APP-BP1 binds to the amyloid precursor protein (APP) carboxyl-terminal domain. Recent work suggests that APP-BP1 participates in a novel ubiquitin-like conjugation pathway involving the ubiquitin-like molecule NEDD8. We show here that, in vivo, in mammalian cells, APP-BP1 interacts with hUba3, its presumptive partner in the NEDD8 activation pathway, and that the APP-BP1 binding site for hUba3 is within amino acids 443–479. We also provide evidence that the human APP-BP1 molecule can rescue the ts41 mutation in Chinese hamster cells. This mutation previously has been shown to lead to successive S phases of the cell cycle without intervening G2, M, and G1, suggesting that the product of this gene negatively regulates entry into the S phase and positively regulates entry into mitosis. We show that expression of APP-BP1 in ts41 cells drives the cell cycle through the S-M checkpoint and that this function requires both hUba3 and hUbc12. Overexpression of APP-BP1 in primary neurons causes apoptosis via the same pathway. A specific caspase-6 inhibitor blocks this apoptosis. These findings are discussed in the context of abnormalities in the cell cycle that have been observed in Alzheimer’s disease.

Amyloid precursor protein (APP),1 a transmembrane protein, is the source of the β-amyloid peptides that accumulate in the brains of patients with Alzheimer’s disease (AD). The possibility that APP may act as a signaling receptor was first proposed on the basis of its predicted amino acid sequence, which suggested that APP was a type 1 intrinsic membrane protein consistent with the structure of a cell surface receptor (1). It has now been demonstrated that a percentage of APP is found on the cell surface in neurons (2–4). Cell-surface APP possesses a neurite-promoting activity that is distinct from that of the secreted APP (5), co-localizes with adhesion plaque components (3, 6), and participates in synaptic vesicle recycling (7), suggesting that a percentage of APP may function as a cell surface receptor, transducing signals from the extracellular matrix to the interior of the cell.

APP-BP1 was identified by its interaction with the intracellular carboxyl terminus of APP (8), which places this molecule in a position potentially to participate in the transduction of signals from the cell surface into the cell. APP-BP1 initially was found to be homologous to the Arabidopsis auxin resistance gene AXR1, and to the amino terminus of the ubiquitin activating enzyme E1. It was puzzling that APP-BP1 lacked a conserved cysteine required for E1 ubiquitin conjugation activity. However, it was subsequently discovered that eukaryotes express a set of ubiquitin-like proteins that, like ubiquitin, are ligated to other proteins (9, 10). In yeast, one of these ubiquitin-like proteins, Rub1 (related to ubiquitin 1), is activated by a heterodimer consisting of the subunits Ula1 and Uba3. Ula1 and Uba3 are related to the NH2- and COOH-terminal domains of the E1 ubiquitin-activating enzyme, respectively, and together fulfill E1-like functions for Rub1 activation. Interestingly, Ula1 is homologous to APP-BP1 (11). Rub1 conjugation also requires Ubc12, a protein related to E2 ubiquitin-conjugating enzymes, which functions analogously to E2 enzymes in the Rub1-protein conjugate. The cellular reactions involving these ubiquitin-like proteins appear to be quite similar to those involving ubiquitin, but the ubiquitin-like proteins have novel regulatory functions not necessarily linked to proteolysis (reviewed in Ref. 12). For example, Rub1 has been shown to be conjugated to Cdc53, a component of a large ubiquitin-protein ligase E3 complex (termed SCF, comprising Cdc53, Skp1, and an F-box protein) that regulates G1/S progression of the cell cycle (11, 13).

The homologous pathway in mammalian cells is the NEDD8 conjugation pathway. NEDD8, the mammalian orthologue of Rub1, was first cloned as a developmentally down-regulated gene expressed in neural precursor cells (14). On the basis of in vitro studies, APP-BP1 has been proposed to be a member of this pathway (15, 16). In vitro, APP-BP1 together with hUba3 behaves like the ubiquitin activating enzyme E1, with hUba3 containing the active cysteine and ATP binding site. In vitro work has also shown that when NEDD8 is activated, it forms a thiol ester bond with hUbc12, the human homologue of Ubc12, which has a function parallel to that of the ubiquitin-conjugating enzyme Cdc34. Subsequently, NEDD8 is covalently coupled to its target proteins.

The functions of the NEDD8 conjugation pathway are still unclear. Recent studies have revealed that NEDD8 modifies cullins, a group of proteins homologous to the yeast Cdc53. Interestingly, cullin-2 is modified by NEDD8 and assembles with the von Hippel-Lindau tumor suppressor protein pVHL into an SCF-like complex, linking the tumor suppressor function of pVHL to NEDD8 conjugation with cullin-2 (17). A recent study (18) showed that the NEDD8-modified form of cullin-1 is localized to interphase and mitotic centrosomes as well as to the cytoplasm, suggesting that NEDD8 modification of cullins
may ensure accurate chromosome segregation in mitosis. These observations hint at a critical role in cell cycle control for the NEDD8 conjugation pathway.

In the present report, we show that APP-BP1 co-immunoprecipitates with hUba3 from mammalian cells, and we identify a 36-amino acid domain of APP-BP1 to which hUba3 binds. We also show that wild type APP-BP1 rescues the cell cycle S-M checkpoint defect in ts41 hamster cells (19, 20), that this rescue is dependent on the binding of APP-BP1 to hUba3, and that dominant negative mutants of hUba3 and Ub12 prevent the rescue. Finally, we show that overexpression of APP-BP1 in primary neurons causes apoptosis by a pathway that also involves hUba3 and Ub12.

MATERIALS AND METHODS

Antibodies and Immunoblot—To generate anti-APP-BP1 antisera, the APP-BP1 cDNA was digested with NcoI and the 37-base pair fragment encoding amino acids 90–213 was inserted into the pGEX-KG vector (21) in frame. The resultant glutathione S-transferase (GST) fusion protein was expressed in bacteria and purified from inclusion bodies as described (22). Antibodies were generated in rabbits, and the serum (BP339) was preadsorbed against a GST column (Research Genetics). The antibody was shown to then immunofluorescence-purified using full-length GST-APP-BP1 purified as a soluble protein from bacteria (23). The anti-progestosterone receptor antibody (B-30, Santa Cruz Biotechnology) was used as a control for BP339 specificity. The rabbit polyclonal antibody HA.11 (Alexis Biosciences) and the mouse monoclonal antibody 12CA5 (gift from Dr. E. Harlow) were used to detect hemagglutinin (HA)-tagged proteins, with the monoclonal anti-myc antibody (ATCC) used as a negative control.

Plasmid Construction—All plasmid constructs were made using standard techniques and were sequenced to verify the correct reading frame. Protein expression was confirmed by immunoblot analysis using the appropriate antibodies. The sequences of the primers used for constructions are written in 5′ to 3′ orientation. The cDNA clone for hUba3 was purchased from ATCC (expressed sequence tag 41156). The hUba3 coding sequence was amplified from this plasmid by the polymerase chain reaction (PCR) with the high fidelity Vent polymerase (New England Biolabs) using the forward primer GGGAATGATCAAGCTGTTCTCGCTG and the reverse primer GGTCGGACCTAGACATAATCATCTTTCACC-14GATGTCGATCCTTAGCTGAACACGAATTTTGCCGATATGG and the reverse primer CCATATCGGCAAAATTCGTGTTCAGCTAAGGATCG-GTTGATGGTGGGTG and the reverse primer GGGAATTCTTAA-
fused into the expression vectors pACT2, pcDNA3, and plasmid pBSVpRPUC. The hUba3 cDNA was amplified by trans-PCR (24). The hUbc12 cDNA was amplified from human fetal brain RNA by reverse transcription-PCR using the forward primer GGGAATGATCAAGCTGTTCTCGCTG and the reverse primer GGTCGGACCTAGACATAATCATCTTTCACC-14GATGTCGATCCTTAGCTGAACACGAATTTTGCCGATATGG and the reverse primer CCATATCGGCAAAATTCGTGTTCAGCTAAGGATCG-GTTGATGGTGGGTG and the reverse primer GGGAATTCTTAA-

RESULTS

APP-BP1 Interacts with hUb in Vivo—We initially used the yeast two-hybrid reporter assay to test whether hUba3 interacts with APP-BP1 in vivo (Fig. 1). The hUba3 and APP-BP1 cDNAs were inserted into the yeast vectors pBHA3 and pH8A vectors, respectively, and transformed into yeast. The expression of the transgenes was confirmed by immunoblot analysis with the anti-HA antibody 12CA5 (Fig. 1B). APP-BP1 interacted with hUba3 very strongly (Fig. 1C), as indicated by activation of the lacZ reporter gene; the color change occurred within 20 min of addition of the 5-bromo-4-chloro-3-indolyl β-D-galactopyranoside substrate. We then tested point and deletion mutants of APP-BP1 for their ability to interact with hUba3. The expression of each mutant was confirmed by immunoblot analysis (Fig. 1B). The APP-BP1 point mutation T328A was made because RGT is a highly conserved sequence that is a potential recognition site for serine/threonine kinases. This mutant showed a decreased interaction with hUba3, in that the color change occurred 30 min after addition of the 5-bromo-4-chloro-3-indolyl β-D-galactopyranoside substrate. A carboxyl-terminal fragment of APP-BP1, comprising amino acids 443–534, interacted with hUba3, although the interaction was weaker. Deletion of amino acids 401–479 from APP-BP1 eliminated its ability to interact with hUba3, suggesting that the hUba3-binding site in APP-BP1 lies within amino acids 443–479. An NH2-terminal fragment of APP-BP1, encompassing amino acids 1–209, did not show an interaction with hUba3, that the fragment consisting of amino acids 145–251, to which APP binding site in APP-BP1 lies within amino acids 443–479. An NH2-terminal fragment of APP-BP1, encompassing amino acids 1–209, did not show an interaction with hUba3, that the fragment consisting of amino acids 145–251, to which APP
tion and point mutants used for the assay. BP1 interacts with hUba3.

4-chloro-3-indolyl b-D-galactopyranoside substrate to turn blue.

The ts41 mutation of Chinese hamster cells disrupts their cell cycle. At nonpermissive temperature, the cells led us to test whether APP-BP1 could rescue the ts41 phenotype. We then used the BP339 antibody to confirm the expression of the transgenes in the APP-BP1 vectors used for the coimmunoprecipitation experiments (Fig. 2 B). hUba3 was co-expressed with wild type APP-BP1 or with mutants of APP-BP1 in Chinese hamster cells, and cell lysates were incubated with anti-HA (12CA5) to immunoprecipitate HA-tagged hUba3. Precipitations were also done with an irrelevant antibody, anti-myc, as a negative control. The immune complexes were blotted with anti-APP-BP1 antibody BP339. Only the deletion mutant d401–479 did not coimmunoprecipitate with hUba3.

Wild Type Human APP-BP1 Rescues the ts41 Cell Phenotype at the Nonpermissive Temperature—The ts41 mutation of Chinese hamster cells disrupts their cell cycle. At nonpermissive temperature, the cells go through successive S phases without progressing into G2, M, and G1 (19, 20); and it has been proposed (20) that the normal protein negatively regulates entry into the S phase and positively regulates entry into mitosis. An informal communication suggesting that the ts41 gene was the hamster orthologue of the APP-BP1 gene (referred to in Ref. 25) led us to test whether APP-BP1 could rescue the ts41 phenotype. We transfected ts41 cells with a pcDNA3 vector expressing APP-BP1 at the permissive temperature; 7 h later, the cells were shifted to the nonpermissive temperature. At selected time points thereafter, cells were trypsinized and counted (Fig. 3A), to measure cell proliferation. Cells transfected with a vector expressing human wild type APP-BP1 maintained a rate of growth at 40 °C that was similar (albeit slightly shifted to the right) to that of cells transfected with the vector alone and maintained at 34 °C. Vector-transfected cells that were shifted to the nonpermissive temperature showed a decreased mitotic index and eventually died, in agreement with previous reports (19, 20).

We then performed the proliferation assay using ts41 cells transfected with vectors expressing APP-BP1 mutants (Fig. 3B). The d401–479 deletion mutant, which does not interact with hUba3, lost the ability to rescue the ts41 phenotype at the nonpermissive temperature, suggesting that interaction between APP-BP1 and hUba3 is necessary for APP-BP1 function in this pathway. Interestingly, the T328A mutation enhanced the ability of APP-BP1 to promote cell proliferation at the nonpermissive temperature, while the Y478F mutation (which is located within the putative hUba3 binding region of APP-BP1) impaired it.

We also transfected ts41 cells with a vector expressing the 37-amino acid region of APP-BP1 (443–479) that is the putative binding site for hUba3. The expression of this fragment, which was HA-tagged, was confirmed by immunoblot analysis (data not shown, but see Fig. 5B). As shown in Fig. 3C, when APP-BP1 and the 443–479 fragment were co-expressed in ts41 cells, the function of APP-BP1 was inhibited significantly at the nonpermissive temperature. These data suggest that the 443–479 fragment competes with APP-BP1 for binding to hUba3, and that this competition interferes with the function of APP-BP1.

As an independent measure of the ts41 phenotype, and of its rescue by APP-BP1, we performed flow cytometry analysis (Fig. 3D). Logarith-
mutations in the NEDD8 conjugation pathway block APP-BP1 function in ts41 cells. We have established that APP-BP1 can rescue the ts41 phenotype at 40 °C. Since APP-BP1 and hUba3 together act as a heterodimeric activating enzyme in the NEDD8 conjugation pathway, we hypothesized that the ts41 phenotype at 40 °C results from a defect in this pathway. To test this hypothesis, we made dominant negative mutants of hUba3 (Fig. 4) and the NEDD8-conjugating enzyme hUbc12 (Ref. 27) or were mock-infected, and were fixed 12 h after infection. The extent of apoptosis in neurons overexpressing APP-BP1. Embryonic day 21 rat cortical cultures were infected with HSV-APP-BP1 at a multiplicity of infection of 2 (which results in infection of ~70–80% of the cells; Ref. 27) or were mock-infected, and were fixed 12 h after infection. The nuclear morphology of the cells was assessed by staining with bisbenzimide, allowing fluorescent visualization of normal and condensed (apoptotic) chromatin. Quantification of a representative experiment is shown in Fig. 5. Cells infected with control HSV/lacZ showed only a few apoptotic cells, and were not significantly different from mock-infected cells (data not shown) in number of apoptotic nuclei. However, cells infected with the HSV vector expressing APP-BP1 showed a significant increase over control (~25% apoptotic nuclei) in the number of apoptotic cells.
Primary neuronal cultures infected with HSV expressing APP-BP1(d401–479), which lacks the hUba3 binding domain, did not evince numbers of apoptotic nuclei greater than background. We also infected neurons with a vector expressing the 37-amino acid region of APP-BP1 (443–479) that is the putative binding site for hUba3. The expression of this fragment, which was HA-tagged, was confirmed by immunoblot analysis (Fig. 5B). As shown in Fig. 5C, when APP-BP1 and the 443–479 fragment were co-expressed in primary cortical neurons, the apoptosis caused by APP-BP1 was inhibited significantly. These data suggest that the 443–479 fragment competes with APP-BP1 for binding to hUba3, and that this competition disrupts the ability of APP-BP1 to cause neuronal apoptosis.

We then co-expressed HA-tagged dominant negative mutants of hUba3 and hUbc12 with APP-BP1 in the cortical cultures (Fig. 6). Immunoblot analysis was performed to confirm expression of the HSV transgenes (Fig. 6A). Both dominant negative hUba3 (C216S) and hUbc12 (C111S) inhibited the ability of APP-BP1 to cause apoptosis in the neurons (Fig. 6, B and C), implicating the NEDD8 conjugation pathway in the apoptosis.

Activation of caspase-3 and caspase-6 occurs during neuronal apoptosis (28, 29). Caspase-3 activation has been detected in hippocampal neurons undergoing granulovacular degeneration in AD brain (30), and APP is processed by caspases during apoptosis (31, 32). To test whether these caspases are involved in APP-BP1-mediated apoptosis, we treated HSV/APP-BP1-infected neurons with specific caspase inhibitors, as shown in Fig. 6D, addition of the cell-permeable broad spectrum caspase inhibitor Boc-d-FMK or of the caspase-6 inhibitor VEID-CHO at the time of infection decreased apoptosis rates in cell lines infected with HSV/APP-BP1. Addition of the cell-permeable caspase-3 inhibitor DEVD-CHO had no effect on apoptosis caused by overexpression of APP-BP1 (data not shown).

**DISCUSSION**

We have shown that APP-BP1 interacts with hUba3 in vivo, using both the yeast two-hybrid report assay and also coimmunoprecipitation, and we have identified a 36-amino acid domain of APP-BP1 to which hUba3 binds. We have also demonstrated that wild type APP-BP1 rescues the cell cycle S-M checkpoint defect in ts41 hamster cells, that this rescue is dependent on the interaction of APP-BP1 and hUba3, and that the functional activity of both hUba3 and Ubc12 is required for the rescue.

Finally, we have shown that overexpression of APP-BP1 in primary neurons causes apoptosis by a pathway that also involves hUba3 and hUbc12, and that is dependent on caspase-6 activity.

Our analysis has established the in vivo importance of APP-BP1 in a pathway that leads to the activation of NEDD8. Our data suggest that, in Chinese hamster cells, this pathway is required for cell cycle progression from S to M phases. APP-BP1 is an essential component of this pathway because without functional APP-BP1 the cell cycle halts at the S phase. In vitro analysis of the NEDD8 conjugation pathway (33) has revealed that the ubiquitin-activating enzyme E2 adds NEDD8 to a polyubiquitin chain with an efficiency comparable to that of ubiquitin. This lack of an intrinsic block to NEDD8 transfer to a polyubiquitin chain by E2 implies that the selectivity of an E2 enzyme for ubiquitin versus NEDD8 is determined by upstream activating enzymes, rather than at the level of the molecule (ubiquitin or NEDD8) being transferred. Either APP-BP1, or hUba3, or both together, may be the determining factor for such selectivity for NEDD8 conjugation. Although we have not proven directly that the interaction of APP-BP1 and hUba3 leads to NEDD8 activation in vivo, it is likely that it does. Our data indicate that cellular functions mediated by APP-BP1 and hUba3 also require hUbc12. hUbc12 is unable to form a thioester linkage with ubiquitin or with another ubiquitin-like protein, SUMO-1, in vitro (15), suggesting that it is specific for NEDD8. Moreover, while it has been shown that ubiquitin is conjugated by multiple species of Ubc, the data accumulated thus far indicate that NEDD8 uses uniquely the conjugating enzyme hUbc12 (15).

We have identified the hUba3-binding site in APP-BP1 within amino acids 443–479. This region contains a DYV motif, identical to sequences that are autophosphorylated in tyrosine kinases, with consequent conformational changes leading to activation or inhibition of kinase activity (34). The Y478F mutation significantly inhibited APP-BP1 function in the ts41...
proliferation assay at the nonpermissive temperature (although it did not affect APP-BP1 binding to hUba3), suggesting that APP-BP1 may have an intrinsic kinase activity that is important for its role in the cell cycle. The hUba3-binding domain of APP-BP1 also includes a KXXS motif (amino acids 457–460), which is a potential recognition site for cGMP-dependent protein kinase or protein kinase C, and an EY motif (amino acids 467–468), another potential autophosphorylation site for tyrosine kinases (34).

The involvement of APP-BP1 in the cell cycle is of interest in the light of numerous findings of cell cycle abnormalities in AD. Evidence has been accumulating (35, 36) that some neurons degenerate via apoptotic pathways in Alzheimer’s disease. Apoptosis and the cell cycle are closely tied together, and the reexpression of cell cycle markers has been linked with the occurrence of certain types of neuronal cell death (37–39). The interpretation of these findings (40) is that a neuron is committed to the permanent cessation of cell division, so if for any reason it is forced to reenter the cell cycle after this commitment, it dies. Notably, ectopic expression of cell cycle proteins and their associated kinases in AD brain have been reported (41–44). Most recently, Busser et al. (45) found abnormal ap-

**Fig. 5.** Overexpression of APP-BP1 in neurons causes apoptosis. A and B, immunoblots demonstrating expression in neurons of the HSV vectors used in the experiments shown in this figure. Note that the BP339 antibody detects a relatively high level of endogenous expression of APP-BP1 in neurons, in addition to the expression of the transgenes. The upper band detected by the 12CA5 antibody in panel B is nonspecific. HSV/LacZ, expressing *E. coli* β-galactosidase, was used as the negative control in these experiments. C, quantification of apoptotic nuclei in primary neuronal cultures infected with HSV vectors expressing APP-BP1, the hUba3-binding fragment of APP-BP1 (443–479), or the deletion mutant of APP-BP1, d401–479. 12 h after infection, fixed cells were stained with bisbenzimide to identify condensed nuclei. The d401–479 mutant of APP-BP1, which does not bind to hUba3, does not cause significant apoptosis (*p* < 0.01; Scheffe post hoc t test). Co-expression of the hUba3-binding domain of APP-BP1 with APP-BP1 inhibits the ability of APP-BP1 to cause neuronal apoptosis (*p* < 0.01; Scheffe post hoc t test).

**Fig. 6.** Dominant negative mutants of hUba3 and hUbc12, and a caspase-6 inhibitor, inhibit the ability of APP-BP1 to cause neuronal apoptosis. A, immunoblots showing expression in neurons of the hUba3 and hUbc12 HSV vectors used in the experiments shown in this figure. B and C, quantification of apoptotic nuclei in primary neuronal cultures infected with HSV vectors expressing APP-BP1 and a dominant negative mutant of hUba3 or hUbc12, respectively. Both dominant negative mutants interfere with the ability of APP-BP1 to cause neuronal apoptosis (HA-hUba3/APP-BP1 versus HA-C216S/APP-BP1, or HA-hUbc12/APP-BP1 versus HA-C111S/APP-BP1, *p* < 0.01, Scheffe post hoc t test). D, quantification of apoptotic nuclei in neurons infected with HSV vectors in the presence of caspase inhibitors (50 μM). The broad spectrum inhibitor Boc-ε-FMK and the specific caspase-6 inhibitor VEID both inhibit the ability of APP-BP1 to cause neuronal apoptosis. APP-BP1/Me2SO sample is significantly different from all other samples (*p* < 0.01, Scheffe post hoc t test).
pearance of cell cycle markers in regions of AD brain where cell death is extensive, and Chow et al. (46) found increases in expression of genes encoding cell cycle proteins in single neurons in late stage relative to early stage AD brain. The phosphopeptide Ser-214 of the microtubule associated protein tau, that appears in the neurofibrillary tangles in AD, is a prominent phosphorsylation site in metaphase but not in interphase of dividing cells expressing tau (47), supporting the view that reactivation of the cell cycle machinery may be involved in tau hyperphosphorylation in AD brain. The possibility that phosphorylation-dependent events occurring during the cell cycle affect the normal function of APP is suggested by the finding that regulation of the phosphorylation and metabolism of this protein occurs in a cell-cycle dependent manner (48, 49). We hypothesize that dysfunction of pathways mediated by APP may be one cause of the reactivation of cell cycle proteins in AD brain. In particular, APP interaction with APP-BP1 may be abnormal in the disease. In this regard, it will be of interest to determine whether NEDD8 activation is disrupted in AD.

Acknowledgments—We thank Drs. Nienwen Chow and Robert Coopersmith for helpful discussions and valuable assistance and Drs. David Thomas and Dina Gould for kind assistance with the FACScan analysis.

REFERENCES

1. Kang, J., Lemaire, H.-G., Unterbeck, A., Salbaum, J. M., Masters, C. L., Greeshchik, K.-H., Beyreuther, K., and Muller-Hill, B. (1987) Nature 325, 733–736
2. Jung, S. S., Nalbantoglu, J., and Cashman, N. R. (1996) J. Neurosci. Res. 46, 336–348
3. Storey, E., Spurck, T., Pickett-Heaps, J., Beyreuther, K., and Masters, C. L. (1996) Brain Res. 735, 59–66
4. Perez, R. G., Zheng, H., Van der Ploeg, L. H. T., and Koo, E. H. (1997) J. Neurolsci. 17, 9407–9414
5. Qiu, W. Q., Ferreira, A., Miller, C., Koo, E. H., and Selkoe, D. J. (1995) J. Neurosci. 15, 2157–2167
6. Yamaazaki, T., Koo, E. H., and Selkoe, D. J. (1997) J. Neurosci. 17, 1004–1010
7. Marquez-Stirling, N. R., Lo, A. C. Y., Sisodia, S. S., and Koo, E. H. (1997) J. Neurosci. 17, 140–151
8. Chow, N., Kerenberg, J. R., Chen, X.-N., and Neve, R. L. (1996) J. Biol. Chem. 271, 11339–11346
9. Haas, A. L., and Siegmann, T. J. (1997) FASEB J. 11, 1257–1268
10. Johnson, P. R., and Hochstrasser, M. (1997) Trends Cell Biol. 7, 408–413
11. Liakopoulos, D., Doenges, G., Matuschewski, K., and Jentsch, S. (1996) EMBO J. 17, 2209–2214
12. Hochstrasser, M. (1998) Genes Dev. 12, 901–907
13. Lammer, D., Mathias, N., Lalapla, J. M., Wang, J., Liu, Y., Callies, J., Goebl, M., and Estelle, M. (1998) Genes Dev. 12, 914–926
14. Kumar, S., Yoshida, Y., and Noda, M. (1993) Biochem. Biophys. Res. Commun. 205, 337–399
15. Osaka, F., Kawasaki, H., Aida, N., Saeki, M., Chiba, T., Kawashima, S., Tanaka, K., and Kato, S. (1998) Genes Dev. 12, 2263–2268
16. Gong, L., and Yeh, E. T. H. (1999) J. Biol. Chem. 274, 12036–12042
17. Liakopoulos, D., Busgen, T., Brychzy, A., Jentsch, S., and Pause, A. (1999) Nat. Neurosci. 2, 325–336
18. Freed, E., Lacey, K. R., Huie, P., Koo, E. H., and Selkoe, D. J. (1996) Proc. Natl. Acad. Sci. U.S.A. 93, 5705–5709
19. Liakopoulos, D., Doenges, G., Matuschewski, K., and Jentsch, S. (1998) Trends Biochem. Sci. 23, 271–277
The Amyloid Precursor Protein-binding Protein APP-BP1 Drives the Cell Cycle through the S-M Checkpoint and Causes Apoptosis in Neurons
Yuzhi Chen, Donna L. McPhie, Joseph Hirschberg and Rachael L. Neve

J. Biol. Chem. 2000, 275:8929-8935.
doi: 10.1074/jbc.275.12.8929

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