Apoprotein B100, an Inefficiently Translocated Secretory Protein, Is Bound to the Cytosolic Chaperone, Heat Shock Protein 70*

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Apoprotein B100 (apoB) is a secretary protein that appears to be constitutively translated but inefficiently translocated into the lumen of the endoplasmic reticulum. Using several experimental approaches, we found that apoB is bound to the cytosolic chaperone protein, heat shock protein 72/73 (commonly referred to as Hsp70). Similar to other chaperone-protein interactions, this binding was transient and ATP-sensitive. The binding of apoB to Hsp70 in HepG2 cells was decreased by treatment with oleic acid, which increases both translocation and secretion of apoB, and was increased by N-acetyl-leucyl-leucyl-norleucinal, a protease inhibitor which efficiently protects apoB from cellular degradation without affecting translocation. The N-terminal 16% of apoB, which is efficiently translocated into the endoplasmic reticulum lumen in stably transfected Chinese hamster ovary (CHO) cells, showed minimal, if any, binding to Hsp70. The N-terminal 50% of apoB, which is very poorly translocated in CHO cells, was found to bind significantly to Hsp70. These results suggest that domains of nascent apoB localized on the C-terminal regions of the molecule are transiently exposed to the cytosol during translation and/or translocation, and that Hsp70 functions as a molecular chaperone to maintain apoB in a translational competent conformation until translocation is completed.

Apoprotein B100 (apoB) is a very large (540 kDa), extremely hydrophobic protein that is necessary for the assembly and secretion of lipoproteins carrying the majority of plasma cholesterol and triglyceride in man. Evidence from several laboratories indicates that apoB secretion is regulated post-translationally, rather than at the transcriptional or translational level (1). The key step in this post-translational regulation appears to be the translocation of newly synthesized apoB across the endoplasmic reticulum (ER) membrane; this step has been shown by most laboratories to be inefficient and slow. Thus, unlike albumin, which is efficiently translocated into the ER and quantitatively secreted into the medium, only a fraction of nascent apoB is assembled with lipids and secreted as very low density lipoprotein. Instead, the majority of newly synthesized apoB is degraded intracellularly. Inefficient translocation allows some portion of apoB to be exposed to the cytosol for a significant period of time (2–6), and this appears to render nascent apoB susceptible to degradation by a cysteine protease (7). An unaddressed issue related to the translocation of apoB is how this hydrophobic molecule is able to retain its native conformation during the period when it is, at least partly, exposed to the cytosol.

Recent studies indicate that many newly synthesized proteins transiently interact with molecular chaperones during their folding, maturation, and transmembrane targeting (8, 9). One class of these molecular chaperones is the 70-kDa heat shock protein family. Evidence indicates that both the constitutively expressed Hsp73 and the highly stress-inducible Hsp72 (subsequently referred to jointly as Hsp70) are cytoplasmic molecular chaperones which can target to the hydrophobic domains of substrate polypeptides. They not only assist various cytosolic proteins as they mature into their final conformation (10), but also participate in post-translational transmembrane targeting of proteins to cellular organelles (11, 12). For example, genetic manipulation in yeast showed that depletion of cytosolic Hsp70 protein in vivo caused the accumulation of presecretory proteins in the cytosol (13). In vitro studies indicated that Hsp70 could stimulate protein translocation into microsomes (14, 15). It is believed that Hsp70 participates in maintaining the translocation competence of proteins that are post-translationally targeted for transport across organelle membranes. Hsp70 also appears to participate in the insertion into the ER of transmembrane proteins destined for transport to the plasma membrane (15). A role for Hsp70 in the translocation of mammalian secretory proteins is still defined at present; it is commonly believed that the transport of such proteins into the ER occurs co-translationally through a pathway involving signal sequences, signal recognition particles and docking proteins (16, 17). Whether Hsp70 interacts with any secretory protein in mammalian cells in vivo is still unknown. In this study, we demonstrate that nascent apoB is associated with cytosolic Hsp70 in HepG2 cells, and that this association is related to apoB translational status. This may be how apoB, a hydrophobic protein, is able to maintain its translational competence while exposed to the aqueous environment of the cytosol.

EXPERIMENTAL PROCEDURES

Growth of Cells and Radiolabeling of Proteins—All tissue culture supplies, chemicals, and radioactive chemicals were obtained from suppliers as described previously (7) or as indicated below. The HepG2 cell culture conditions were maintained as described previously (7). Monolayer cultures of HepG2 cells (90% confluent) were preincubated with

1 The abbreviations used are: apoB, apolipoprotein B100; Hsp70, heat shock protein 70; ER, endoplasmic reticulum; PAGE, polyacrylamide gel electrophoresis; ALLN, N-acetyl-leucyl-leucyl-norleucinal; CHO, Chinese hamster ovary; BSA, bovine serum albumin; PBS, phosphate-buffered saline; MEM, minimal essential medium; LDL, low density lipoprotein, ATP-5'-adensine 5'-O-(thiotriphosphate); MTP, microsomal triglyceride transfer protein.

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Serum-free minimum essential medium (MEM) containing 1.5% bovine serum albumin (BSA) for 60 min followed by starving with serum-free, leucine-free MEM for 15 min at 37°C. The cells were treated and radiolabeled with \[^{3}H\]leucine (200 \(\mu\)Ci/ml) in leucine-free medium according to the protocols described in the legends to the figures. A plasmid encoding 16% of the N terminus of human apoB cDNA (−10 to +2282) was derived from clone pB274 (18) with insertion of a stop signal (TAA) following amino acid 671. The plasmid encoding 50% of the N terminus of human apoB cDNA was constructed as described previously (18). The expression of truncated apoB proteins in both constructions was driven under the promoter derived from cytomegalovirus. Stable transfection of Chinese hamster ovary (CHO) cells were carried out with using published methods (19). These cell lines were grown in MEM containing 5% fetal bovine serum and 300 \(\mu\)M of G418 until 90% confluent before experiments were performed.

**Immunoprecipitation**—Radiolabeled cell monolayers were washed with ice-cold phosphate-buffered saline (PBS), placed on ice, lysed, and immunoprecipitated at 4°C under either non-denaturing or denaturing conditions (8, 20). For non-denaturing immunoprecipitations, radiolabeled cells were pretreated by the addition of PBS containing 0.1% Triton X-100, 50 units/ml arylase (Sigma, grade VIII), and protease inhibitors (phenylmethylsulfonyl fluoride (2 mm), ALLN (2 \(\mu\)g/ml), leupeptin (5 \(\mu\)g/ml), and pepstatin (5 \(\mu\)g/ml)). After a 15-min incubation at 4°C, the cells were lysed by adjusting the buffer to 1% Triton X-100, 1% sodium deoxycholate, and 0.1% SDS in PBS. They were then incubated for another 30 min at 4°C. The lysates were clarified by centrifugation (5 min, 14,000 \(\times\) g), and the supernatants were used for immunoprecipitation (4°C, 2.5 h). A mouse monoconal anti-human Hsp72/73 antibody was purchased from Boehringer Mannheim. The immunoprecipitates were collected with protein A-Sepharose 4B (4°C, 1.5 h) and analyzed on SDS-PAGE gradient gels followed by fluorography. Molecular mass markers mixed with human LDL (as a source of apoB) were run in the end lane of the gel and stained with Coomassie Blue. The fluorograph indicates that non-denaturing immunoprecipitation with anti-Hsp70 resulted in coprecipitation of Hsp70 and a protein of molecular mass similar to that of apoB. Sequential immunoprecipitation with either premature mouse serum IgG as a control or anti-Hsp70 antibody under denaturing conditions, PBS containing 2% SDS was added to the immunocomplexes, and the mixture was boiled for 5 min. The supernatants were diluted with 1% Triton X-100 to a final concentration of 0.1% SDS and used for a second immunoprecipitation with anti-apoB antibody. In these sequential immunoprecipitations, anti-apoB antibody precipitated apoB from the complex that was first precipitated with anti-Hsp70 antibody but not from the complex that was initially precipitated with mouse IgG (lane 1).

**RESULTS AND DISCUSSION**

**Nascent ApoB Is Associated with Hsp70 in HepG2 Cells**—We examined the interaction between Hsp70 and apoB in HepG2 cells, a human hepatoma cell line, using immunoprecipitation and immunoblotting techniques. HepG2 cells were radiolabeled for 30 min. Since ongoing ATP binding induces Hsp70 conformational changes that lead to dissociation of Hsp70 from bound proteins, we added apyrase, an ATP-hydrolyzing enzyme, to exhaust endogenous ATP before lysing the cells (8).

When these lysates were subjected to immunoprecipitation with a mouse monoclonal antibody against human Hsp70 under non-denaturing conditions, followed by resolubilization on SDS-PAGE and autoradiography, we observed a number of proteins which coimmunoprecipitated with Hsp70 (Fig. 1A, lane 2). In contrast, only a single, non-specific band was immunoprecipitated when premature mouse IgG was used as a control (Fig. 1A, lane 1). One of the bands in lane 2 migrated at the position of Hsp70 when the latter protein was uniquely immunoprecipitated under denaturing conditions (Fig. 1A, lane 3). Another band in lane 2 migrated in the position of apoB when the latter was uniquely immunoprecipitated by an anti-human apoB polyclonal antibody under denaturing conditions (Fig. 1A, lane 4). This large molecular weight protein in lane 2 also migrated in the position of human low density lipoprotein (LDL), which was added to the molecular mass markers and stained with Coomassie Blue (noted to the left of the fluorograph). ApoB is essentially the only protein in LDL.

To confirm the coimmunoprecipitation of Hsp70 and apoB, the immunocomplexes from the first non-denaturing precipitations with either anti-Hsp70 or preimmune mouse IgG (control) were subjected to a second (sequential) immunoprecipitation with anti-apoB antibody under denaturing conditions (20). ApoB was isolated from the anti-Hsp70/anti-apoB sequential immunoprecipitate (Fig. 1B, lane 1) but not from the IgG/anti-apoB control precipitate (Fig. 1B, lane 1). If the labeled cells were chased for 3 h, we observed much less coimmunoprecipitation of newly synthesized, radiolabeled apoB with Hsp70 (data not shown). These results indicated that newly synthesized apoB is transiently associated with Hsp70 in HepG2 cells.

Additional confirmation of the findings in labeled HepG2 cells was obtained using immunoblotting techniques. After subjecting anti-Hsp70 immunoprecipitates obtained under non-denaturing conditions to immunoblot analysis using anti-apoB antibody as the probe, we could demonstrate the presence of apoB (Fig. 2A, lane 4). Similarly, if we subjected anti-apoB immunoprecipitates obtained under non-denaturing conditions to immunoblotting with anti-Hsp70 antibody as the probe, we could demonstrate a Hsp70 band (Fig. 2A, lane 4). This large molecular weight protein in lane 4 migrated in the position of LDL, which is added to the molecular mass markers and stained with Coomassie Blue (noted to the left of the fluorograph). ApoB is essentially the only protein in LDL.
A blocking, the membranes were probed with anti-apoB antibody. Whole 
SDS-PAGE and then transferred to a nitrocellulose membrane. After 
multiple mouse IgG (lane 1). The immunocomplexes were resolved with 
lane 4 were immunoprecipitated with anti-Hsp70 antibody (lane 4). B, when the same 
procedures were used, except that anti-apoB antibody was used for 
lane 4, immuno blotting, the results demonstrated that Hsp70 could be identified 
the complex immunoprecipitated by anti-apoB antibody under non-

anti-Hsp70 non-denaturing immunoprecipitate (Fig. 2C, lane 
This result not only demonstrated that Hsp70 does not bind 
to typical secretory proteins such as albumin, but also sug-
ggested that Hsp70 does not bind nonspecifically to apoB after 
cell lysis occurs. 

Association of Hsp70 with ApoB is ATP-sensitive—It is 
known that Hsp70 binds ATP at a site separate from the 
protein-binding region, that Hsp70 has ATPase activity, and 
that binding of ATP results in dissociation of Hsp70 from bound 
proteins (21). Therefore, we examined whether apoB binding to 
Hsp70 is affected by ATP availability. HepG2 cells were radio-
labeled, and pretreated either with apyrase, which would ex-
haust the available endogenous ATP, or Mg-ATP (Sigma), 
or with the nonhydrolyzable ATP analog, ATPγS (Sigma) be-
fore subjecting the cells to lysis. We then carried out sequential 
immunoprecipitation with anti-Hsp70 antibody under non-
denaturing conditions, followed by immunoprecipitation with 
anti-apoB antibody under denaturing conditions. We found that 
apyrase treatment resulted in increased coimmunoprecipi-
tation of Hsp70 with apoB compared to lysates from cells pre-
treated with exogenous Mg-ATP (Fig. 3A). Binding of apoB to 
Hsp70 in cells with added ATPγS, which does not affect Hsp70 
binding to proteins, was similar to that observed in the 
apyrase-treated cells. These results demonstrated that the 
association of Hsp70 and apoB is physiologically regulated by 
ATP availability. This is consistent with Hsp70 acting as a 
chaperone for nascent apoB. 

In all of the previous experiments, use of detergents raised 
the possibility that the association between apoB and Hsp70 
could have occurred during lysis, e.g., the association could have 
been artifactual. Therefore, we carried out additional experi-
ments in which cells incubated with either BSA or BSA plus 
ALLN (40 μg/ml) were treated with PBS containing 0.1% Tri-
ton X-100 and 5 mM MgCl2 for 15 min on ice with either (a) no 
adDITION, (b) apyrase alone (100 units/ml), or (c) Mg-ATP (2.5 
mM) followed by treatment with apyrase for an additional 15 min 
(15 min). All of the cells were then lysed, and sequential immu-
no precipitation was carried out as mentioned above. The results are 
presented as counts/min from aliquots of immunoprecipitates. The inset 
presents the fluorograph of separate aliquots of immunoprecipitates 
from the ALLN-treated cells. The results indicate that minimal binding 
of Hsp70 to apoB occurred under conditions (ATP/apyrase) where 
maximal artifactual binding was favored.
showed greater immunoprecipitation of apoB by anti-Hsp70 antibody; these results are consistent with the in vivo effects of apyrase on Hsp70 binding to cytosolic proteins (see Fig. 3A). Finally, in the cells exposed to 0.1% Triton X-100 and Mg-ATP, followed by exposure to apyrase, there was very little Hsp70-bound apoB, particularly in ALLN-treated cells which had much more apoB present. These results are incompatible with significant artificial association of apoB with Hsp70 during incubation in 0.1% Triton X-100-PBS, during cell lysis, or during immunoprecipitation. The results are, however, compatible with a physiologically regulated interaction of apoB and Hsp70 in vivo. The inset in Fig. 3B depicts the results of sequential immunoprecipitation with anti-Hsp70 followed by anti-apoB antibodies under each of the conditions in the ALLN-treated cells.

Differences in apoB Binding to Hsp70 Correspond to Alterations in ApoB Translocation Status—Studies in HepG2 cells suggest that triglyceride availability is a major factor in the post-translational regulation of apoB secretion (1). We have proposed that (a) lipid-facilitated translocation and proteolysis are distinct but competitive processes that post-translationally regulate apoB secretion from HepG2 cells and (b) translocation of newly synthesized apoB into the ER lumen makes it unavailable for proteolysis (7, 22). We investigated if the extent of apoB binding to Hsp70 would, therefore, be affected by either oleate treatment, which would facilitate translocation, or by ALLN treatment, which would inhibit proteolysis directly, but which would not increase the rate of translocation of nascent apoB (7). The results (Fig. 4) demonstrate that both oleate and ALLN treatments increased total cellular apoB to comparable levels. However, whereas oleate treatment modestly increased apoB secretion and reduced Hsp70-bound apoB (two outcomes consistent with increased translocation of apoB), ALLN treatment modestly increased apoB secretion but markedly increased Hsp70-bound apoB (two outcomes consistent with direct proteolysis of nascent apoB) (Fig. 4).

Hsp70-bound apoB (two outcomes consistent with direct protection of untranslocated apoB). Thus the differences in apoB binding to Hsp70 with oleate and ALLN treatments could not have been due simply to differences in cell total apoB content, but seemed to result from differences in the location of apoB within the cells during the two treatment protocols. These data suggest that, in the oleate-treated cells, the majority of the newly synthesized apoB does not bind to cytosolic Hsp70, probably because most of apoB molecules are efficiently translocated across the ER membrane into the secretory pathway. In the presence of ALLN (without oleate), however, translocation may not change significantly even though proteolysis is inhibited. In this case, the newly synthesized apoB molecules accumulate in a partially translocated position, with increased numbers of molecules partially exposed to the cytosol, leading to increased binding to Hsp70. A recent report by Yang et al. (23) demonstrated increased Hsp70 binding to a mutant cystic fibrosis transmembrane conductance regulator that was mislocalized to the ER; the mutant protein accumulated in the ER membrane and was associated with Hsp70 much more than was the wild-type protein.

Hsp70 Binds to ApoB50 but Not ApoB16—Previous studies of truncated forms of apoB transfected into CHO fibroblasts have shown that apoB15, the N-terminal 15% of apoB, is able to cotranslationally translocate across the ER membrane prior to secretion into medium (24). In contrast, apoB53, a much longer N-terminal portion of apoB, translocates very inefficiently across the ER membrane and remains exposed on the cytoplasmic side (24). We therefore examined the binding of Hsp70 to two apoB truncations, apoB16 and apoB50, in stably transfected CHO cells. Although a strong apoB16 signal could be detected after immunoprecipitation of non-denatured lysates of CHO apoB16 cells with anti-apoB antibody, no Hsp70 band could be seen (Fig. 5A, lane 1). When anti-Hsp70 antibody was used to immunoprecipitate non-denatured lysates from CHO apoB16 cells, only Hsp70 was precipitated; there was no apoB16 co-immunoprecipitation (Fig. 5A, lane 2). These results were further confirmed by immunoblot analysis (data not shown).
shown). In contrast, immunoprecipitation of non-detergent lysates of CHO apoB50 cells with anti-Hsp70 revealed both a major band of Hsp70 and a band corresponding to apoB50 (Fig. 5B, lane 2). We confirmed that this band was apoB50 by Western blotting (data not shown). Immunoprecipitation of the same lysates with anti-apoB antibodies produced an intense band of apoB50, as well as a band corresponding to Hsp70 (Fig. 5B, lane 1). These results indicated that the N-terminal 16% portion of apoB, which, like apoB15 (24), efficiently translocates across the ER membrane, associates minimally, if at all, with Hsp70. However, apoB50, whose translocation across the ER is markedly delayed and very inefficient (24), associates significantly with Hsp70.

We believe that this is the first demonstration of an association between Hsp70 and a secretory protein in a mammalian cell. Since Hsp70 is present in the cell cytoplasm under normal conditions and is not found within the lumen of the ER (25), our results indicate that domains other than the N-terminal 16% of newly synthesized apoB must be exposed, at least transiently, to the cytosol (2–6, 24). The exposure of hydrophobic domains in apoB to the aqueous cytosol would trigger transient associations with Hsp70. Through such interactions, those hydrophobic domains would be shielded from the polar environment of cytosol, and the nascent apoB would be maintained in a translocation-competent conformation and protected from aggregation or misfolding until its translocation was completed.

The fact that apoB has a signal peptide and has no typical membrane spanning domains (26) suggests that it should be cotranslationally translocated by the signal recognition particle pathway (16, 17). Chuck and Lingappa (27, 28) have, however, suggested that apoB has sequences that cause it to pause during translocation. Several groups, including ours, have presented evidence, based on protease sensitivity or immunologic methods (2–6, 24), that apoB domains are exposed to the cytosolic surface of isolated microsomes or ER. There are other investigators (29, 30), however, who have reported contrasting findings using similar methods. We believe that our new data confirm and extend the previous studies that indicated that apoB is not fully translocated cotranslationally. Our finding of an association of Hsp70 with apoB is compatible with a pathway in which this very large, extremely hydrophobic secretory protein is maintained in a transmembrane position until adequate core lipid is available in the ER lumen to allow assembly of a nascent lipoprotein (1, 31). It is in this transmembrane position that apoB appears to be very sensitive to proteolysis; the association with Hsp70 may protect cytosolic domains of apoB from degradation. Since the association of Hsp70 with proteins appears to be an “on and off” phenomenon, dependent on its ATP/ADP state, the likelihood that apoB will be degraded could depend on the length of time that it remains exposed in a transmembrane position. Of note in this regard is the recent demonstration that the human disorder abetalipoproteinemia, in which apoB is synthesized normally but appears to be degraded rather than secreted, is associated with mutations in an ER protein, microsomal triglyceride transfer protein (MTP) (32–33). It is likely that MTP mediates the transfer of newly synthesized triglyceride from the ER membrane to a luminal domain of nascent apoB, a step that is necessary before translocation of apoB can be completed (34, 35). In the absence of normal MTP activity, apoB would remain in a transmembrane position and be degraded. It will be interesting to determine if Hsp70 also plays an active role in apoB translocation and intracellular degradation, and if apoB secretion from HepG2 cells can be affected by manipulation of Hsp70 levels.

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