APP-BP1, a Novel Protein That Binds to the Carboxyl-terminal Region of the Amyloid Precursor Protein*

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β-Amyloid protein precursors (APPs, 695–770 amino acids) are the source of the 39–43-amino acid β-amyloid (Aβ) peptides that comprise diffuse and fibrillar deposits in the cerebral cortex and vasculature of Alzheimer's disease brains. Aβ is thought to play a role in the pathogenesis of Alzheimer's disease, and, hence, considerable effort has been invested in defining the means by which Aβ is generated from the APPs. Knowledge of the normal function of the APPs is sure to provide insights into the genesis and pathological persistence of Aβ in Alzheimer's disease. APP is a cell surface protein with a large extracellular amino-terminal domain, a single transmembrane segment, and a short cytoplasmic tail. Its location and structural features characteristic of a receptor for signal transduction led us to search for potential effector proteins capable of binding and interacting with its cytoplasmic domain. Here, we report the cloning of a cDNA encoding one such protein. This ubiquitously expressed 59-kDa APP-binding protein, called APP-BP1, is 61% similar to a protein encoded by the Arabidopsis AXR1 gene, required for normal response to the hormone auxin, and is a relative of the ubiquitin activating enzyme E1.

The human β-amyloid precursor protein (APP)† gene (Kang et al., 1987; Goldgaber et al., 1987; Tanzi et al., 1987a; Robakis et al., 1987) encodes a set of APPs (695, 714, 751, and 770 amino acids) that are derived from alternatively spliced mRNAs. These APPs were initially identified as precursors of β-amyloid (Aβ, 39–43 amino acids), which forms abnormal extracellular deposits in the cerebral cortex and blood vessel walls in the Alzheimer's disease brain (for a recent review, see Ashall and Goate (1994)). The chain of events culminating in the deposition of these pathological fragments remains obscure. Knowledge of the normal activity, trafficking, and cleavage of APP is an essential precursor to our understanding of how one or more of these processes goes awry to create aberrant amyloidogenic fragments.

APP is a member of a family of proteins that also includes two human amyloid precursor-like proteins, APLP1 (Wasco et al., 1992) and APLP2 (Wasco et al., 1993). The amino acid sequences of APP and APLPs are highly conserved, and the protein structures of APP and APLPs are similar. APLPs, like APP, are located on the cell surface. They have a large extracellular amino-terminal domain, a single transmembrane region, and a short cytoplasmic tail. Within the extracellular domain, a cysteine-rich region, a zinc-binding motif, an acidic region, and N-glycosylation sites are conserved in all members of this gene family. Some forms generated from alternatively spliced mRNA possess a Kunitz class protease inhibitor domain in the extracellular portion of the molecule. However, only APP has the Aβ segment, whose amino terminus is extracellular and whose carboxyl terminus is within the cell membrane.

APP is ubiquitously expressed, but the relative levels of different APP isoforms vary among cell types, with APP-695 expressed preferentially in the brain. The biological function of the membrane-bound form of APP is unknown. Its extracellular domain can be enzymatically cleaved either within or upstream of the Aβ sequence, to release secreted forms of APP. The Kunitz class protease inhibitor-containing secreted forms may act as inhibitors of extracellular serine proteases (Olterdorff et al., 1989) and of the platelet coagulation factor XIa (Smith et al., 1990). Secreted APPs have been shown to participate in cell adhesion (Schubert et al., 1989; Breen et al., 1991; Small et al., 1992; J in et al., 1994), neurite outgrowth (Koo et al., 1993; Small et al., 1994; J in et al., 1994), and synaptic plasticity (Matus et al., 1993). Deletion of the Appl gene in Drosophila (Luo et al., 1992) or partial inactivation of the Appl gene in mice by gene targeting (Müller et al., 1994) results in impairment of learning and memory in those organisms. Mice with complete deletion of the Appl gene exhibited a compromised neuronal function (Zheng et al., 1995). Very little is known about the role of membrane-bound APP in cellular function. Notably, APP has structural features characteristic of cell surface receptors (Kang et al., 1987) with signal-transducing properties (Nishimoto et al., 1993). To learn more about the intracellular signals propagated by APP, we sought proteins with the potential to bind and interact with the cytoplasmic domain of this molecule. Here we report the cloning and sequencing of a cDNA encoding an APP-binding protein homologous to a protein encoded by the auxin hormone-resistant gene AXR1 in the plant Arabidopsis (Leyser et al., 1993). Our data suggest that this binding protein, called APP-BP1, may transduce signals mediated by the APP.

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** The abbreviations used are: APP, β-amyloid protein precursor; APLP, amyloid precursor-like protein; GST, glutathione S-transferase; PCR, polymerase chain reaction; PBS, phosphate-buffered saline; MBP, maltose-binding protein; PAGE, polyacrylamide gel electrophoresis; bp, base pair(s).
Expression Screening with GST-APP-C100—An array of human fetal brain cDNAs 
was screened with a GST-APP-C100 fragment. The 3′ reverse primer contained a sequence for six histidines. The PCR fragment was inserted in-frame into pGStag (Ron and Dressler, 1992). The glutathione S-transferase (GST)-GST-C100His6 fusion protein was purified on a ProteinGcolumn under native conditions (Invitrogen) with modifications (Hay and Hull, 1992). The fusion protein was immobilized onto glutathione-agarose beads (Sigma) and labeled with a catalytic subunit of CAMP-dependent kinase (Sigma) in the presence of γ-32PATP (6000 Ci/mmol, DuPont NEN) (Kaelin et al., 1992; Ron and Dressler, 1992). After labeling, the APP-C100His6 was cleaved from the matrix-bound GST with thrombin (Sigma). A human 22–24-week fetal brain cDNA library in Xgt11 (Neve et al., 1986) was plated (2 × 108 plaque-forming units) and screened at 4°C. Replica filters were blocked overnight in phosphate-buffered saline (PBS) containing 5% milk, 1 mM MgCl2, 1.2 mM CaCl2, 0.2 mM phenylmethylsulfonfyl fluoride, 1 mM dithiorethrol. The APP-C100His6 probe (108 cpm) was added to the filters, and incubation was continued overnight. The filters were then washed with PBS for 3 min, in PBS containing 0.1% Nonidet P-40 for 3 min, and in PBS for 3 min), dried, and exposed to X-ray films. Phage plaques that gave duplicated signals were purified and subcloned into pBluescript (pBS, Stratagene).

Isolation of Full-length cDNA—The initial clone isolated contained a partial coding sequence. To isolate full-length cDNA clones, a human fetal skeletal muscle Xgt11 library was screened by PCR (Friedman et al., 1989). Two primers: 5′-GTAATACGACTCACTATAGG and 5′-GATCTAGATGACACTATAGGACTAGT-3′, defining a segment of the known sequence of the partial cDNA were used. A total of three different phage clones were retrieved. Digestion of the phage cDNA with EcoRI generated one fragment each for each clone, and one of the fragments was identical with the initially retrieved cDNA. The clone isolated contained a fragment containing the full-length APP-BP1 coding region and some 3′ noncoding sequences. PCR analysis indicated that this fragment was bicistronic and was cloned into a modified pcDNA I vector (Kammesheid et al., 1988; Field, 1993). Two primers: 5′-AGAGGAGGAGGAGGAGG and 3′-CTCTCTCTCTCTCTCTCTCTCTCT were used to amplify APP-BP1 as a cDNA clone. Then, it was used as a probe to map the chromosomal location of the gene by fluorescence in situ hybridization (FISH). The probe was labeled with biotin-16-dUTP (Life Technologies, Inc.) using nick translation. Then, it was hybridized to metaphase chromosomes prepared from normal male peripheral blood lymphocytes by the bromodeoxyuridine synchronization method (Korenberg and Chen, 1995; Korenberg et al., 1993). Hybridized DNAs were detected with avidin-conjugated fluorescein isothiocyanate (Vector). Two amplifications were carried out using biotinylated anti– avidin. To generate reverse bands, metaphase chromosomes were counterstained with chromomycin A3 followed by diactin A. The image was captured using the Photometric Cooled-CCD camera (CH250) and the BDS image analysis system (ONCOR Imaging).

In Situ Hybridization—To isolate cDNAs encoding cellular proteins capable of interacting with the intracellular cytoplasmic domain of APP, the 100-amino acid carboxyl-terminal fragment of APP (APP-C100) was chosen as a probe for library screening. APP-C100 encompasses the Aβ and cytoplasmic domains and has a tendency to self-aggregate (Dyrks et al., 1988). To increase its solubility and to facilitate its purification, we fused six histidine residues to the carboxyl terminus of this fragment. The APP-C100His6 fragment then was subcloned into a GST tag vector (Ron and Dressler, 1992). The glutathione S-transferase (GST)-APP-C100His6 fusion protein was radiolabeled by phosphorylation with the catalytic subunit of cAMP-dependent protein kinase and then was cleaved with thrombin to release APP-C100His6 from the matrix-bound GST. The radiolabeled APP-C100His6, which migrated as a single 22-kDa band by SDS-PAGE (data not shown), was used to screen a human fetal brain Xgt11 expression library (Neve et al., 1986). A single positive clone was identified. The clones were sequenced with a Macintosh computer and a desktop scanner as described by Shea (1994).
with a 323-bp insert was isolated and determined, by sequence analysis, to be a partial cDNA clone. The known sequence was used to design a pair of primers to screen, by the PCR, a human fetal skeletal muscle library. Three positive clones revealed identical EcoRI restriction patterns. Sequence analysis showed that these cDNA clones contained a complete coding sequence. The complete sequence of the clone with the shortest poly(A) tail together with the sequence of the 5' untranslated region, compiled from all three clones, is shown in Fig. 1. The predicted open reading frame encodes a protein of 534 amino acids with a relative molecular mass of 59,000. The sequence encompassing the putative initiation codon (GCCATGG) matches the optimal sequence for initiation of translation (ACCATGG) by eukaryotic ribosomes (Kozak, 1986) with only one mismatch in position 23.

APP-BP1 Binds to the Carboxyl-terminal Domain of APP in Vitro—The protein encoded by this cDNA was designated APP-binding protein 1 (APP-BP1). In vitro binding assays were carried out to confirm that the protein product of the APP-BP1 cDNA binds to APP. The full-length APP-BP1 cDNA was used as a template for the in vitro synthesis of RNA, following which the RNA was translated in a wheat germ lysate in the presence of [35S]methionine. SDS-PAGE of the in vitro translation products revealed a closely spaced doublet with apparent mobility of ~66 kDa (Fig. 2A). These in vitro translations of APP-BP1 were used in in vitro binding assays with GST-fusion proteins. APP-C100, Aβ, APP-C57 (the carboxyl-terminal 57 amino acids of APP), and an unrelated protein, GAP-43 (Neve et al., 1986) fused to glutathione S-transferase (GST) were immobilized on glutathione-agarose beads and tested for their ability to bind APP-BP1. [35S]Methionine-labeled APP-BP1 was incubated with control GST or GST-fusion proteins on beads for 1 h. At the end of incubation, complexes were washed extensively to avoid nonspecific binding. The radiolabeled APP-BP1 specifically retained by the beads was analyzed on a 10% SDS-polyacrylamide gel, followed by autoradiography. These assays revealed (Fig. 2A) that APP-BP1 interacted with GST-C100 (lane 4) and GST-C57 (lane 6). Only background levels of APP-BP1 were seen in the GST-Aβ4 lane. To ensure the binding specificity of APP-BP1 to the carboxyl-terminal domain of APP, assays were done in the presence of free APP-C57 or of an irrelevant protein, maltose binding protein (MBP). Only APP-C57 competed for binding of APP-BP1 to GST-C100 and GST-C57 on beads, but MBP did not (Fig. 2B). APP-BP1 seemed to...
tibodies to APP (X-100. The detergent-soluble fraction was incubated with an-
zyme (E1), which is a highly conserved molecule with a mass of

 APP-BP1 was incubated with GST-C100 (lanes 2 and 4) or GST-C57 (lanes 2 and 4). The amounts of competitor protein in each reaction were about the same as the GST-fusion protein on beads. C, binding of 35S-labeled APP-BP1 to GST-C100 is a linear function of the APP-BP1 concentration in the reaction ($R^2 = 0.994$). In vitro binding assays were performed with various amounts of APP-BP1 ranging from 2 to 12% (v/v) in final concentration. The result shown was calculated from two sets of assays.

Fig. 3. Coimmunoprecipitation of APP-695 with APP-BP1. COS cells were transiently transfected with APP-695 and Myc-tagged APP- BP1 expression constructs. The lysates from control cells (lanes 1–3) and from cotransfected cells (lanes 4–6) were incubated with no antibody (lanes 1 and 4) and with antibodies 10D5 (lanes 2 and 5), or anti-Myc (lanes 3 and 6). Immuno- complexes were analyzed by Western blot, and the filters were incubated with antibodies 369 to APP (A) or anti-Myc to the tagged APP-BP1 (B).

Myc-tagged APP-BP1 (Anti-myc, lanes 3 and 6). The immuno- complexes were pulled down with protein G-Sepharose beads and analyzed by Western blots with antibodies to APP (Fig. 3A) or to APP-BP1 (Fig. 3B). The APP could be found in the complexes immunoprecipitated with anti-Myc antibodies (Fig. 3A, lane 6), and the APP-BP1 could be found in the complexes immunoprecipitated with 10D5 (Fig. 3B, lane 5). APP-BP1 was shown to interact effectively with full-length APP in mammalian cells.

cDNA Sequence Analysis—Amino acid sequence searches using the BLAST program of the GCG package revealed that the APP-BP1 protein sequence is 61% homologous to and 39% identical with the protein encoded by the Arabidopsis auxin resistance gene, AXR1 (Leyser et al., 1993). The APP-BP1 sequence also showed 57% similarity and 37% identity to a protein encoded by a Caenorhabditis elegans gene on chromosome III. This C. elegans gene product was defined using GENE FINDER analysis of the genome sequence data (Wilson et al., 1994), and no study of its function has been reported. The proteins encoded by AXR1 and the C. elegans gene are 55% similar and 33% identical. Alignment of these three sequences (Fig. 4A) reveals 115 highly conserved residues interspersed throughout the sequences. Kyte-Doolittle hydrophathy analysis (1982) of the predicted amino acid sequence shows no hydrophobic domains long enough to form membrane-spanning $\alpha$-helices (data not shown).

APP-BP1 and AXR1 are relatives of ubiquitin-activating en-
zyme (E1), which is a highly conserved molecule with a mass of

Immunoprecipitation of APP-695 and APP-BP1—We also examined whether full-length APP interacts with APP-BP1 in mammalian cells. COS cells were cotransfected with full-length APP-695 and APP-BP1 tagged with the epitope Myc (Glu-Gln-Lys-Leu-Ile-Ser-Glu-Glu-Asp-Leu). Three days after transfection, the cells were harvested in a buffer containing 1% Triton X-100. The detergent-soluble fraction was incubated with anti-
bodies to APP (10D5, lanes 2 and 5) or with antibodies to the
cellular proteins that are targeted for rapid degradation. Alignment of APP-BP1 with the amino-terminal 600 amino acids of E1 from human (Kok et al., 1993), wheat (Hatfield et al., 1990; Hatfield and Vierstra, 1992), and mouse (Imai et al., 1992) reveals a 46–47% similarity (Fig. 4).

Gene Characterization and Chromosomal Mapping—Human genomic DNA was digested with the restriction enzymes EcoRI, BamHI, PstI, and HindIII, transferred to a nylon membrane, and probed with the APP-BP1 cDNA. The limited number of positively hybridizing bands on the genomic Southern blot suggests that APP-BP1 is a single copy gene (Fig. 5). The APP-BP1 was localized to human chromosome 16 band q22 using fluorescent in situ hybridization (Fig. 6). Two independent experiments were performed, and more than 100 metaphase cells were evaluated. Signals were clearly visible on two chromatids of at least one chromosome in 45% of the cells. No

FIG. 4. Alignment of amino acid sequences of APP-BP1 with related proteins. Alignment was performed using the Pileup program of the GCG package. Pairwise comparisons between the proteins were done using a Gap program, and the results are shown in the text. Hyphens indicate gaps introduced to maximize alignment. A, APP-BP1, AXR1, and the predicted open reading frame of a C. elegans gene on chromosome III. Amino acid residues identical in at least two of the three sequences are displayed as white letters in black boxes. B, APP-BP1 and the amino-terminal 600 amino acids of ubiquitin-activating enzyme E1 from human, wheat, and mouse. Residues identical in at least four of the six E1 proteins are boxed, and the residues in APP-BP1 identical with these highly conserved amino acids are shown as white letters in black boxes.
other chromosomal sites with consistent signals were detected in more than 1% of the cells.

Expression of APP-BP1 mRNA—We used RNA blot analysis to examine the pattern of expression of APP-BP1 mRNA in human fetal tissues. The 1.8-kilobase APP-BP1 transcript was detected in all tissues examined (Fig. 7A). It was also present in all subregions of the adult human brain that were analyzed (Fig. 7B).

In situ hybridization histochemistry was used to localize APP-BP1 mRNA in the rat brain. The data revealed that APP-BP1 mRNA is expressed throughout the brain. In the hippocampus, APP-BP1 showed robust expression in granule cells of the dentate gyrus and in the pyramidal cell layer (Fig. 8, A and B). Within the cerebral cortex, APP-BP1 riboprobe hybridized strongly to cells in the piriform cortex (Fig. 8, C and D). In the cerebellum, the APP-BP1 probe labeled only the Purkinje cells (Fig. 8, E and F).

**DISCUSSION**

A human cDNA encoding a 59-kDa protein was isolated by screening expression cDNA libraries with the radiolabeled carboxyl-terminal region of APP. This protein, termed APP-BP1, was shown to interact with the carboxyl-terminal region of APP in in vitro binding assays and with the full-length APP in immunoprecipitation assays. APP-BP1, like APP, is ubiquitously expressed in neural and non-neural tissues. Comparison of the deduced amino acid sequence with protein sequences in the data base revealed that APP-BP1 is highly homologous (61%) to AXR1, a protein encoded by the Arabidopsis auxin resistance gene. Southern blot analysis of human genomic DNA suggested that APP-BP1 is a single-copy gene, and fluorescence in situ hybridization was used to localize the gene to chromosome 16q22.

Although the function of cell-surface APP remains obscure, its structural features, a large extracellular amino-terminal domain, a single transmembrane region, and a short cytoplasmic tail, are reminiscent of those of integrins (reviewed by Dustin and Springer (1991)), which are the major receptors for extracellular matrix proteins. In addition to these features, the carboxyl terminus of APP shares with the integrins and with other known plasma membrane receptors (Tamkun et al., 1986) a highly conserved stretch of five amino acids (683–688 in the APP-695 sequence) representing the consensus sequence surrounding a tyrosine that is autophosphorylated in the epidermal growth factor receptor (Downward et al., 1984).

If the membrane-bound APP does function as a cell-surface receptor, by what mechanism are signals transduced from the cell surface to its interior? For many hormone and growth factor receptors, signal transduction across the cell membrane occurs by direct interaction of the receptor cytoplasmic domain with its intracellular target protein. In this study, we report the identification of such a target protein for APP, APP-BP1, supporting the idea that APP may function as a cell surface receptor. Numerous effects of integrin activation have been described. They include reorganization of the cytoskeleton (Burridge et al., 1988), alterations in tyrosine phosphorylation (Körnberg et al., 1991; Schaller et al., 1992), activation of calcium-dependent proteases (Fox et al., 1985), activation of the Na+/H+ antiporter (Banga et al., 1986), and changes in the...
subcellular distribution of phosphoinositide 3-kinase (Zhang et al., 1992). Although direct involvement of APP has not been demonstrated in such cellular pathways, the known role of membrane-bound APP in neurite extension (Qiu et al., 1995; LeBlanc et al., 1992; Milward et al., 1992), its synaptotrophic effects (Mucke et al., 1994), and its possession of an RHDS sequence that promotes cell adhesion and is blocked by an anti-(β1-integrin) antibody (Ghiso et al., 1992) are consistent with an integrin-like function for APP. Breen et al. (1991) have shown that membrane-bound APP mediates cell-cell binding and cell adhesion to a collagen substrate in a manner similar to that of the neural cell adhesion molecule, which modulates both process outgrowth and synaptic plasticity (Rutishauser and Jessell, 1988). Membrane-bound neural cell adhesion molecule is associated with cell-surface heparan sulfate proteoglycans in a complex in which heparan sulfate proteoglycan mediates cell-substratum adhesion (Kallapur and Akeson, 1992). Several studies suggest that the membrane-bound form of APP similarly is associated with a heparan sulfate proteoglycan (Schubert et al., 1988; Kalari et al., 1992; Su et al., 1992) which may also, by analogy, regulate cell-extracellular matrix interactions.

The Arabidopsis AXR1 is thought to mediate the action of the plant hormone auxin, which is required for cell division, elongation, and differentiation (Leyser et al., 1993). Mutations in the AXR1 gene result in a variety of morphological defects presumably due to reduced auxin sensitivity (Lincoln et al., 1990). AXR1 may interact directly with auxin-binding site(s) (for a review, see Goldsmith (1993)) or indirectly via binding to intermediate protein(s) in the signal transduction pathway. The fact that APP-BP1 is a human homologue of AXR1 is consistent with the idea that APP functions as a membrane receptor and that APP-BP1 plays a role transducing APP-mediated signaling into the cell.

The biochemical activities of APP-BP1 and AXR1 are still unknown. Despite the sequence similarity between APP-BP1 and ubiquitin-activating enzyme E1, APP-BP1, AXR1, and the putative C. elegans protein probably define a new family of proteins. The overall degree of protein sequence similarity within the members of this family is greater than that between any member and E1, and, conversely, two Arabidopsis E1 proteins are more similar to E1 proteins from other species than they are to AXR1 (Leyser et al., 1993). It is unlikely that AXR1 and APP-BP1 have the same activity that E1 does, because a conserved cysteine at position 626, required for ubiquitin-conjugation activity in wheat (Hatfield and Vierstra, 1992), is located outside the region of similarity, and because two consensus ATP-binding domains identified in yeast E1 (McGrath et al., 1991) are missing in AXR1 and in APP-BP1. These data do not, however, rule out the possibility that APP-BP1 with an activity different from E1 plays a role in a cellular ubiquitination pathway. Several cell surface receptors, such as the platelet-derived growth factor receptor (Mori et al., 1992), the T cell antigen receptor (Cenciarelli et al., 1992), and the immunoglobulin E (IgE) receptor (Paolini and Kinet, 1993), are ubiquitinated in response to ligand binding. Ubiquitination of proteins marks the selective degradation for many polypeptides. Activation-induced ubiquitination of the platelet-derived growth factor and the T cell antigen receptor may lead to a rapid degradation of ligand-receptor complexes. However, the activation-induced ubiquitination of the IgE is rapidly reversible. It suggests that the function of the IgE receptor may be regulated by ubiquitination. By analogy, cell surface APP might be ubiquitinated upon ligand binding by a mechanism in which the APP-associated APP-BP1 is involved directly or indirectly.

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