A Recycling Pathway for Resecretion of Internalized Apolipoprotein E in Liver Cells*

We have investigated the recycling of apoE in livers of apoE−/− mice transplanted with wild type bone marrow (apoE+/− → apoE−/−), a model in which circulating apoE is derived exclusively from macrophages. Nascent Golgi lipoproteins were recovered from livers of apoE+/− → apoE−/− mice 8 weeks after transplantation. ApoE was identified with nascent d < 1.006 and with d 1.006–1.210 g/ml lipoproteins at a level ~6% that of nascent lipoproteins from C57BL/6 mice. Hepatocytes from apoE+/− → apoE−/− mice were isolated and cultured in media free of exogenous apoE. ApoE was found in the media primarily on the d < 1.006 g/ml fraction, indicating a rescretion of internalized apoprotein. Secretion of apoE from C57BL/6 hepatocytes was consistent with constitutive production, whereas the majority of apoE secreted from apoE+/− → apoE−/− hepatocytes was recovered in the last 24 h of culture. This suggests that release may be triggered by accumulation of an acceptor, such as very low density lipoproteins, in the media. In agreement with the in vivo data, total recovery of apoE from apoE+/− → apoE−/− hepatocytes was ~6% that of the apoE recovered from C57BL/6 hepatocytes. Since plasma apoE levels in the transplanted mice are ~10% of control levels, the findings indicate that up to 60% of the internalized apoE may be reutilized under physiologic conditions. These studies provide definitive evidence for the sparing of apoE and its routing through the secretory pathway and demonstrate that internalized apoE can be rescreted in a quantitatively significant fashion.

Apolipoprotein E (apoE) is unique among the plasma lipoprotein apoproteins because of its many different functions in the metabolism of lipids and lipoproteins. Its role as a ligand for the receptor-mediated endocytosis of lipoproteins is well established (1–3). Additionally, apoE interacts with lipoprotein lipase and hepatic lipase to modulate triglyceride hydrolysis (4, 5). Even within the cell, apoE is known to serve biologically relevant roles. Studies suggest that apoE directs the intracellular routing of internalized remnant lipoproteins, with smaller β-migrating very low density lipoproteins (VLDL) particles routed to the perinuclear region of the mouse macrophage in a fashion similar to low density lipoproteins (LDL), whereas larger β-VLDL remain closer to the plasma membrane (6, 7). Schwiegelshohn et al. (8) report that apoE modulates intracellular lipid metabolism, in particular the hydrolysis and utilization of triglyceride. ApoE is also linked to and may be a regulator of cholesterol efflux from macrophages (9–11), an effect with significant repercussions on vascular health and the process of atherogenesis. Finally, increasing evidence points to a role for apoE in hepatic lipoprotein assembly and the incorporation of triglycerides into newly forming VLDL (12–14). Due to its critical role in a number of biological processes within the cell, apoE may follow unique pathways of secretion and internalization that maximize its impact on cellular functions.

Wong (15) was among the first to suggest that apoE may be recirculated. He reported that 62–66% of the infrathepic apoE, compared with 7–10% of the infrathepic apoB, was derived from plasma. This suggested that internalized apoE may not undergo complete degradation and may therefore follow a unique intracellular routing pathway. We previously reported that a portion of the apoE component of internalized lipoproteins is spared degradation and routed through the Golgi apparatus (16). After injection of radioiodinated mouse d < 1.019 g/ml lipoproteins into C57BL/6 mice, radioactivity found in the Golgi apparatus-rich fractions from livers of the recipient mice was almost exclusively due to apoE, although the injected lipoproteins had less than 10% of their label associated with apoE. The ratio of apoE/apoB48 in the Golgi fraction increased 10-fold relative to serum, and only traces of apoB100 were detected. Furthermore, the apoE recovered in the Golgi fraction was part of a d 1.019–1.210 g/ml complex, indicating an association of recycled apoE with newly formed lipoproteins. Quantitatively, similar results were obtained when labeled VLDL was injected into mice deficient in either apoE or the LDL receptor, indicating that the phenomenon of apoE recycling is not influenced by the production of endogenous apoE and is not dependent on the presence of LDL receptors. Although our studies clearly demonstrated the presence of a mechanism in vivo by which apoE escapes degradation, the appearance of internalized apoE within the liver Golgi may have been influenced in part by the bolus delivery of apoE in this model.

To address this issue and to explore hepatic apoE recycling in the steady state, we have completed experiments utilizing an in vivo model based on bone marrow transplantation. Recon-
Lipoproteins were adsorbed from the media using Liposorb (PHM-L washed in phosphate-buffered saline, and frozen. Cells were recovered at the end of the experiment (45-h time point), apoE into the system. Media was collected at 4, 21, and 45 h after incubations did not contain serum to avoid introduction of exogenous medium. The media used during the isolation, plating, washing, and fresh media was added to 20 ml. The cells son) at a density of 1.2g of normal macrophages into the apoE present in the mouse is derived from macrophages. Our labo-ratory (17) has shown that within 3 weeks of the introduction of normal macrophages into the apoE−/− mouse, serum apoE levels reach 10% of normal, resulting in complete normalization of plasma cholesterol levels by virtue of an active hepatic clearance of remnant lipoproteins. Since hepatocytes in this model do not produce endogenous apoE but internalize apoE on remnant lipoproteins, this approach provides an excellent model for investigating the routing of internalized apoE through the secretory pathway via the Golgi apparatus in the absence of endogenously produced apoE. The studies reported in this manuscript demonstrate clearly that internalized apoE undergoes a unique routing through the secretory pathway and is resorbed.

**EXPERIMENTAL PROCEDURES**

Mice—ApoE-deficient (apoE−/−) mice on the C57BL/6 background were obtained from The Jackson Laboratory (Bar Harbor, ME). A colony of C57BL/6J mice is established in our animal facility. All mice were housed in cages of 8 mice on a 12/12-h dark cycle and were fed a normal mouse-chow diet (RP5015; PMI Feeds Inc., St. Louis, MO). Food and water were available ad libitum. All animal procedures were carried out in accordance with institutional guidelines with approval from the Animal Care Committee of Vanderbilt University.

Bone Marrow Transplantation (BMT)—BMT was carried out as described previously (17). One week before and 2 weeks after BMT, 100 mg/liter neomycin and 10 mg/liter polymyxin B sulfate (Sigma) were added to the water. Bone marrow was collected from donor mice by flushing femurs with RPMI 1640 media containing 2% fetal bovine serum and 10 units/ml heparin (Sigma). Recipient mice were lethally irradiated (9 gray), and 4 h later, 5 × 10^6 bone marrow cells in 0.3 ml were transplanted by tail vein injection. Animals were used for studies from 6 to 12 weeks after transplantation.

Isolation of Golgi Apparatus-rich Fractions and Nascent Lipoproteins—Golgi apparatus-rich fractions were prepared as described previously (18). Golgi fractions were isolated from 4–5 mice (total liver 5–6 g). Typically we are able to isolate 200–300 μg of Golgi protein from 5–6 g of liver. Nascent lipoproteins were released from the Golgi apparatus using sodium carbonate treatment (19) and lipoprotein classes isolated from Golgi contents and hepatocytes by using sodium carbonate treatment (19) and lipoprotein classes isolated from Golgi contents. Golgi apparatus-rich fractions were isolated from 6 to 12 weeks after transplantation using sodium carbonate treatment (19) and lipoprotein classes isolated from Golgi contents.

Preparation and Culture of Mouse Hepatocytes—Hepatocytes were isolated from mouse livers as described by Horton et al (19). Isolated hepatocytes were dispersed by shaking followed by filtration through 100-μm nylon cell strainers (Falcon cell strainer, Becton Dickinson, Franklin Lakes, NJ). The liver capsule and dish were rinsed with RPMI 1640 media containing 2% fetal bovine serum and 10 units/ml heparin (Sigma). The capsule and cell debris were pelleted by centrifugation using a Beckman Optima TLX ultracentrifuge (Beckman Coulter) and 120.2 rotor (120,000 × g; 30 min). The supernatant was dialyzed against normal saline, and lipoproteins were adsorbed using Liposorb as described above.

Lipoproteins classes were isolated from Golgi contents and hepatocyte culture media by ultracentrifugation using the Beckman tabletop ultracentrifuge. Golgi lipoprotein classes (d < 1.006 g/ml and d 1.006–1.210 g/ml) were isolated as described previously using a 12.0 rotor (18). Lipoproteins from the culture media were recovered using the 100.4 rotor. The d < 1.006 g/ml lipoproteins were isolated in 6 h at 100,000 rpm and recovered using tube slicing (Beckman CentriTubes Slicer). The density of the infranatant was raised to 1.210 g/ml using sodium carbonate treatment (19) and lipoprotein classes isolated from 60 min with Promix L-35S in vitro cell-labeling mix (100 μCi/ml, Amersham Pharmacia Biotech). The media was removed, and the cells were washed twice with phosphate-buffered saline and chased for 3, 6, and 12 h in the same media. apoE was immunoprecipitated from the media using an anti-human polyclonal antibody (Biodesign Internation-al, Inc., Redmond, WA), and immunoprecipitates were washed extensively, and incubated with horseradish peroxidase-conjugated secondary antibodies. Bands were visualized using enhanced chemiluminescence (Amersham Pharmacia Biotech).

In Vivo Hepatic VLDL Triglyceride Production—Hepatic VLDL triglyceride production was measured using Triton WR1339. Mice were fasted overnight, anesthetized with ketamine/xylazine mixture, and injected via the retro-orbital plexus with Triton WR1339 (800 mg/kg of body weight). Triton (Sigma) was dissolved in normal saline at a concentration of 25 mg/ml. Preliminary studies in our laboratory demonstrated a linear increase in VLDL triglyceride over a 6-h period using this concentration of Triton, providing strong evidence that plasma VLDL clearance is completely inhibited under these conditions. Blood samples (~50 μl) were taken from the retro-orbital plexus before injection (0 h) and 1, 2, 3, and 4 h after Triton injection. Plasma triglycerides were measured using enzymatic assays adapted to microtiter plates (Rainich, San Diego, CA). Slopes of the lines were determined by GraphPad Prism (v. 3.01). Hepatic triglyceride production rates were calculated from the slopes and presented as μmol of triglyceride produced/kg/h assuming the plasma volume to be 33 μl/g (22).

**RESULTS**

ApoE Recycling in ApoE−/− Mice—Transplanted Bone Marrow from C57BL/6 Mice—ApoE−/− mice were transplanted with bone marrow from C57BL/6 mice (apoE−/− → apoE−/−), and 8 weeks post-BMT, hepatic Golgi apparatus-rich
fractons were isolated. Previous studies in our laboratory show that the Golgi fractions are enriched in galactosyl transferase with minimal contamination from components of the endocytic compartment (18). Reconstitution of apoE<sup>−/−</sup> mice with marrow from C57BL/6 mice leads to the appearance of apoE on plasma lipoproteins, promoting clearance of lipoprotein remnants and normalization of plasma cholesterol (17). In C57BL/6 mice, apoE was easily detected in the d < 1.006, d 1.006–1.210, and d > 1.210 g/ml fractions (Fig. 1), and the relative distribution of apoE among the three fractions as determined by densitometric scanning was ~55, 40, and 5%, respectively. ApoE was also found in the nascent Golgi lipoproteins from the apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice (Fig. 1), with a distribution that was very similar to that of control C57BL/6 preparations (~50% in the d < 1.006 and 50% in the d 1.006–1.210 g/ml fractions). No apoE was detected in the d > 1.210 g/ml fraction, perhaps reflecting the small amount of total apoE recovered with the Golgi fractions. The apoE in nascent hepatic Golgi lipoproteins from apoE<sup>+/+</sup> → apoE<sup>−/−</sup> animals normalized to the amount of apoB48 was ~6% that found with Golgi lipoproteins from control animals.

Ex Vivo Resecretion of ApoE—To determine if the apoE that was internalized was secreted, primary hepatocytes were isolated from C57BL/6 mice and apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice. Fig. 2 presents a micrograph of the cultured hepatocytes from C57BL/6 mice stained with hematoxylin and eosin. The cultures were also immunostained for the presence of Kupffer cells using the monocyte-macrophage marker MOMA-2. Cell counts from numerous fields from three different preparations showed less than 1–2% contamination of the hepatocyte cultures with Kupffer cells. Fig. 3 shows the results of experiments in which the media from the first two time points (4 and 21 h) were combined, and lipoproteins were adsorbed using Liposorb. As can be seen, apoE is clearly present in the media from the apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice. This suggests that apoE, internalized in vivo, is routed to the secretory pathway and is secreted from the hepatocytes in culture.

The time course of appearance of apoE in the media of the hepatocytes from C57BL/6 mice and apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice is shown in Fig. 4A. ApoE was present in the media from the C57BL/6 hepatocytes at each time point. The mass of apoE appeared proportional to the time in culture. In addition, apoE was found in the cells at the end of the experiment. ApoE was also observed in the media of the hepatocytes from apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice. At the early time points, little apoE was detected, but at the later time points there appeared to be a greater release of the apoprotein. There was little to no apoE detected in the cells from the apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice at the end of the 45-h culture period. Furthermore, the cells appeared healthy after the 45-h culture period, with no evidence of massive cell death. In C57BL/6 hepatocytes, ~10% of the total apoE
was secreted in the first 4 h with 40% secreted in the next 17 h and 49% secreted in the last 24 h (Fig. 4B). This suggests a constant production of apoE throughout the culture period. In contrast, in hepatocytes from the apoE<sup>−/−</sup> mice transplanted with C57BL/6 marrow, only 1.7% of the total secreted apoE was recovered in the media after 4 h, whereas 15.2% appeared in the next 17 h, and ~83% was recovered in the final 24 h of incubation (Fig. 4B). In two separate experiments the total apoE secreted from the BMT hepatocytes over the 45-h period was 6.5% of the apoE secreted from C57BL/6 hepatocytes over the same period.

**Synthesis and Secretion of ApoE in Primary Cultures of Mouse Hepatocytes**—The secretion of radiolabeled apoE from primary hepatocytes from C57BL/6 mice and apoE<sup>−/−</sup> → apoE<sup>−/−</sup> mice is shown in Fig. 5. Newly synthesized apoE was easily detected in the media from C57BL/6 hepatocytes but was not detected in the hepatocyte cultures from apoE<sup>−/−</sup> → apoE<sup>−/−</sup> mice at any of the time points. As expected, the recycling of unlabeled apoE was observed at all time points (data not shown). These results demonstrate clearly that apoE in the media of hepatocytes from apoE<sup>−/−</sup> → apoE<sup>−/−</sup> mice does not derive from contaminating Kupffer cells but represents apoE internalized in vivo and subsequently resorbed in culture.

**Density Distribution of Resorbed ApoE**—In the media from C57BL/6 hepatocytes, apoE was distributed approximately equally between the d < 1.006 and d 1.006–1.210 g/ml fractions, whereas in the hepatocytes from apoE<sup>−/−</sup> → apoE<sup>−/−</sup> mice, most of the apoE was found with the d < 1.006 g/ml fraction (Fig. 6). This may reflect the affinity of apoE for triglyceride-rich lipoproteins in the media that are apoE-deficient, but it may also suggest that apoE-deficient triglyceride-rich lipoproteins in the media stimulate apoE release from the cells, or that recycling apoE induces assembly of triglyceride-rich lipoproteins, a possibility that was investigated in the next set of experiments.

**Hepatic Triglyceride Production Rate**—Hepatic triglyceride production rates using the Triton method were measured in C57BL/6, apoE<sup>−/−</sup> mice, apoE<sup>−/−</sup> → apoE<sup>−/−</sup> mice, and apoE<sup>−/−</sup> mice transplanted with apoE<sup>−/−</sup> marrow. The production rates for all groups were linear over the time period, with r values of 0.947–0.993 for the four groups. As has been shown previously (13, 14), hepatic triglyceride production rates in apoE<sup>−/−</sup> mice were ~50% that found in C57BL/6 mice (Fig. 7). Hepatic triglyceride production rates in mice transplanted with marrow from either apoE<sup>−/−</sup> or apoE<sup>−/−</sup> mice were similar and not significantly different from the rates found in apoE<sup>−/−</sup> mice, suggesting that any effect of recycling apoE on triglyceride production is not of the magnitude to induce a bulk increase in lipoprotein accumulation.
The resecretion of internalized apoE in hepatocytes

**DISCUSSION**

The present study explored the recycling of apoE in the livers of apoE−/− mice transplanted with wild type bone marrow. In this model all of the apoE derives from macrophages, and plasma apoE levels are at steady state, with the production of apoE by macrophages and its internalization and potential resecretion by the liver at equilibrium. Therefore any apoE appearing in the secretory pathway in the liver or recovered in the media of hepatocytes isolated from these mice is derived from internalized extrahepatic apoE. Using the BMT model we have demonstrated the presence of apoE within nascent hepatic Golgi lipoproteins, providing strong evidence that at least a portion of internalized extrahepatic apoE is routed to the secretory pathway. Additional studies using primary hepatocytes from the apoE−/− → apoE−/− mice not only confirmed the routing of internalized apoE to the secretory pathway but also demonstrated the resecretion of internalized apoE. These results coupled with our earlier in vivo studies (16) provide overwhelming support for the hypothesis that a portion of apoE that is internalized with lipoproteins is not completely degraded but is in fact resecreted. The physiologic relevance of the reutilization and recycling of apoE is unknown. Our studies show that introduction of apoE via BMT does not affect hepatic triglyceride production rates, but the lack of an effect may simply reflect suboptimal concentrations of intracellular recycling apoE. Alternatively, the functional role of recycling apoE may be linked to effects that are independent from or more subtle than the bulk secretion of triglyceride-rich lipoproteins. Our finding of apoE with nascent lipoproteins in Golgi apparatus-rich fractions from apoE−/− → apoE−/− mice in the present study (Fig. 1) provides definitive evidence for the routing of internalized apoE through the secretory pathway under physiologic conditions. The finding of apoE within the Golgi fractions was not due to contamination of the preparations with elements of the endocytic compartment, as studies in our laboratory have established the purity of the hepatic Golgi fractions by this technique (18). Contamination of our fractions with Golgi from Kupffer cells, a possible source of apoE, is not expected to play a role here since engraftment of Kupffer cells in liver is less than 20% at 8 weeks and only ~35% of total macrophages 6 months after transplantation (29). In addition, it is unlikely that Kupffer cell Golgi apparatus isolates with hepatocyte Golgi apparatus, as Kupffer cells do not produce triglyceride-rich lipoproteins that contribute to the buoyancy of the hepatocyte-derived organelle (24). Therefore the appearance of apoE in the hepatic Golgi fractions of the apoE−/− → apoE−/− mice represents routing of internalized apoE through the secretory pathway.

The resecretion of apoE from primary cultures of hepatocytes from apoE−/− → apoE−/− mice provided additional evidence for apoE recycling. In contrast to the constitutive pattern of secretion of apoE from hepatocytes from C57BL/6 mice, the majority of apoE recovered in the media of hepatocytes from apoE−/− → apoE−/− mice was released in the last 24 h (Fig. 4). This release was not caused by cell death, as the cells from both control and transplanted animals appeared healthy after the 48-h culture period. Rensen et al. (25), studying the retroendocytosis of apoE from HepG2 cells, report that the presence of high density lipoproteins or lipid emulsion in the media resulted in a significantly increased rate of secretion of intact protein compared with media with no acceptor. Heeren et al. (26) also report that high density lipoprotein seemed to serve as an extracellular acceptor for the resorption of apoE from fibroblasts. Although in our experiments the media did not contain an exogenous acceptor to stimulate the release of apoE, the hepatocytes do secrete apoE-deficient VLDL (Fig. 1), which may serve as acceptor for and stimulator of apoE release from hepatocytes. A threshold concentration of apoE-deficient VLDL, attainable only during the 24-h culture period, may be required to trigger the release of apoE. In this regard, it is important to note that apoE recovered in the media is found mainly with the d < 1.006 g/ml lipoproteins (Fig. 6).

Although Kupffer cells in our hepatocyte cultures may contribute to the apoE recovered in the media, our data suggest that their contribution is minimal. Immunocytochemical staining using antibody to MOMA-2, an established marker for macrophages, indicates that less than 1–2% of the cells in culture is of macrophage origin. Dawson et al. (27) report that Kupffer cells in rat liver account for less than 1% (0.7%) of the total liver apoE mRNA and that the level of apoE mRNA in Kupffer cells was approximately one-third that of hepatocytes. The total recovery of apoE in the media of the hepatocytes from apoE−/− → apoE−/− mice is ~5–6% of apoE recovered in the media from C57BL/6 hepatocytes. Assuming the secretion of apoE is proportional to the apoE mRNA content of the Kupffer cells and hepatocytes, the number of Kupffer cells in our preparation cannot account for the mass of apoE found in the media. In addition, the kinetics of appearance of apoE in the media is not consistent with what might be predicted for a constitutively secreted apoprotein as observed in the secretion of apoE from C57BL/6 hepatocytes, and as noted above, the engraftment of liver Kupffer cells in mice after BMT is less than 20% of total tissue macrophages 8 weeks after transplantation (23). Finally and perhaps most importantly, newly synthesized apoE could not be detected in hepatocyte cultures from apoE−/− → apoE−/− mice (Fig. 5). Therefore, based on the mass of apoE found in the media, the number of cells identified as Kupffer cells using immunocytochemistry, the secretion kinetics, the kinetics of engraftment of liver Kupffer cells, and the absence of newly synthesized apoE in hepatocyte cultures from
apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice, we conclude that the apoE recovered in the media does not derive from Kupffer cells but represents recycled apoE.

The content of apoE with nascent hepatic Golgi VLDL from apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice was ~6% that found with control Golgi VLDL, and the mass of apoE released from hepatocytes from apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice was ~6% that of apoE secreted by hepatocytes from C57BL/6 mice. Since serum apoE levels in apoE<sup>+/+</sup> → apoE<sup>−/−</sup> mice are ~10% of control levels (17), the results suggest that as much as 60% of the internalized apoE is reutilized. Under normal conditions, when the hepatocyte is faced with 10 times more apoE, the amount of apoE that is recycled may change. Heeren et al. (26) incubated radiolabeled apoE-containing triglyceride-rich lipoproteins with Hep3b cells and fibroblasts and demonstrated that ~60% of the labeled apoprotein internalized by the cell was released intact into the medium after a 90-min chase. The released apoproteins were primarily apoE and apoC. Rensen et al. (25) also report that as much as 26% of the apoE taken up on triglyceride-rich emulsions by HepG2 cells was released. Finally, Taka-hashi and Smith (28) estimate that as much as 30% of apoE internalized by the murine macrophage RAW 264 cell line was reserected. It seems clear that the process of apoE sparing and reutilization may be variable among different cells but is not simply limited to the liver and is quantitatively important.

The physiologic relevance of apoE reutilization and reserection is unknown. Recycling may provide a mechanism whereby the impact of apoE on intracellular and extracellular functions can be maximized. Accumulating evidence points to a critical role for apoE in VLDL assembly. Hepatic VLDL triglyceride production is decreased by nearly 50% in the apoE<sup>−/−</sup> mice compared with C57BL/6 mice (13, 14), and the reconstitution of apoE expression via adenoviral transfer with the human apoE gene markedly increases hepatic VLDL triglyceride production (29). Our studies confirm that hepatic triglyceride production rates are decreased in apoE<sup>−/−</sup> mice compared with C57BL/6 mice (Fig. 7). However, introduction of apoE via BMT did not alter this rate, suggesting that apoE is routed to a site in the secretory pathway distal to VLDL assembly or triglyceride production. Alternatively, introduction of apoE via BMT, an intervention that reconstitutes only 10% of the total serum apoE, may not provide intracellular concentrations of apoE needed to affect hepatic triglyceride production and VLDL secretion. Finally, it is plausible that recycling apoE may have other effects, such as increasing remnant uptake through the secretion-capture mechanism (30–32).

In conclusion, apoE internalized by the liver as a component of lipoprotein particles escapes the degradative pathway, is routed to the Golgi apparatus, and is subsequently secreted in quantitatively significant proportions. Further studies are needed to identify the functional correlates of this newly described cellular process.

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