 was previously reported (8). E. coli BL21 (Invitrogen, Carlsbad, CA) or XL1-Blue (Stratagene, Ceda Creek, TX) was used for expression of the recombinant proteins. E. coli DH10B (Invitrogen) was used for the construction of the cDNA library. Plasmids pGBK7 and pADT7 were purchased from Clontech (Palo Alto, CA), and used for construction of the bait CNF1 and prey cDNA libraries, respectively. Anti-LRP polyclonal antibody was purchased from Abcam (Cambridge, UK). Anti-CN1 monoclonal antibody NG8 (17) was a generous gift from Dr. Allison O’Brien (Uniformed Services University of the Health Sciences, Bethesda, MD). Plasmid pGEX-2T (Amersham Biosciences) was used for construction of GST fusion proteins.

cDNA Construction and Yeast Two-hybrid Screen—For bait construction, the N-terminal segment of cnf1 (nCNF1) was amplified by PCR from E44 chromosomal DNA using primers, 5′-aagaattcagggattgccgacggc-3′ and 5′-agctgagcctgctagctgatctgctctg-3′. The amplified fragments (amino acids 1–299) were cloned into pGBK7 vector via EcoRI and BamHI sites (underlined) to create the bait plasmid pGBK7:nCNF1. Full-length CNF1 (cCNF1, amino acids 1–1007) and the C-terminal
fragment of CNF1 (cCNF1, amino acids 720–1007) were amplified using forward primers 5′-aagattgcatcataagcagc-3′ (CNF1) and 5′-aagattgcatcataagcagc-3′ (CNF1) and reverse primer 5′-aagattgcatcataagcagc-3′ and cloned into pGBK7:CNF1 and pGBK7:CNF1, respectively, following the same strategies as described above. The cDNA library from mRNA of HBMEC was constructed with the SuperScript Choice system (Invitrogen) following the manufacturer's protocol, and ligated into prey vector, pGADT7 (Clontech). pGBK7 contains the DNA binding domain and c-myc epitope, and pGADT7 contains the activation domain and hemagglutinin epitope at the N terminus of the multicloning sites. The whole screening procedure was performed according to the MATCHMAKER protocol from Clontech using yeast strain AH109 as host.

**Identification of Recombinant Proteins and Ligand Overlay Assay.**—The N-terminal domain of CNF1 (nCNF1), C-terminal domain of CNF1 (cCNF1), and full-length CNF1 (fCNF1) were in vitro translated from pGBK7:CNF1, pGBK7:CNF1, and pGBK7:CNF1, respectively, using TNT quick coupled transcription/translation systems (Promega, Madison, WI) according to the manufacturer's protocol. pGADT7:LRP (89–295) was used for in vitro translation of LRP (89–295) following the same protocol. For ligand overlay assay, HBMEC membrane proteins or the bacterial lysates from *E. coli* BL21 containing pGADT7:LRP (89–295) were separated in a SDS-PAGE gel and transferred to a PVDF membrane. After washing, the membrane was blocked overnight with 5% skim milk in phosphate-buffered saline at 4 °C. Blotting was performed with GST-LRP (Promega, Madison, WI) containing pGADT7:LRP (89–295) and the mixture was incubated at 37 °C for 1 h. After incubation, the mixture was precipitated with anti-CNF1 monoclonal antibody NGS in the presence of protein A-Sepharose (Roche Diagnostics, Indianapolis, IN) in 0.5 ml of co-immunoprecipitation buffer (20 mm Tris-HCl, pH 7.5, 150 mm NaCl, 1 mm dithiothreitol, 5 μg/ml aprotinin, 0.5 mm phenylmethylsulfonyl fluoride, 0.1% Tween 20 (v/v)). After washing, each well of the plate was aspirated and the cells were washed five times with binding buffer. After washing, the cells were incubated with GST-phosphate-buffered saline containing 0.05% Tween 20 and different concentrations of GST-CNF1 or no ligand in binding buffer (phosphate-buffered saline containing 0.05% Tween 20 and 2% bovine serum albumin) were added to each well. After 1 h incubation at room temperature, the ligand was aspirated and the cells were washed five times with binding buffer. After washing, anti-GST polyclonal antibody (Amersham Biosciences) was added, and the cells were further incubated for 1 h at room temperature. The cells were washed again for 1 h at room temperature with anti-goat IgG conjugated with alkaline phosphatase. The bound GST-CNF1, p-nitrophenol phosphate was added to each well and the color change was quantitated at 405 nm on a microplate spectrophotometer.

**Antisense ODN Treatment.**—Based on the human LAMR1 cDNA sequence, antisense and sense phosphorothiate oligodeoxynucleotides, respectively, were designed against nucleotides 1–20. They were antisense, ACATCAAGGGCTCCGGACAT, and sense, ATGTCCGGAGCCTTGTAGT. HBMEC were transfected with antisense and sense phosphorothionate ODNs with OligofectAMINE (Invitrogen) followed by manufacturer's protocol and 48 h was allowed for HBMEC cells to uptake the ODNs.

**RESULTS**

Identification of LRP as a CNF1 Receptor by the Yeast Two-hybrid System and Coimmunoprecipitation.—In an attempt to identify the CNF1 receptor, we screened a cDNA library of HBMEC by the yeast two-hybrid system using the N terminus of CNF1 (nCNF1) as bait. We screened more than 2 × 10^9 individual clones from a HBMEC cDNA library and identified nine positive clones at the highest stringency selection conditions (Trp-, Leu-, His-, Ade-). Sequence analysis revealed that one of the nine colonies contained a putative transmembrane domain, which showed a 100% match to the partial sequence (amino acids 89–295) of LAMR1 encoding laminin receptor precursor (LRP). LRP is comprised of a cytoplasmic N-terminal domain (amino acids 1–85), and an extracellular C-terminal domain (amino acids 102–295) that are separated by a transmembrane domain (amino acids 86–101) (19). This clone was further characterized for its interaction with CNF1 by retransformation. A yeast colony co-transformed with pGADT7:LRP (89–295) and pGBK7:CNF1 was positive in both growth on the selection medium (Leu-, Trp-, His-, Ade-) and 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside (X-gal) assays (Fig. 1a). Similarly, interaction between fCNF1 and LRP (89–295) in yeast was observed (Fig. 1a). In contrast, co-transformation
with pGADT7:LRP-(89–295) and pGBK7:cCNF1 or pGBK7\(\text{t}c\)CNF1 vector alone did not restore growth ability or enzyme activity (Fig. 1a), suggesting that the LRP-(89–295) binds to full-length CNF1 and nCNF1, but not to cCNF1 in \textit{vivo}.

To validate the results obtained with the yeast two-hybrid system in \textit{vitro}, communoprecipitation was performed as described under “Experimental Procedures.” When the bacterial lysates containing CNF1 were mixed with \textit{in vitro} translated radiolabeled LRP-(89–295) (\textsuperscript{35}S)LRP-(89–295), LRP-(89–295) was detected in immunoprecipitates with anti-CNFA monoclonal antibody whereas no LRP-(89–295) was detected in the absence of CNF1 (Fig. 1b).

\textbf{Identification of LRP by Ligand Overlay Assays}—In parallel with the yeast two-hybrid screening, a \textsuperscript{35}SICNF1 ligand overlay assay was performed to identify and confirm the cell surface receptor for CNF1. Membrane proteins of HBMEC were subjected to SDS-PAGE, and the overlay assay was performed. In this experiment, a protein of 37 kDa was identified as an interacting protein with either \textsuperscript{35}SnCNF1 or \textsuperscript{35}ScCNF1, but no membrane protein was detected with \textsuperscript{35}ScCNF1 (Fig. 2a). To verify the specific interactions between CNF1 and the putative receptor, we performed the overlay assay after preincubation of the membrane with non-radiolabeled nCNF1, which totally blocked binding of radiolabeled nCNF1 to the membrane (Fig. 2a). Because LRP was identified as a CNF1 receptor with yeast two-hybrid screening, we speculated that this 37-kDa protein might be LRP. We next recovered the prey vector containing tagged hemagglutinin (pGADT7:LRP-(89–295)) from the yeast and introduced it into \textit{E. coli}. Biological lysates containing HA-tagged LRP-(89–295) were subjected to \textsuperscript{35}SnCNF1 ligand overlay assay to verify that CNF1 indeed binds to LRP-(89–295) \textit{in vitro}. \textsuperscript{35}SnCNF1 bound LRP-(89–295) when the protein was expressed (Fig. 2b, \textit{left panel, lane 2}), whereas bound \textsuperscript{35}SnCNF1 was not detected in the absence of LRP-(89–295) (Fig. 2b, \textit{left panel, lane 1}). Western blot using anti-hemagglutinin monoclonal antibody indicates that the protein detected with the \textsuperscript{35}SnCNF1 overlay assay migrates at the same molecular weight as HA-tagged LRP-(89–295) (Fig. 2b, \textit{right panel}). These results taken together indicate that the extracellular domain of LRP binds to CNF1 and thus is likely to be the receptor that mediates the CNF1 biologic activity, such as RhoA activation and enhancement of bacterial uptake.

\textbf{LRP Inhibits CNF1-induced RhoA Activation}—We and others have previously shown that CNF1 activates RhoA in HBMEC and other eukaryotic cells such as HEp-2 cells (8–10). To determine the effect of LRP on CNF1-induced RhoA activation, HBMEC or HEp-2 cells were treated with CNF1 with or without GST-LRP, and total lysates were compared for the activated GTP-bound form of RhoA as described previously (8). The amount of RhoA-GTP was quantitated from the blot using an imaging densitometer, and normalized to the values of controls where the cells were treated with only GST. CNF1, as expected, increased RhoA activation in HBMEC and HEp-2 cells by 60 and 91%, respectively (Fig. 3). However, when CNF1 was added in the presence of GST-LRP, the levels of RhoA activation decreased by 44 and 50%, respectively, in HBMEC and HEp-2 cells when compared with CNF1-treated HBMEC or HEp-2 cells in the presence of GST. GST alone did not have any inhibitory effect on CNF1-induced RhoA activation (Fig. 3). These results suggest that exogenous LRP competes with endogenous LRP for CNF1 binding, and acts as an inhibitor of RhoA activation by CNF1 in both HBMEC and HEp-2 cells.

\textbf{LRP Decreases CNF1-enhanced Bacterial Invasion}—We have previously shown that CNF1 increases \textit{E. coli} K1 invasion of HBMEC (8). We next examined whether exogenous LRP inhibited CNF1-induced enhancement of bacterial uptake. CNF1-treated cells showed an approximately 400% increase in \textit{E. coli} E44 invasion compared with non-treated cells (Fig. 4). Consistent with the results obtained from RhoA-GTP assays where GST-LRP decreased CNF1-mediated RhoA activation in...
RhoA in each lane. The values were then normalized to those of control, calculated by comparing the densities of RhoA-GTP bands with those of total RhoA. Quantification of the RhoA-GTP amount with densitometry showed 42% higher activation of RhoA by CNF1 in LRP overexpressing cells than in the control cells (Fig. 5c). These results support our finding that LRP acts as the CNF1 receptor, thus mediating CNF1-mediated bacterial uptake and RhoA activation in HBMEC.

**LRP-Antisense ODN Treatment Decreased CNF1 Effects on RhoA Activation and Bacterial Uptake**—To confirm correlation between CNF1 effects and level of LRP expression, HBMEC were treated with LRP antisense ODNs before RhoA-GTP or invasion assays. Treatment of HBMEC with LRP antisense ODNs decreased LRP expression by 62% compared with the sense ODN-treated HBMEC (Fig. 6a). CNF1 effects on RhoA activation were decreased when the expression of LRP was reduced by antisense ODN treatment, whereas sense ODN treatment did not show noticeable changes in CNF1 effects, when compared with wild type HBMEC (Fig. 6b). For example, RhoA activation by CNF1 in HBMEC was 74% decreased with LRP antisense ODNs compared with non-treated cells, whereas the effect of LRP sense ODNs was negligible (Fig. 6b). CNF1-mediated bacterial uptake was also significantly (p < 0.01) decreased in LRP antisense ODN-treated HBMEC compared with sense ODN-treated HBMEC (Fig. 6b). These results taken together indicate that LRP acts as the CNF1 receptor, thus mediating CNF1-mediated bacterial uptake and RhoA activation.

**DISCUSSION**

We have previously shown that CNF1 contributes to *E. coli* K1 invasion of HBMEC in vitro and traversal of the blood-brain barrier in the experimental hematogenous meningitis animal model (8). CNF1 is a protein belonging to the group of dermonecrotizing toxins, produced by pathogenic *E. coli* (20, 21). It is described as AB toxins, such as diphtheria, choler, and tetanus toxins, which are comprised of catalytic domain, cell binding domain, and membrane translocation domain (22). Entry of CNF1 into eukaryotic cells includes binding to a host receptor and internalization via an endocytic mechanism (16). Endocytosed CNF1 is routed to the degradative pathway, and internalization via an endocytic mechanism (16). Previous competition experiments suggested the presence of the receptor for CNF1 and the specific interaction between CNF1 and HBMEC via LRP, thus supporting the concept that LRP acts as the CNF1 receptor, and correlating the activity of CNF1 with the expression levels of LRP.

LRP has been known to be cell surface non-integrin laminin-binding protein receptors in several cell types, and involved in a variety of cellular mechanisms such as cell migration, adhesion, angiogenesis, and metastasis (23–25). According to the previous study, the N-terminal domain of LRP (amino acids 1–85) is a cytoplasmic domain, and the C-terminal domain of LRP (amino acids 102–295) is an extracellular domain, which

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**Fig. 3. Inhibitory effects of exogenous LRP on CNF1-mediated RhoA activation.** HBMEC or HEp-2 cells were incubated with the proteins (lane 1, GST; lane 2, GST-LRP; lane 3, CNF1; lane 4, CNF1 mixed with GST LRP; lane 5, CNF1 mixed with GST) for 30 min at 37 °C. Cells were lysed with lysis buffer as described under “Experimental Procedures,” and the cytosolic fractions were collected after centrifugation at 4 °C for 5 min. The cytosol fractions containing equal amounts of total proteins were incubated with GST-rhotekin beads for 60 min at 4 °C. After washing, the GTP-bound form of RhoA was separated by SDS-PAGE and detected by Western blotting with a RhoA specific antibody. Before performing rhotekin incubation, an aliquot of each sample was analyzed by Western blotting using anti-RhoA monoclonal antibody, showing equal amounts of proteins in all samples (total RhoA). The blots shown are representative of three independent experiments. The densities of RhoA-GTP bands were quantitated using an imaging densitometer, and the levels of RhoA activation were calculated by comparing the densities of RhoA-GTP bands with those of total RhoA in each lane. The values were then normalized to those of control, where only GST was treated to the cells, and expressed as -fold increases.

**Fig. 4. Inhibitory effects of exogenous LRP in *E. coli* invasion into HBMEC.** HBMEC monolayers were incubated with a mixture of 3 μg/ml CNF1 and 30 μg/ml GST-LRP or GST in experimental medium for 2 h before addition of bacteria and invasion assays were carried out as described under “Experimental Procedures” (*, p < 0.05 compared with CNF1 or CNF1 + GST, calculated using two-tail paired t test). Experiments were performed in triplicate. Error bars represent standard deviation.

response to CNF1, the enhancement of *E. coli* uptake into HBMEC was significantly (p < 0.05) decreased when CNF1 was co-incubated with GST-LRP compared with CNF1 alone or with GST incubation (Fig. 4). These results suggest that GST-LRP effectively inhibits *E. coli* invasion by sequestering CNF1.

**Binding and Effects of CNF1 in LRP-overexpressing HBMEC**—To confirm the binding of CNF1 to LRP in HBMEC, HBMECs were stably transfected with pcDNA3.1:LRP and the binding of GST-CNF1 to HBMEC was analyzed by enzyme-linked immunosorbent assay. The binding of CNF1 to HBMEC was dose-dependent, but was markedly greater when LRP was overexpressed, compared with control vector-transfected cells (Fig. 5a). These results suggest a specific interaction between CNF1 and HBMEC via LRP, thus supporting the concept that LRP is the receptor for CNF1. In addition, CNF1-mediated bacterial uptake was significantly (p < 0.05) greater in LRP overexpressing cells (Fig. 5b). Also, CNF1-mediated RhoA activation was markedly greater in LRP-overexpressing HBMEC (Fig. 5c).
are separated by a transmembrane domain (amino acids 86–101) (19). Because the cDNA clone identified in this study matches the extracellular domain of LRP containing the transmembrane domain (amino acids 89–295), it is likely that LRP is a receptor for CNF1. In vivo interaction between the N-terminal binding domain of CNF1 and extracellular domain of LRP was verified by cotransformation experiments where yeasts expressing LRP-(89–295) could grow on selection medium only when they are co-expressing fCNF1 or nCNF1, but not cCNF1. This finding is consistent with the previous demonstration that the receptor binding domain is located at the N terminus of CNF1 (14). Co-immunoprecipitation experiments showed specific interaction between LRP-(89–295) and CNF1 in vitro, and the ligand overlay assay indicated that the CNF1 binding to LRP (or host cell) is mediated by direct interaction between CNF1 containing N-terminal domain and the extracellular domain of LRP. For example, LRP-(89–295) bound to fCNF1 and nCNF1, but not cCNF1. This finding is consistent with the previous demonstration that the receptor binding domain is located at the N terminus of CNF1 (14). Co-immunoprecipitation experiments showed specific interaction between LRP-(89–295) and CNF1 in vitro, and the ligand overlay assay indicated that the CNF1 binding to LRP (or host cell) is mediated by direct interaction between CNF1 containing N-terminal domain and the extracellular domain of LRP. For example, LRP-(89–295) bound to fCNF1 and nCNF1, but not cCNF1. The interaction between LRP-(89–295) and [35S]nCNF1 was abolished by preincubation with non-labeled nCNF1, proving the specific interaction between nCNF1 and LRP-(89–295). Indeed, exogenous recombinant LRP could inhibit CNF1 activities such as RhoA activation and enhancement of bacterial uptake in HBMEC, by competing with cellular LRP in binding to CNF1. The inhibitory effect of LRP on CNF1 activation of RhoA also occurs in HEp-2 cells, where CNF1 has been shown to induce cytoskeletal rearrangements and bacterial uptake (12, 13), suggesting pcDNA3.1:LRP-transfected HBMEC. HBMEC stably transfected with pcDNA3.1:LRP (●) or empty plasmid pcDNA3.1 (●) were incubated with different concentrations of GST-CN1F. Absorbance was normalized by subtracting the background value where no CNF1 was added. b, invasion assays with E. coli K1 strain E44 in pcDNA3.1:LRP-transfected cells were included (*, p < 0.05, calculated using two-tail paired t test). c, CNF1-induced RhoA activation in pcDNA3.1:LRP-transfected HBMEC. pcDNA3.1 or pcDNA3.1:LRP-transfected HBMECs were treated with 3 μg/ml GST-CN1F for 30 min and RhoA assays were performed as described above. For control, an equivalent level of GST alone was added to transfected HBMEC. The densities of RhoA-GTP bands were quantitated using an Imaging Densitometer, and normalized to the values of controls, where only GST was treated to the cells, to calculate fold increases.
that LRP is a receptor for CNF1 in a variety of eukaryotic cells. Enzyme-linked immunosorbent assay experiments showed higher binding of CNF1 to HBMEC transfected with pcDNA3.1:LRP than control vector-transfected HBMEC, illustrating the specific interaction between CNF1 and HBMEC via LRP. The effects of CNF1 on bacterial uptake and RhoA activation were, as expected, much higher in LRP-overexpressing HBMEC, possibly because of higher binding of CNF1 to LRP. In contrast, the CNF1 effects were inhibited when the expression of LRP was decreased by antisense ODN, indicating that LRP functions as the receptor for CNF1. The LRP antisense ODN could not totally inhibit the effects of CNF1 when the expression of LRP is reduced by antisense ODN, suggesting that there may be an alternative pathway for CNF1 entry into eukaryotic cells, and this issue is currently being investigated in our laboratory.

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Jin Woong Chung, Suk Jin Hong, Kee Jun Kim, Daniel Goti, Monique F. Stins, Sooan Shin, Valina L. Dawson, Ted M. Dawson and Kwang Sik Kim

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