Degradation of Newly Synthesized Apolipoprotein B-100 in a Pre-Golgi Compartment*

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The synthesis and secretion of apolipoprotein (apo) B-100 have been studied in a human hepatoblastoma cell line, the Hep G2 cells. Pulse-chase analysis showed that apoB-100 was not quantitatively recovered in the culture medium. To reveal the intracellular degradation of apoB-100 prior to secretion, cells were incubated with 1 μg/ml Brefeldin A (BFA) which impeded protein transport from the endoplasmic reticulum (ER) to the Golgi apparatus and the fate of apoB-100 remained intact. ApoB-100 degradation was temperature dependent, no degradation was observed below 20 °C. This degradation process was not inhibited by chloroquine, leupeptin, pepstatin, and chymostatin, suggesting that lysosomal proteases were not involved and that apoB-100 was degraded in a pre-Golgi compartment which is either part of, or closely related to, the ER. Preincubation of cells with low density lipoproteins (LDL) induced a 22-32% increase in the degradation of apoB-100. This result raised the possibility that secretion of apoB-100 might be regulated through the intracellular degradation of apoB-100. These results suggest the existence of the degradation pathway for apoB-100 in a pre-Golgi compartment and an unique regulatory mechanism for apoB-100 secretion.

Apolipoprotein B-100 is a major protein component of LDL and very low density lipoprotein of human plasma. It consists of 4536 amino acid residues and has been shown to be essential for the formation and secretion of these lipoproteins in the liver (1-3). It has been established that apoB-100 is synthesized on the rough ER and then transported from the ER, through the Golgi apparatus, to secretory vesicles. Immunochemical studies have indicated that the assembly of apoB-100-containing lipoproteins occurs at the border between the rough and smooth ER (4). Several studies support the hypothesis that apoB-100 is bound to the rough ER and Golgi apparatus membrane, and this association between apoB-100 and the membrane may be necessary for the addition of lipid components to the nascent lipoprotein particles (5-8). Furthermore, the findings reported by Janero and Lane (9) and Higgins (10) indicate that maturation of the lipoprotein particles occurs within the Golgi region. These results support the view that apoB-100-containing lipoproteins are assembled by the sequential association of their components in both the ER and the Golgi apparatus.

It is, however, as yet unclear how synthesis, intracellular transit and secretion of apoB-100 are regulated in the liver. Borchardt and Davis (11) have observed in pulse-chase experiments that a significant proportion of de novo synthesized apoB is lost from rat hepatocytes, but not recovered in the culture medium. Davis et al. (12) have recently shown that the degradation products of apoB were detectable in rough and smooth ER and suggested that the site of apoB degradation was ER. We also have been studying the regulation of synthesis and secretion of apoB-100 in Hep G2 cells (13) and found that a proportion of apoB-100 was degraded prior to secretion. In this study we used Brefeldin A (BFA) in order to further investigate the precise site of intracellular degradation of apoB-100 in Hep G2 cells. BFA strongly inhibits its protein transport from the ER to the Golgi apparatus (14-17). In these studies we examined the fate of apoB-100 retained in the ER. In addition we further investigated the possible roles of lysosomes and LDL in the intracellular degradation of apoB-100.

EXPERIMENTAL PROCEDURES

Materials—Tran-S-label (1251 Ci/mmol for Met) was purchased from ICN Radiochemicals. Goat anti-human apoB antiseraum and apoB antiserum, containing a specific antibody against apoB protein, were from Tago Inc. (Burlingame, CA). Sheep anti-human apoB antiseraum IgG was from The Binding Site Limited (Birmingham, United Kingdom). Protein A-Sepharose CL-4B was obtained from Pharmacia (Uppsala, Sweden). Dulbecco's modified Eagle's medium and modified Eagle's medium (Met- and Gln-free) were from Flow Laboratories, Inc. (Irvine, UK). Chloroquine and phenylmethylsulfonyl fluoride were obtained from Sigma. Leupeptin, pepstatin A and chymostatin, and antipain were purchased from Peptide Institute Inc. (Osaka, Japan).

Cell Culture—Stock cultures of Hep G2 were obtained from American Type Culture Collection. Cells were cultured as described previously (13). In all experiments, confluent cells were precultured in serum-free medium for 18 h prior to radiolabeling.

Pulse-chase Studies—Confluent Hep G2 cells, in 9-cm2 dishes, were precultured with serum-free medium at 37 °C for 18 h. The culture medium was removed and the cells were washed 3 times with phosphate buffer saline (PBS). The cells were incubated with Met-free modified Eagle's medium for 1 h and then pulsed for 15 min with 150 μCi of [35S]Met and chased for various periods. After each chase period, the culture medium was removed and centrifuged at 10,000 rpm for 5 min to pellet any cells dislodged from the dish. The attached cells were lysed by gently shaking in PBS containing 1% Triton X-100. The lysates were sonicated, centrifuged at 10,000 rpm for 5 min, and the supernatant was stored. To avoid proteolytic breakdown, protease inhibitors (2 μg/ml antipain, 5 μg/ml chymostatin, 5 μg/ml leupeptin, 2 μg/ml pepstatin) and EDTA disodium salt (1 mM) were added to all stored samples.

Pulse-chase Studies Using BFA—Confluent cells were precultured with serum-free medium for 18 h. The culture medium was...
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removed and the cells were washed 3 times with PBS. The cells were incubated with Met-free medium containing 1 μg/ml BFA for 1 h and then pulsed with 150 μCi of [35S]Met for 15 min. The culture medium for pulse and chase contained 1 μg/ml BFA.

Preparation of LDL—LDL was isolated from human serum by NaBr density gradient ultracentrifugation (20). The serum was adjusted to density = 1.21 g/ml with solid NaBr. A discontinuous NaBr gradient was formed by layering the NaBr solutions (density = 1.005, 1.015, and 1.068 g/ml) above the serum. Centrifugation was carried out at 25,000 rpm at 4 °C for 24 h (Hitachi RPS 27). The LDL fractions (density 1.019-1.063 g/ml) were pooled and the density of this fraction adjusted to 1.21 g/ml with NaBr. The second centrifugation was carried out at described above. The LDL fractions (density 1.030-1.063 g/ml) were dialyzed at 4 °C against PBS containing 0.04% EDTA and sterile-filtered through a 0.45-mm filter (Millipore Corp.). The LDL contained only apoB-100 as checked by SDS-PAGE. The ratios of total cholesterol and phospholipids to triglyceride content on a weight basis were 4.4:1:7.1:1, respectively.

Pulse-chase Studies on the Effect of Certain Agents on the Degradation of ApoB-100—Confluent cells were preincubated with 1 μg/ml BFA and one of the following agents: leupeptin (100 pg/ml), pepstatin (100 pg/ml), and chymostatin (100 μg/ml) (21). Pulse-chase studies were carried out as described above in the presence of BFA and one of these agents.

Effect of Certain Agent on Lyosomal Cell Protein Degradation—Cell protein degradation by lysosomes was monitored by the increase in release of acid-soluble radioactivity from radiolabeled cells during withdrawal of serum from medium (22). Cells were labeled with 10 μCi of [35S]Met in Met-free medium containing 10% serum for 16 h and chased in 10% serum medium for 3 h. The cells were then incubated with one of the above-listed agents in the presence or absence of 10% serum. After 1 h preincubation, the medium was removed and replaced with the same fresh medium. Aliquots of media were collected at 2 h and the acid-soluble material was obtained by precipitation with a mixture of 5% trichloroacetic acid. Serum was added to the serum-free medium before precipitation. The increase in release of acid-soluble radioactivity during serum deprivation was measured and the percent inhibition of this increase by each agent treatment (relative to no treatment) was calculated.

Pulse-chase Studies on the Effect of LDL on Synthesis and Secretion of ApoB-100—In order to examine the effect of exogenous LDL on the synthesis and secretion of apoB-100 in the cells which had never been exposed to BFA, confluent cells were preincubated with serum-free medium in the presence or absence of LDL (80 μg of cholesterol/ml medium) for 18 h, followed by pulse-chase studies in the absence of LDL.

Pulse-chase Studies on the Effect of LDL on Degradation of ApoB-100—Confluent cells were preincubated with serum-free medium in the presence or absence of LDL (80 μg of cholesterol/ml medium) for 48 h and the medium replaced by fresh medium every 24 h. Pulse-chase studies were carried out in the presence of BFA as described above. LDL was removed from the medium during the pulse and chase period to prevent interference of cold apoB-100 with the immunoprecipitation analysis. The cells were preincubated with Met-free medium containing 1 μg/ml BFA followed by pulse-chase studies.

Analytical Methods—The total cholesterol content of LDL was determined by V-cholestase kit (Nissui Seiyaku Co., LTD., Tokyo, Japan).

RESULTS

Pulse-chase Studies on the Synthesis and Secretion of ApoB-100 and A-1—We followed the synthesis and secretion of pulse-labeled apoB-100 in Hep G2 cells (Fig. 1). A small amount of radiolabeled apoB-100 appeared in the culture medium at 30 min into the chase and continued to be secreted at a linear rate up to 120 min. On the other hand, the cellular content of radiolabeled apoB-100 rapidly decreased during the second 30 min (30-60 min into the chase) and continued to fall more gradually to 120 min. Consequently the total radioactivity recovered in the cells and medium decreased during the second 30 min (30-60 min into the chase), but did not decrease thereafter. At 120 min, 65% of the total radiolabeled apoB-100 observed at 30 min into the chase was recovered in the cells and medium.

The pattern of synthesis and secretion of apoA-1 was quite different from that of apoB-100. The total radioactivity of apoA-1 (sum of cells and medium) remained virtually constant throughout the chase period (Fig. 1, right panel).

Effect of BFA on the Processing of α₁-Antitrypsin—Firstly, we examined the inhibitory effect of BFA on the processing of olosaccharide chains of α₁-antitrypsin in Hep G2 cells. Pulse-chase studies with [35S]Met were carried out to confirm that 1 μg/ml BFA was sufficient to inhibit protein transport from the ER to the Golgi apparatus. At 30 min into the chase, two forms of α₁-antitrypsin, mature and precursor forms, were detected in the cells which had never been exposed to BFA, whereas only the precursor form, whose olosaccharide chains had not yet been processed in the Golgi apparatus, was observed in the presence of the drug (Fig. 2). At 1.5 h into the chase, mature α₁-antitrypsin was observed in the medium in the absence of BFA, whereas precursor form was still detected in the cells in the presence of the drug. In addition, preincubation of cells with 1 μg/ml BFA for 1 h had little effect on

FIG. 1. Pulse-chase analysis of de novo synthesized apoB-100 and apoA-1 in cells and medium. Hep G2 cells were pulse-labeled with [35S]Met (150 μCi) for 15 min. Cultures were harvested at the times indicated and the radioactivity of both apoB-100 and apoA-1 was determined following immunoprecipitation and SDS-PAGE. The amount of radioactivity in the cell is shown by the closed circles. The amount of radioactivity recovered in the culture medium is shown by the open circles. Each value represents the average of duplicate incubations.

FIG. 2. Effect of BFA on the processing of α₁-antitrypsin. Hep G2 cells were preincubated with or without 1 μg/ml BFA for 1 h. Cells were then pulsed with [35S]Met (150 μCi) for 15 min. After the indicated chase time, cultures were harvested and the α₁-antitrypsin immunoprecipitates were subjected to 12.5% SDS-PAGE. Lane M, medium. Molecular mass (in kilodaltons) of each form was indicated at the left side of the gels.
incorporation of [35S]Met into total cell proteins and blocked the secretion of radiolabeled proteins almost completely (97%) (data not shown).

Intracellular Degradation of ApoB-100—As shown in Fig. 1, a significant amount of pulse-labeled apoB-100 was lost from the cells during the chase period. This gives rise to the following three possibilities: (i) apoB-100 is intracellularly degraded prior to secretion into the culture medium; (ii) apoB-100 secreted into the medium is rapidly taken up and degraded by the cells; (iii) after secretion, apoB-100 is degraded in the medium. In preliminary experiments we examined the re-uptake of radiolabeled apoB-100 secreted into medium. After cells were pulsed with [35S]Met for 30 min and chased in serum-free medium for 3 h, the culture medium was administered to fresh Hep G2 cells. Ninety-two and three percent of radiolabeled apoB-100 were recovered in the medium and the cells at 2 h, respectively. These findings suggest that very little radiolabeled apoB-100 was taken up by the cells and degraded in the culture medium. In addition, the total radioactivities of apoB-100 did not decrease after 60 min into the chase (Fig. 2). These results suggest that apoB-100 is degraded intracellularly, probably at an early stage in the secretory pathway for apoB-100. To further investigate the intracellular degradation of apoB-100, cells were incubated with 1 μg/ml BFA and the fate of radiolabeled apoB-100, retained in the ER, was traced. The radioactivity of intracellularly retained apoB-100 by BFA decreased during the chase period, whereas that of apoA-1 remained constant (Fig. 3A). The whole gel after immunoprecipitation of apoB-100 is shown in Fig. 3B. The gradual disappearance of bands corresponding to apoB-100, which were not immunoprecipitated in the presence of LDL, was observed during the chase period. The protein smaller than intact apoB-100 (arrow), which was immunoprecipitated specifically by apoB-100 antiserum, was detected at 40 and 65 min. It also disappeared during the chase period and might be the proteolytic fragment of apoB-100.

Temperature Dependence of ApoB-100 Degradation—Temperature affects many events, including proteolytic cleavage by enzymes, membrane transport of proteins and protein structure. To investigate the temperature dependence of apoB-100 degradation, we pulsed cells with [35S]Met at 37 °C and chased for various times at the different temperatures: 37, 20, and 4 °C in the presence of BFA. At 37 °C, the amount of radiolabeled intracellular apoB-100 was reduced to 60% of the value at 4 °C after only 15 min and continued to decrease up to 65 min (Fig. 4). Below 20 °C no degradation was observed, suggesting that apoB-100 is degraded in a temperature-dependent manner.

Effects of Several Protease Inhibitors on ApoB-100 Degradation—In order to investigate the nature of the protease activities involved in apoB-100 degradation, the effects of agents known to inactivate proteases were examined. Inhibitors of lysosomal function, leupeptin, pepstatin, chymostatin, and chloroquine, had no effect on the degradation of apoB-100 (Table I). On the other hand, these agents inhibited (36.8-64.2%) lysosomal cell protein degradation, which was monitored by the increase in release of acid-soluble radioactivity during serum withdrawal from the medium. These results suggest that lysosomal proteases were not involved in intracellular degradation of apoB-100.

Effect of LDL on Synthesis and Secretion of ApoB-100—In order to investigate the regulation of apoB-100 degradation, we examined the effect of exogenous LDL on the synthesis and secretion of apoB-100. We conducted pulse-chase studies after 18 h preincubation in the presence or absence of LDL, in the absence of BFA. Secretion of radiolabeled apoB-100 from the cells which were cultured in the presence of LDL, was reduced throughout the chase period (30-150 min) (Fig. 5B). After 105 min into the chase, the total radioactivities in both cells and medium were lower in the LDL-treated cells as compared with the nontreated cells (Fig. 5, A and B). This
The synthesis and secretion of apoB-100 was reduced by more than 95% as compared with that in the absence of LDL. The cells were preincubated with 1 fig/ml BFA for 15 min and chased for 15 min or 65 min in the presence of BFA and an agent. The apoB-100 immunoprecipitates in the cells were subjected to 6% SDS-PAGE. The bands corresponding to apoB-100 were quantified by densitometric scanning. The percent inhibition of degradation of apoB-100 during 50 min chase period (15-65 min) by each treatment (relative to no treatment) is shown. Each value represents the average of duplicate incubations. B, cells were labeled and chased as described under “Experimental Procedures.” Lysosomal cell protein degradation was monitored by the increase in release of acid-soluble radioactivity during withdrawal of serum from medium. The percent inhibition of cell protein degradation by each treatment is shown. Each value represents the average of triplicate incubations. Similar results were obtained in two additional experiments.

**Table I**

| Treatment               | % inhibition of degradation |
|-------------------------|-----------------------------|
|                         | ApoB-100 (A)                | Cell protein (B)            |
| Leupeptin (100 μg/ml)   | 0.1                         | 54.6                        |
| Chloroquine (100 μM)    | 2.2                         | 64.2                        |
| Pepstatin (100 μg/ml)   | 1.8                         | 36.8                        |
| Chymostatin (100 μg/ml) | 3.5                         | 47.9                        |

**DISCUSSION**

It is widely accepted that apoB-100-containing lipoproteins are assembled by the sequential association of their components during transport from the ER to the Golgi apparatus (4-10). However, the regulation of synthesis and secretion of lipoproteins remains unclear. In the present study, we have shown that a proportion of apoB-100 is degraded in a pre-Golgi compartment during its intracellular transit, and that this degradation may control lipoprotein secretion.

Since the total radioactivities recovered in the cells and medium decreased during the second 30 min (30-60 min into the chase) and did not decrease thereafter (Fig. 1), this would suggest the occurrence of intracellular degradation of apoB-100. To further investigate whether the degradation of apoB-100 occurs in a pre- or post-Golgi compartment, we examined the fate of apoB-100 retained in the ER by BFA. Under these conditions, a significant amount of apoB-100 retained in the ER was degraded in a temperature-dependent manner and the fate of apoB-100 was different from that of apoA-1. Additionally we confirmed that neither α1-antitrypsin (Fig. 2) nor apoE (data not shown) was degraded intracellularly. It has been reported that over 50% of apoB-100 in the ER is associated with the membrane, whereas a large portion of apoA-1, albumin and macroglobulin is recovered from the luminal contents (5, 7, 8). These results support the possibility that membrane-associated apoB-100 is susceptible to degradation.

**Fig. 5. Effect of LDL on synthesis and secretion of apoB-100.** Hep G2 cells were incubated with LDL (80 μg of cholesterol/ml) for 24 h followed by pulse-chase studies with [35S]Met in the absence of LDL. Cells were preincubated with 1 fig/ml BFA for 15 min and chased for 30, 60, 105, and 150 min. The amounts of radiolabeled apoB-100 and apoA-1 were determined as described in the legend to Fig. 1. Open circles, the control cells; closed circles, the LDL-treated cells. A, intracellular apoB-100; B, apoB-100 secreted in the medium; C, intracellular apoA-1; D, apoA-1 secreted in the medium. Values and vertical bars represent mean and standard error of four incubations. The statistical significance of differences between observed values for the control cells and the LDL-treated cells was tested by Student’s t test. * and ** represent p < 0.05 and p < 0.01, respectively. Similar results were obtained in two additional experiments.

**Fig. 6. Effect of LDL on intracellular apoB-100 degradation.** Hep G2 cells were incubated with LDL (80 μg of cholesterol/ml) for 2 days followed by pulse-chase studies with [35S]Met in the absence of LDL. The cells were preincubated with 1 μg/ml BFA for 1 h, pulsed for 15 min and chased in the presence of BFA. After the indicated time, cells were lysed and the apoB-100 and apoA-1 immunoprecipitates were subjected to 6 and 15% SDS-PAGE, respectively. The bands corresponding to apoB-100 and apoA-1 were quantified by densitometric scanning. Area of the peak at 15 min into the chase) and did not decrease thereafter (Fig. 1), this would suggest the occurrence of intracellular degradation of apoB-100. The percent inhibition of degradation of apoB-100 by LDL treatment results in a decrease in its secretion.

**Effect of LDL on the Intracellular Degradation of ApoB-100**

In order to confirm the effect of exogenous LDL on the intracellular degradation of apoB-100, cells were preincubated in serum-free medium in the presence or absence of LDL for 48 h and pulse-chase studies were conducted in the presence of BFA. There were no significant differences in cell growth and protein synthesis rate between control and LDL-treated cells. LDL induced a statistically significant increase in the intracellular degradation of apoB-100 throughout the chase period, whereas apoA-1 retained in the cells was not degraded either in the presence or absence of LDL (Fig. 6). These results suggest that the increase in intracellular degradation of apoB-100 by LDL treatment results in a decrease in its secretion.

**Effect of various agents on degradation of apoB-100 and cell proteins**

A, cells were preincubated with BFA and protease inhibitor as described under Methods. Cells were pulsed for 15 min and chased for 15 min or 65 min in the presence of BFA and an agent. The synthesis and secretion of apoB-100 was reduced by more than 95% as compared with that in the absence of LDL (data not shown). The synthesis and secretion of apoB-100, however, was not affected by LDL treatment (Fig. 5, C and D).
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dation in a pre-Golgi compartment.

Using inhibitors of lysosomal function we found that lysosomal proteases were not responsible for the degradation of apoB-100, but that this occurs in a pre-Golgi compartment which is either part of, or closely related to, the ER. It is likely that as yet unidentified proteases, which are insensitive to these agents, participate in the degradation of apoB-100 in a pre-Golgi compartment.

Analogous studies have shown that unassembled T cell antigen receptor subunits and inactive acetylcholinesterase, which does not form oligomer in muscle cells, are degraded in a pre-Golgi compartment or the Golgi cisternae, but not in lysosome (23-26). In addition, T cell antigen receptor was also degraded in a temperature-dependent manner (23, 24). These observations suggest that unassembled apoB-100, rather than that assembled in the lipoprotein particles, is also degraded in the same region. Thus, a common nonlysosomal degradation pathway may exist in a pre-Golgi compartment.

The regulation of apoB-100 degradation is of great interest. We selected LDL for these studies, since LDL is known to regulate 3-hydroxy-3-methylglutaryl coenzyme A reductase activity (27) and the expression of LDL receptors (28). Secretion of apoB-100 in the absence of BFA was reduced by LDL treatment, which seems to result from acceleration of intracellular apoB-100 degradation. In separate experiments we found neither mevalonate (5 mM) nor a hydroxymethylglutaryl-CoA reductase inhibitor (CS-514, 500 µg/ml) affected the degradation of apoB-100 retained in Hep G2 cells by BFA (data not shown). These results suggest that the degradation of apoB-100 was enhanced by exogenous LDL, but was not affected by changes in intracellular cholesterol content. Further studies would be necessary to elucidate how LDL stimulates the degradation of apoB-100 and which components in LDL are responsible for the acceleration of the degradation. From another aspect of regulation of apoB-100 secretion, Davis et al. (29) demonstrated that apoB secretion is regulated via degradation and not by changes in mRNA. In addition, several lines of evidence suggest that abetalipoproteinemia, a recessive disease associated with the lack of detectable plasma apoB, is caused by a posttranslational defect in apoB-100 processing or secretion (30).

In this study we found that apoB-100 is degraded in a pre-Golgi compartment, in a temperature-dependent manner, and that this degradation is enhanced by exogenous LDL. Modulation of apoB-100 degradation rate may be a novel mechanism for acute regulation of secretion of apoB-100-containing lipoproteins.

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