PDZ Domain-dependent Suppression of NF-κB/p65-induced Aβ42 Production by a Neuron-specific X11-like Protein*

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It is widely believed that one of the causes of Alzheimer's disease (AD) is the generation and secretion of β-amyloid (Aβ) from amyloid precursor protein in the brain. Here we report that a transcription factor, NF-κB/p65, induces increased secretion of amyloidogenic Aβ42 but not Aβ40. The κB motif-dependent production of Aβ42 was suppressed by binding of NF-κB/p65 to the PDZ domain of the X11-like protein (X11L), which a human homologue protein of LIN-10. The results suggest that the PDZ domain of X11L can control the ability of NF-κB/p65 to induce expression of protein(s) involved in Aβ42 production. The amino acids 161–163 in Rel homology domain (RHD) of NF-κB/p65 is important in interaction of NF-κB/p65 with X11L. Another subunit NF-κB/p50 and heterodimers of p65 and p50 do not bind to X11L. Our findings indicate NF-κB and X11L may, in novel way, regulate Aβ production in neuronal cells. Targeting X11L by specific therapy may provide the possibility to control the progression of AD.

X11-like (X11L) is a member of a family of proteins homologous to human LIN10 and is thought to function as a scaffold protein in neuron (reviewed in Ref. 1). Human X11L (hX11L) was originally isolated when it was found to be bound to amyloid precursor protein (APP)1 (2). APP is a precursor protein of β-amyloid (Aβ), whose deposition and accumulation in the brain are hallmarks of Alzheimer's disease (AD) (reviewed in Refs. 3–5). While the mechanisms regulating the proteolytic cleavage of APP and secretion of Aβ are as yet not well understood, we and others recently reported that X11 (6, 7) and X11L (2) proteins regulate metabolism and/or Aβ production. The phosphotyrosine interaction domain of X11L interacts with the cytoplasmic domain of APP, and the PDZ (a repeated sequences in the brain-specific protein PSD-95, the Drosophila septate junction protein disks-large, and the epithelial tight junction protein ZO-1, RHD, Rel homology domain of NF-κB.)
recovered using protein A- or protein G-Sepharose beads, respectively, and revealed by immunoblot using the indicated antibodies.

Quantification of Aβ42 with a Sandwich ELISA—HEK293 cells stably expressing human APP695 (9, 10) were transfected as above. The cells were supplied with fresh growth medium 12 h after the start of transfection, and conditioned medium from cells (9 × 10^6 cells) was collected 72 h after the medium change. Aβ40 and Aβ42 peptides secreted into the medium (100 μl) were quantified by sandwich ELISA (9, 10). Expression of hX11L and FLAG-p65 was examined by immunoblot analysis of cell lysate with UT-29 and anti-FLAG antibody M2. The relative ratios of the levels of Aβ observed using cells transfected with the pCDNA3 vector alone were determined.

Luciferase Activity Assay—One of the p55IgkLuc, pcATLuc, and pIFNLuc reporter construct plasmids (1.25 μg) together with any two of the effector plasmids (each 1.25 μg), pcDNA3-FLAG-NF-κBp65, pcDNA3-hX11L, and pcDNA3, were triply transfected into either HEK293 cells stably expressing human APP695 or human neuroblastoma SH-SY5Y cells (—5 × 10^6 cells/well in 24-well dishes). The cells were supplied with fresh growth medium 12 h after the start of transfection. After 48 h, the culture medium was removed and cell lysis buffer (100 μl) was added. Luciferase activity in the cell lysate was assayed using Luciferase Assay System (Promega) and measured with Luminometer (11). Results were expressed in an arbitrary unit.

Electrophoretic Mobility-Shift Assay (EMSA)—EMSA was performed with a procedure described previously (12). Oligonucleotide Ig κ containing self-complementary region was radiolabeled with polynucleotide kinase and [γ-32P]ATP, and the labeled probe was self-annealed. HEK293 cells (—2 × 10^6 cells) were transfected with pcDNA3-FLAG-NF-κBp65, pcDNA3-FLAG-NF-κBmut encoding p65 carrying the ALA substitution of the 75-SLV-77 sequence, or pcDNA3 as described above. After 48 h, the cells were collected and nuclear extract was prepared (13). Reaction mixture (20 μl) contained 16 μM Tris-HCl (pH 7.5), 50 mM NaCl, 1 mM dithiothreitol, 1 mM EDTA, 1% (w/v) Nonidet P-40, 5% (v/v) glycerol, 0.5-2 μl (approximately 0.3-1.2 μg) of protein of nuclear extract, and 2-4 fmol of [32P]-labeled probe. The mixture was incubated and loaded to 4% (w/v) polyacrylamide gel (12). Expression of FLAG-NF-κBp65 and FLAG-NF-κBmut was examined by Western blot using whole cell extracts and anti-FLAG antibody M2.

RESULTS

Interaction of NF-κB/p65 with XI1L—Using the yeast two-hybrid system, cDNA encoding full-length NF-κB/p65 interacting with the PDZ domain of hX11L was isolated. The hX11L protein contains two PDZ domains (Fig. 1a) (2), and the His reporter gene assay demonstrated that it was the most carboxyl-terminal domain (PDZ2) that was responsible for the interaction with NF-κB/p65 (Fig. 1b).

Interaction of hX11L and NF-κB/p65 in mammalian cells was demonstrated by co-immunoprecipitation experiments (Fig. 1c). COS7 cells that transiently express hX11L and NF-κB/p65 were lysed and the co-precipitation assay performed. The hX11L protein was detected in the sample immunoprecipitated with the anti-NF-κB/p65 antibody, sc-109. NF-κB/p65 was also detected in the sample immunoprecipitated with two of the anti-hX11L antibodies UT-29 and UT-50, but detection with the third, UT-30, was weak because UT-30 competes with NF-κB for the recognition sequence. Neither hX11L nor NF-κB/p65 could be detected in the sample immunoprecipitated using non-immune rabbit antibodies, indicating that the co-immunoprecipitation of hX11L and NF-κB/p65 was specific.

NF-κB/p65 consists of a Rel homology domain (RHD), a nuclear localization signal (NLS), and transcription activator domain (TA) (Fig. 1d) (reviewed in Refs. 14 and 15). To determine whether the RHD participated in the binding of NF-κB/p65 to hX11L, we performed another co-immunoprecipitation experiment using COS7 cells co-expressing hX11L and the RHD tagged with a FLAG sequence at their amino-terminal ends (Fig. 1d). The expression of the FLAG constructs of RHD and hX11L could be detected in the crude cell lysate (data not shown). When the lysate from cells expressing FLAG-RHD was subjected to immunoprecipitation with anti-FLAG antibody M2, the hX11L protein could also be detected (Fig. 1d, wt), indicating that some sequence in RHD can interact with PDZ2 of hX11L. It is known that PDZ generally binds to S/T-I/V motif, and X11L contains four potential PDZ-binding sequences, 75-SLV-77, 141-FQV-143, 141-FQV-143, and 217-DKV-219.

FIG. 1. Interaction of hX11L with NF-κB/p65. a, structure of human X11L and NF-κB/p65. PI, phosphotyrosine interaction domain; PDZ, PDZ domain; RHD, Rel homology domain; NLS, transcription activation domain. Numbers refer to amino acid positions. b, yeast two-hybrid assays with NF-κB/p65 and PDZ domain constructs derived from hX11L, PDZ1, and PDZ2 were performed on selective medium (−) or control medium (+). c, immunoprecipitation of hX11L and NF-κB/p65 with anti-FLAG antibody M2. The immunoprecipitates were subjected to SDS-PAGE and analyzed by immunoblotting with antibodies UT-30 (upper panel) and sc-109 (lower panel). Control IgG, non-immune rabbit IgG; sc-109, polyclonal anti-NF-κB/p65 antibody; UT-29, UT-30, and UT-50, polyclonal anti-X11L antibodies. H indicates the heavy chain of IgG. Numbers are the molecular masses (kDa) of the protein standards. d, determination of the hX11L-binding site of NF-κB/p65. COS7 cells transiently expressing hX11L and NF-κB/p65 were lysed and the crude lysate was used for immunoprecipitation (IP) with the indicated antibodies. The immunoprecipitates were subjected to SDS-PAGE and analyzed by immunoblotting with antibodies UT-30 (upper panel) and M2 (lower panel).

Since NF-κB can function as homo- and heterodimers of p65 and/or p50 (reviewed in Ref. 18), we assessed whether the p50 subunit is as able to bind to the PDZ domain of XI11L as the p65
cells were expressed with FLAG-RHD(p50), NF-X11L could also be detected in the precipitate. However, when lower panel (crude) and immunoprecipitates (M2. The lysate (crude) was used for immunoprecipitation (IP) with anti-FLAG antibody M2. The lysate (crude, left panel) and immunoprecipitates (IP, right panel) were subjected to SDS-PAGE and analyzed by immunoblotting with anti-X11L antibody UT-29 (upper panel) and M2 (lower panel). Transfection with the vector pcDNA3 alone acted as a negative control. b, co-immunoprecipitation of hX11L and NF- \( \kappa \)B/p65 together with FLAG-RHD(p50) or FLAG-RHD(p65). COS7 cells transiently expressing hX11L and NF- \( \kappa \)B/p65 together with FLAG-RHD(p50) or FLAG-RHD(p65) were lysed, and the lysate (crude) was used for immunoprecipitation (IP) with anti-FLAG antibody M2. The lysate (crude) and immunoprecipitates (IP) were subjected to SDS-PAGE and analyzed by immunoblot with UT-29 (upper panel), anti-NF- \( \kappa \)B antibody sc-109 (middle panel), and M2 (lower panel). Immunoprecipitation was performed on duplicate assays. Numbers indicate molecular masses (kDa) of protein standards.

For this purpose, FLAG constructs of RHD from NF-\( \kappa \)B/p50 (FLAG-RHD(p50)) and hX11L were expressed transiently in COS7 cells. When FLAG-RHD(p50) was isolated from cell lysate by immunoprecipitation with anti-FLAG antibody, hX11L could not be detected in the precipitate (Fig. 2a). Thus, X11L associates with the p65 but not the p50 subunit of NF-\( \kappa \)B. Consistent with this finding is the observation that the p50 subunit does not contain the PDZ binding motif found in p65 (data not shown).

To determine whether the heterodimer of NF-\( \kappa \)B/p65 and p50 can associate with X11L, COS7 cells were transiently and triply transfected with pcDNA3-hX11L and pcDNA3-NF-\( \kappa \)B/p65 together with either pcDNA3FLAG-RHD(p50) or pcDNA3FLAG-RHD(p65). The protein lysates were immunoprecipitated with anti-FLAG antibody M2 and immunoprecipitates were analyzed by immunoblot with the anti-X11L antibody UT-29, the anti-p65 antibody sc-109, and M2 (Fig. 2b). When cells expressed FLAG-RHD(p65), both NF-\( \kappa \)B/p65 and X11L could also be detected in the precipitate. However, when cells were expressed with FLAG-RHD(p50), NF-\( \kappa \)B/p65, but not X11L, could be detected in the precipitate. Thus, NF-\( \kappa \)B/p65 associates with FLAG-RHD(p50), but this heterodimer cannot bind to X11L. Although we did not determine whether the NF-\( \kappa \)B/p65 homodimer is able to associate with X11L, the present results suggest that only monomeric NF-\( \kappa \)B/p65, not homo- and heterodimers, can interact with X11L.

Induction of A\( \beta \) Production by NF-\( \kappa \)B/p65 and Suppression of the A\( \beta \) Production by X11L—It is known that X11L is a potential modulator of A\( \beta \) production (2) and that NF-\( \kappa \)B acts as a transcriptional activator of many genes (reviewed in Refs. 14 and 15). Therefore, we examined the effect of NF-\( \kappa \)B/p65 on the generation of both A\( \beta \)40 and A\( \beta \)42. HEK293 cells that stably expressed human APP695 were transiently co-transfected with any two combinations of cDNA encoding hX11L, NF-\( \kappa \)B/p65 with a FLAG tag (FLAG-p65) and vector alone. At 72 h, a sandwich ELISA was used to quantify A\( \beta \)40 and A\( \beta \)42 secreted into the medium. That hX11L and FLAG-p65 were expressed was verified by immunoblot analysis using UT-29 and M2 (data not shown). The negative control consisted of the A\( \beta \) released by cells containing pcDNA3 together with pcDNA3. This amount was set at 1.0 and levels in test samples related to this (Fig. 3). NF-\( \kappa \)B/p65 alone increased the level of A\( \beta \)42 but not A\( \beta \)40. As expected and reported previously, hX11L did not alter the level of A\( \beta \)42 but slightly decreased the level of A\( \beta \)40 (2). Surprisingly, however, when hX11L was co-transfected with NF-\( \kappa \)B/p65, the NF-\( \kappa \)B/p65-induced secretion of A\( \beta \)42 was suppressed. The secretion level of A\( \beta \)40 was not, however, altered in this situation. Thus, NF-\( \kappa \)B/p65 may activate the expression of one or more genes participating in A\( \beta \)42 production and hX11L is able to suppress this.

Whether hX11L can suppress \( \beta \)B motif-dependent gene activation was examined with a reporter gene assay using non-neutral (HEK293) and neuronal (SH-SY5Y) cells (Fig. 4). HEK293 cells stably express human APP695 and SH-SY5Y cells express endogenous APP. These cells were transfected with either the positive reporter plasmid p55lgLuc, which consists of three tandemly repeated \( \beta \)B motifs upstream of a minimal interferon-\( \beta \) promoter (\(-55 \) to +19) and the luciferase structural gene (Fig. 4a) (11), or the \( \beta \)B-independent reporter plasmids pActLuc and pIFNLuc as negative controls. The reporter plasmid was co-transfected transiently with NF-\( \kappa \)B/p65 and hX11L genes (Fig. 4, b and c). When FLAG-p65 was present, transcription of the reporter gene pActLuc was activated. When pActLuc and pIFNLuc, reporter genes containing defective \( \beta \)B motifs, were used instead of p55lgLuc, no effect on gene activation by NF-\( \kappa \)B was observed, indicating that the activation of the reporter gene depends on the \( \beta \)B motif. The \( \beta \)B motif-dependent activation of genes was also supported an an electrophoretic mobility-shift assay (Fig. 5). When p65 was present, specific complex composed of p65 and a probe containing \( \beta \)B motif was observed, which definitely demonstrated NF-
translocation into the nucleus. Further supporting the notion via other, as yet unidentified, proteins. To this aim, we used regulation of APP processing by directly interacting with APP or role in this process (2). It was, however, not clear whether X11L reduction of Aβ production depends on genes activation by NF-κB metabolism (6, 7). From these observations, we hypothesized also been demonstrated by others that X11 modulates APP production by complexing with NF-κB may increase the production of Aβ42 via κB motif-dependent transcriptional activation of certain gene(s) and further suggest that hX11L may inhibit this process by binding NF-κB to its PDZ domain, thereby retaining NF-κB in the cytoplasm and impeding its translocation into the nucleus. Further supporting the notion that Aβ42 production depends on genes activation by NF-κB is the finding that the mutant NF-κB containing an ALA substitution in the 75-SLV-77 sequence (whose binding to X11L is not impaired (Fig. 1d)) failed to activate κB motif-dependent genes and did not enhance Aβ42 production (Fig. 6). This mutant NF-κB has lost an ability to bind to κB motif (Fig. 5).

**DISCUSSION**

In our previous study (2), X11L was found to bind to the cytoplasmic domain of APP and regulate Aβ production. It has also been demonstrated by others that X11L modulates APP metabolism (6, 7). From these observations, we hypothesized that X11L may regulate Aβ production by complexing with APP and that the PDZ domains in X11L may play an important role in this process (2). It was, however, not clear whether X11L regulates APP processing by directly interacting with APP or via other, as yet unidentified, proteins. To this aim, we used yeast two-hybrid screening to identify proteins able to bind to the PDZ of X11L and thus identified NF-κB/p65 as a PDZ-binder. NF-κB/p65 could induce the production of Aβ42 through κB motif-dependent gene activation. The 5′-regulatory region of the APP gene contains two NF-κB binding sequences (18) and NF-κB might thus be expected to increase the expression of APP and concomitantly result in increased levels of Aβ42. However, this is not the case because when HEK293 cells stably expressing APP695 under the control of cytomegalovirus enhancer-promoter are transiently transfected with NF-κB/p65, the production of Aβ40 is not changed, while the production of Aβ42 is increased. Furthermore, overexpression of NF-κB/p65 did not alter the synthesis and maturation of APP695 (data not shown), and the κB sites of APP gene interact with NF-κB/p50 but not NF-κB/p65 (18). The observations suggest the significance of NF-κB signaling system connects to Aβ42 generation by activating expression of gene(s), which encodes protein concerning with a γ-secretase pathway, and also support the concept of two independent γ-secretases.

Expression of the neuron-specific protein X11L suppressed

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**Fig. 4.** Effect of hX11L on κB motif-dependent gene activation by NF-κB in vivo. a, structure of reporter gene constructs. κB, κB motif; IFNβ, interferon β gene promoter; Actin, actin gene promoter; Luc, luciferase structure gene. A positive reporter gene, p55IgLuc or p55Igk, and negative reporter genes, pActLuc or pAct and IFNLuc or IFN, are indicated. HEK293 cells stably expressing human APP695 (b) and human neuroblastoma SH-SY5Y (c) cells were transfected with a positive or negative reporter and a combination of effector plasmids. Luciferase activity was assayed and shown is the average of four independent assays (n = 4). The error bar indicates S.D. (***, p < 0.001).

**Fig. 5.** Binding activity of NF-κB/p65 to κB-motif. a, nuclear extract (lane 1, 0.5 µl; lane 2, 1.0 µl; lane 3, 2.0 µl) derived from HEK293 cells that express FLAG-NF-κB/p65 (p65), FLAG-NF-κB/p65mut (p65mut) encoding p65 carrying the ALA substitution of the 75-SLV-77 sequence, and vector alone (vector) was subjected to EMSA using 32P-labeled probe containing the Igκ B motif. b, nuclear extract (2 µl each) was subjected to EMSA in the presence (+) or the absence (−) of 100-fold excess of unlabelled probe. Arrow 1 indicates a specific complex including FLAG-NF-κB/p65, and arrow 2 indicates a complex composing of endogenous NF-κB. The asterisk indicates an unrelated complex composing of DNA-repair protein Ku (S. Tomita, T. Fujita, Y. Kirino, and T. Suzuki, unpublished observation). c, whole cell extract (−5 µg of protein) was assayed by Western blot with anti-FLAG antibody M2. The arrow indicates FLAG-NF-κB/p65 protein. Transfection was performed in duplicate and FLAG-NF-κB/p65 expresses 4-fold higher than FLAG-NF-κB/p65 NF-κB/p65mut.
production. This suggests that X11L binds to NF-κB and activated NF-κB and that brain inflammation activates NF-κB.

The quantity of Aβ42 with either pcDNA3-NF-κB or pActLuc reporter gene. a vector luciferase activity was assayed and shown is the average of four independent assays (n = 4). b, Aβ42 in the medium was measured (n = 5). The quantity of Aβ42 is indicated as the ratio of the levels of Aβ42 and/or p50 subunits and binds to DNA (reviewed in Refs. 14 and 15). We showed that the p50 subunit and a heterodimer consisting of p65 and p50 could not bind to the PDZ domain of X11L. X11L may thus be an anchor protein specific for monomeric NF-κB/p65, although it remains to be seen if X11L can bind p65 homodimers.

In many protein-protein interactions involving PDZ domain recognition, the PDZ domain associates with carboxyl termini of proteins such as those occurring in receptors or channels (25, 26). However, a recent report has revealed that PDZ domains can also bind to non-terminal consensual motifs such as those of neuronal nitric-oxide synthase (nNOS) (15, 16). The PDZ domains of X11L also recognized to non-terminal motif in NF-κB/p65. The interaction between NF-κB/p65 and X11L indicates a novel function for the PDZ domain in that it is involved in regulation of protein metabolism via transcriptional activation. Since NF-κB is thought to regulate cell death or survival through activation of several types of genes, analysis of the molecular mechanism(s) of NF-κB activation in neuronal cell is important in the understanding of neurologic disease such as AD.

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