Asb6, an Adipocyte-specific Ankyrin and SOCS Box Protein, Interacts with APS to Enable Recruitment of Elongins B and C to the Insulin Receptor Signaling Complex* ♦

Received for publication, June 2, 2004, and in revised form, June 22, 2004
Published, JBC Papers in Press, July 1, 2004, DOI 10.1074/jbc.M406101200

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EXPERIMENTAL PROCEDURES

* This work was supported by project grants from Diabetes UK and Novo Nordisk. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† This article was selected as a Paper of the Week.

The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EBI Data Bank with accession number(s) AY665653 (for the Asb6 sequence).

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Insulin promotes glucose transport into target tissues by causing the exocytosis of the glucose transporter GLUT4 from intracellular vesicles to the plasma membrane (1). There are thought to be two pathways required for insulin-stimulated glucose transport: an insulin receptor substrate-PI3-kinase-dependent pathway and a PI3-kinase-independent pathway involving APS, CAP, and c-Cbl. The PI3-kinase-independent pathway is initiated by the binding of APS to the activation loop of the insulin receptor (2, 3). APS is constitutively bound to CAP and undergoes tyrosine phosphorylation on Tyr618 allowing it to bind to the variant SH2 domain of c-Cbl (3, 4). This is followed by the tyrosine phosphorylation of c-Cbl on tyrosines 700 and 774 resulting in the phosphorylated c-Cbl binding to the SH2 domain of Crk (3, 5). Following the insulin-stimulated phosphorylation of c-Cbl, the CAP/Cbl complex migrates to the caveolin-rich lipid rafts, a movement facilitated by the interaction of the CAP SOHO domain with flotillin, a protein in lipid rafts (6). This allows the Crk/C3G complex to be recruited to this microdomain, where C3G activates the small G protein TC10 (7–10). The activation of TC10 occurs independently of PI3-kinase and is crucial for insulin-stimulated Glut4 translocation (1).

The domain structure of APS includes proline-rich regions and a number of candidate tyrosine, serine, and threonine phosphorylation sites (11, 12), implying that APS has the potential to generate a repertoire of novel protein-protein interactions involved in insulin-stimulated signal transduction pathways. We initiated a search for such proteins using the yeast two hybrid system and identified a member of the Asb family that is specifically expressed in adipocytes.

EXPERIMENTAL PROCEDURES

Anti-APS antibody (goat), Anti-GAL4 DNA-BD antibody (mouse), and anti-Elongin B and C were purchased from Santa Cruz Biotechnol (Santa Cruz, CA). Anti-FLAG-M2-horseradish peroxidase antibody, anti-Myc antibodies and Et-3,4 dephostatin were purchased from Sigma. Peroxidase conjugates of anti-goat and anti-mouse antibodies were purchased from Sigma (Dorset, UK). Alexa-Fluor 488 donkey anti-rabbit IgG (green) and Alexa-Fluor 594 donkey antigoat IgG 2 mg/ml (red) were purchased from Molecular probes. The 3T3-L1 adipocyte library was kindly provided by Dr. Alan Saltiel (Life Sciences Institute, Ann Arbor, MI).

Yeast Two-hybrid Screening—The Matchmaker GAL4 Two-Hybrid System 3 (Clontech) was used to identify APS interacting proteins. Full-length APS was fused to the C-terminal of the GAL4 DNA binding domain in the pGBK7T7 vector to generate the bait plasmid pGBK(APS). Standard yeast two-hybrid procedures were used to transform Saccharomyces cerevisiae strain AH109 initially with the pGBK(APS) bait, followed by transformation with a 3T3-L1 adipocyte library in

1 The abbreviations used are: PI, phosphatidylinositol; SH, Src homology; APS, adapter protein with a pleckstrin homology and SH2 domain; CAP, c-Cbl-associated protein (Ponsin); CHO, Chinese hamster ovary; SOCS, suppressor of cytokine signaling; Asb, ankyrin and SOCS box; aa, amino acids; GST, glutathione S-transferase; Ank, ankyrin; VHL, von Hippel-Lindau.
FIG. 1. Nucleotide sequence and deduced amino acid sequence of Asb6 showing the domain structure with ankyrin repeats and SOCS box. The ankyrin repeats are shaded. The SOCS box is shown underlined with the consensus BC box marked with shaded circles. Potential serine and threonine phosphorylation sites identified by NetPhos are shown with an X.
and amino acid sequences were compared with submitted sequences in a plasmid library. The library plasmids were sequenced, and nucleotide XL10Gold (Stratagene) under ampicillin selection to select for the lissence.

rabbit polyclonal anti-Asb6 antibody.

performed on the His H11001-galactosidase reporter gene. Library plasmids were rescued from the pGAD-GH vector (kindly provided by Alan Saltiel, Life Sciences Institute). The resulting transformants were plated on selective medium °(3-amino-1,2,4-triazole) and incubated at 30 °C until colonies formed. The library plasmids were purified according to standard procedures as described previously. Briefly, DH5a E. coli strain XL10Gold were transformed with the GST construct and grown overnight at 37 °C; the next day the culture was diluted 1:10 in LB broth and further grown at 37 °C until A900nm, was 0.6. GST protein expression was induced by 0.1 mM isopropyl-1-thio-β-D-galactopyranoside for 2 h and the bacterial pellet lysed by sonication in phosphate-buffered saline, 0.1% Triton X-100 containing fresh protease inhibitor mixture (Roche Applied Science), 1 mM phenylmethyl-sulfonyl fluoride, and 0.2 mg/ml lysozyme. After centrifugation, the cleared lysate was incubated with glutathione-agarose beads at 4 °C overnight with gentle rotation. After washing the beads three times with phosphate-buffered saline, 0.1% Triton X-100 the purified fusion proteins were quantified by Coomassie Blue staining after SDS-PAGE analysis. For the in vitro interaction assay, cell lysate from CHO.T-APS cells (4) were incubated with immobilized GST fusion proteins overnight at 4 °C. After extensive washing, bound proteins were eluted by heating in 30 μl of 1× Laemmli sample buffer, separated on a polyacrylamide gel, and analyzed by immuno blotting.

Generation of Asb6 Antibody—Purified GST-Asb6 protein was prepared as described above, dissolved in 1× Laemmli sample buffer, electroforetosed, and a slice excised from the gel at 70 kDa. The gel slice was dried and used to generate antisera in two rabbits by Eurogentec (Herstal, Belgium). The resulting antisera was tested on 373-L1 adipocyte lysate separated on a SDS-PAGE with non-immune sera as a negative control.

Immunofluorescent Staining—Immunofluorescence and confocal imaging of Asb6 and APS in CHO cells or 373-L1 adipocytes were performed as described previously (2) using goat anti-APS (Santa Cruz Biotechnology) or rabbit anti-Asb6 and Alexa-Fluor 594 donkey-anti-goat and Alexa-Fluor 488 anti-rabbit (heavy and light chains).

RESULTS

Yeast Two-hybrid Screening Identifies Asb6 as an Interactor—One of the clones identified in the yeast two-hybrid screen contained the complete coding sequence of an ankyrin and suppressor of cytokine signaling (SOCS) box protein Asb6, in frame with the GAL4 DNA binding domain (Fig. 1). The predicted amino acid sequence of Asb6 shows that it is a 418-amino acid-long peptide consisting of a novel N-terminal region, followed by a series of six ankyrin repeats (aa 65–286) and a C-terminal SOCS box (aa 358–413). The SOCS box contains the BC box consensus sequence. The predicted size of Asb6 is ~46.2 kDa, but on SDS gels, the protein displays a molecular mass of 50 kDa possibly as a result of phosphorylation. There are a number of consensus serine/threonine phosphorylation sites predicted by NetPhos (13).

Asb6 Is Specifically Expressed in Adipocytes—In a previous study by Kile et al. (14), the expression of a number of different Asb family members was examined by Northern blotting. Interestingly, there was no detectable Asb6 expression in all the tissues examined in the Northern blot suggesting that it has a highly restricted expression. Consistent with this, we could not

FIG. 2. Expression of Asb6 in adipocytes. a, whole cell lysates from CHO cells co-expressing insulin receptor, APS and Asb6, and 373-L1 adipocytes were subjected to electrophoresis and immunoblotting with a rabbit polyclonal anti-Asb6 antibody and visualized using chemiluminescence. b, human adipose tissue lysates obtained from needle biopsies were analyzed by electrophoresis and immunoblotting with the same rabbit polyclonal anti-Asb6 antibody.
detect it in CHO cells or 3T3-L1 fibroblasts, but it was readily
detectable using a specific anti-Asb6 antibody in transfected
cells, 3T3-L1 adipocytes, and human adipose tissue biopsies
(Fig. 2).

**APS and Asb6 Interact in Transfected Cells**—We analyzed
the interaction of APS and Asb6 in intact cells using ectopic
expression in CHO.T cells (Fig. 3a). Asb6 was tagged with the
FLAG epitope and stably transfected into CHO cells stably
expressing insulin receptor and APS (CHO.T-APS cells) (2, 4).
Asb6 was then immunoprecipitated using anti-FLAG-agarose,
and the immunoprecipitates were blotted with anti-APS anti-
body. The results reveal that these proteins were constitutively
bound in transfected cells, and insulin stimulation did not alter
the interaction. Although a number of tyrosine-phosphorylated
bands were observed in the immunoprecipitates (Fig. 3a,
third panel), these did not change with insulin, and Asb6 did not
appear to undergo tyrosine phosphorylation. The SOCS box is
known to function to bind Elongins B and C. We tested for the
presence of Elongin C in the anti-FLAG immunoprecipitates
and found that Elongin C was readily detectable in the im-
munoprecipitates of transfected CHO cells expressing Asb6
(Fig. 3a).
**ASB6 and APS Interact in Adipocytes and Elongins B and C Are recruited**—In 3T3-L1 adipocytes, we used a rabbit anti-Asb6 antibody to study the interaction, since the endogenous protein was not tagged. The specificity of the antibody was tested both for immunoblotting and immunoprecipitation in adipocytes (Fig. 3b, upper panel) and CHO.T-APS-Asb6 cells (Fig. 3b, lower panel). Next, the insulin receptor was activated using dephostatin (15), and the insulin receptor was isolated using insulin-agarose to enhance the efficiency of precipitation, since many insulin receptor monoclonals do not bind to mouse receptors with high affinity. Furthermore, this was done to minimize the potential of IgG cross-reaction, since Asb6 co-migrates with the immunoglobulin heavy chain at 50 kDa. As shown in Fig. 3c, activation of the insulin receptor, demonstrated by antiphosphotyrosine immunoblotting, was accompanied by recruitment of APS and Asb6. In addition, Elongins B and C could be detected in the immunoprecipitates after insulin receptor activation.

**APS and Asb6 Co-localize in Cells**—Using immunofluorescence and confocal imaging, we analyzed the cellular distribution of APS and Asb6 in transfected CHO cells and 3T3-L1 adipocytes. In CHO cells, APS and Asb6 were labeled using antiFLAG and antiMyc antibodies. Fig. 4). In 3T3-L1 adipocytes, endogenous APS and Asb6 were visualized using goat anti-FLAG and anti-rabbit anti-Asb6 (Fig. 5). In both cell types, co-localization of APS and Asb6 was observed when the immunofluorescent images were merged.

**Mapping the Regions of APS and Asb6 That Interact**—The regions of APS and Asb6 that interact were mapped using pull-downs with wild-type and deletion mutants of GST fusion proteins. To establish the region of Asb6 that mediates the binding to APS a series of deletions of the GST-Asb6 constructs were made and purified. The series of immobilized GST-Asb6 deletions were used for GST “pull-downs” of APS derived from CHO.T-APS cells (Fig. 6), with GST alone used as a negative control. The panel shows that APS is precipitated by the full-length Asb6, Asb6(aa 1–275) and Asb6(aa 123–418), and to a lesser extent to Asb6(aa 69–418) and Asb6(aa 269–418), with no APS binding to Asb6(aa 1–82) and Asb6(aa 1–133) detected. Similar levels of GST-Asb6 fusion protein deletions and negative GST control were used for the pull-down. These results indicated that the region of Asb6 primarily responsible for binding to APS lies between amino acids 123 and 275.

Similarly, regions of APS were expressed as GST fusions, and the purified fusion proteins were incubated with cell lysates derived from CHO.T-Asb6 cells in a “pull-down assay” (Fig. 7). The precipitates were then probed by immunoblotting with anti-FLAG antibody. The region of APS that interacts with Asb6 is contained in amino acids 117–466.

**Asb6 Undergoes Insulin-stimulated Degradation along with APS**—Since Asb6 contains a SOCS box that binds to Elongins, it is likely that the recruitment of Asb6 facilitates degradation of associated proteins. To test this hypothesis, we examined the effects of prolonged insulin stimulation on the degradation of Asb6 and APS in CHO cells (Fig. 8). Serum-starved CHO cells were stimulated with varying concentrations of insulin overnight and the lysates were analyzed for the levels of Asb6 and APS. Insulin caused a dose-dependent decrease in the levels of both Asb6 and APS.

**DISCUSSION**

In a search for novel interactors for the APS adapter protein expressed in adipose tissue, we screened a 3T3-L1 adipocyte library using the yeast two-hybrid system. One of the interactors we identified is the Asb6 protein (16). Asb6 is specifically expressed in 3T3-L1 adipocytes and human fat tissue but not in fibroblasts. In an analysis of Asb1 knock-out mice, Asb6 was not expressed in any of the tissues examined by Kile et al. (14), suggesting that it is highly selectively expressed. The interaction of Asb6 and APS was confirmed using several techniques including GST fusion protein pull-downs and co-precipitation in both transfected and native cells expressing endogenous levels of protein. Finally, co-localization studies with immunofluorescence and confocal microscopy in both overexpressing and CHO cells and 3T3-L1 adipocytes confirmed the cellular interaction of APS and Asb6. Since neither APS nor Asb6 are expressed in commonly used cultured cells, it was necessary to overexpress them in a heterologous expression system to analyze the interaction in detail.

Ankyrin repeats are found in more than 400 different proteins that contain from 2 to more than 20 tandemly arrayed repeat units. In each case where ankyrin repeat structures...
have been examined, they have been shown to comprise helix-turn-helix motifs linked together by loops. There is evidence that the loops are sites for protein-protein interactions for which ankyrin repeats provide a stable platform (17). SOCS boxes are 40 amino acids long and are found in five distinct families of proteins (16). The SOCS boxes bind to Elongins B and C, potentially acting as an adaptor to couple proteins to the ubiquitination or proteasomal compartments (18, 19). There have been studies into Asb1 knock-out mice that showed an increase in testicular anomalies; mice that overexpressed full-length and truncated forms of Asb1 all showed normal development, indicating some sort of redundancy between protein family members (14).

The amino acid structure of Asb6 predicts a 418-residue peptide, made up of a novel N-terminal region, followed by a series of six ankyrin (Ank) repeats (aa 31–256) and a C-terminal SOCS box (aa 358–413) domain. By using deletions of GST-Asb6 fusion proteins the region of Asb6 involved in the interaction with APS lies within the C-terminal region of the Ank repeat region (aa 123–275). This is consistent with the proposed role of Ank repeats being involved as a stable platform for protein-protein interactions (17). The SOCS box was first identified in the protein SOCS-1 (20), and it was demonstrated that overexpression of SOCS-1 inhibited both interleukin-6-induced receptor phosphorylation and STAT activation. The SOCS family of proteins consist of variable N-terminal regions, followed by a central SH2 domain and a C-terminal SOCS box. The other members of the family that possess a SOCS box differ from the SOCS family proteins in the domains upstream of this motif and have been characterized accordingly. In place of the SH2 domains the Asb proteins contain ankyrin repeats, the WD-40 SOCS boxes contain WD-40 repeats, the SPRY SOCS boxes contain SPRY domains, and the Ras-like proteins contain GTPase domains. It has been demonstrated that the SOCS box associates with Elongins B and C (18, 19). The region within the SOCS box responsible for binding Asb6 proteins contain ankyrin repeats, the WD-40 SOCS boxes contain WD-40 repeats, the SPRY SOCS boxes contain SPRY domains, and the Ras-like proteins contain GTPase domains. It has been demonstrated that the SOCS box associates with Elongins B and C (18, 19). The region within the SOCS box responsible for binding Asb6 proteins.
Interaction of Asb6 with APS

Fig. 8. Expression of Asb6 facilitates the insulin-stimulated degradation of APS. CHO.T APS cells and CHO.T-APS-Asb6 cells were stimulated with varying concentrations of insulin (0–100 ng/ml) for 16 h. The cells were then lysed, and the lysates were analyzed by electrophoresis and immunoblotting with anti-phosphotyrosine RC20, anti-FLAG antibody (to detect Asb6), anti-APS antibody, and actin as a loading control.

Fig. 9. A schematic summary of the bimodal role of APS in insulin signaling. APS can act as a positive mediator by recruiting CAP and c-Cbl and as a modulator by recruiting ASB6 and the Elongin BC complex to facilitate degradation.

It is interesting to note that the APS knock-out mice (34) later that this is due to loss of the negative regulatory function of Asb6 associated with APS.

In summary (Fig. 9), we have identified the ankyrin and SOCs box protein Asb6, along with the Elongin BC complex, as a component of the insulin receptor signaling complex recruited by the APS adapter protein in 3T3-L1 adipocytes and ectopically transfected CHO cells. We have satisfied the criteria for a bona fide interaction using co-precipitation and co-localization in both transfected and untransfected native cells. We have also demonstrated a functional consequence of the interaction that is likely to be of physiological relevance. Furthermore, we have identified a function for an orphan member of the A2b family, which has hitherto not been suspected. Previously we and others (2, 3, 35) have shown that APS plays a positive role in insulin signaling. The identification of a SOCs box protein recruited by APS would suggest that APS may also play a negative role in regulating signal transduction by enabling the recruitment of Asb6 and the Elongins.

Acknowledgments—We are especially grateful to Dr. Alan Saltiel for generously providing the 3T3-L1 adipocyte library. We thank Tim Self for assistance with the confocal microscopy.

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*J. Biol. Chem.* 2004, 279:38881-38888.
doi: 10.1074/jbc.M406101200 originally published online July 1, 2004

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