Apolipoprotein E Recycling
Implications for Dyslipidemia and Atherosclerosis

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Abstract—After receptor-mediated endocytosis, the intracellular fate of triglyceride-rich lipoproteins (TRLs) is far more complex than the classical degradation pathway of low-density lipoproteins. Once internalized, TRLs disintegrate in peripheral endosomes, followed by a differential sorting of TRL components. Although core lipids and apolipoprotein B are targeted to lysosomes, the majority of TRL-derived apolipoprotein E (apoE) remains in peripheral recycling endosomes. This pool of TRL-derived apoE is then mobilized by high-density lipoproteins (HDLs) or HDL-derived apoA-I to be recycled back to the plasma membrane, followed by apoE resecretion and the subsequent formation of apoE-containing HDL. The HDL-induced recycling of apoE is accompanied by cholesterol efflux and involves the internalization and targeting of HDL-derived apoA-I to endosomes containing both apoE and cholesterol. These findings point to a yet unknown intracellular link between TRL-derived apoE, cellular cholesterol transport, and HDL metabolism. Recent studies provide first evidence that impaired recycling of TRL-derived apoE4, but not apoE3, is associated with intracellular cholesterol accumulation, which might explain some well-documented effects of apoE4 on HDL metabolism. This review summarizes the current understanding of apoE recycling and its potential role in the regulation of plasma apoE levels in the postprandial state. (Arterioscler Thromb Vasc Biol. 2006;26:442-448.)

Key Words: apolipoprotein E ■ HDL ■ endocytosis ■ cholesterol efflux ■ triglyceride-rich lipoproteins

Intestinal chylomicrons (CMs) and liver-derived very low-density lipoproteins (VLDLs) represent the 2 classes of triglyceride-rich lipoproteins (TRLs) responsible for the transport of lipids to other cells of the body. CMs mediate the transport of dietary lipids, whereas VLDLs deliver endogenous lipids to peripheral tissues. In humans, TRLs can be distinguished by their apolipoprotein B (apoB) composition. ApoB48 is found exclusively in CMs, and apoB100 is required for the assembly of VLDL. In the bloodstream, both TRLs are immediately hydrolyzed by lipoprotein lipase (LPL), leading to the formation of TRL remnants.1,2 During lipolysis, these remnants become enriched with high-density lipoprotein (HDL)–derived apoE. LPL remains associated predominantly with postprandial apoB48-containing CM remnants (CRs).3,4 TRL remnants are then trapped in the Space of Disse by interaction with heparan sulfate proteoglycans1 before they are rapidly internalized by hepatocytes. Remnant uptake is mediated via binding of apoE and LPL to the α2-macroglobulin receptor/low-density lipoprotein (LDL) receptor–related protein 1 (α2MR/LRP1, also known as CD91; referred to here as LRP1)4–7 and via apoB100 and apoE interacting with the LDL receptor (LDLR).1,8 The involvement of both receptors in the clearance of TRL remnants in vivo was finally established in double-knockout mice, deficient for both LDLR and hepatic LRP1, which showed a significant accumulation of remnant lipoproteins.6 Studies with the “apoB48-only” and “apoB100-only” mice on the LDLR-deficient background then demonstrated that blocking LRP1 binding sites resulted in the accumulation of apoB48-containing remnants in the plasma.9 These findings implicate that LRP1 facilitates the clearance of postprandial CRs but plays no significant role for the catabolism of lipoproteins containing apoB100. As mentioned above, CR-associated LPL also contributes to and initiates LRP1-mediated internalization of remnants.4,10 The involvement of LPL in TRL metabolism is complex and has been reviewed in more detail previously.2,11,12 Here, we focus on the growing evidence, obtained at the cellular and physiological level, of the involvement of internalized TRL-derived apoE in the regulation of cellular cholesterol transport and HDL metabolism.

Disintegration of TRL Particles in the Endosomal Compartment
Because of their short half-life, isolation of TRL is difficult, and various “model particles” have been established and used for cellular studies. This soon revealed that the intracellular processing of TRL was far more complex than the classical degradation pathway of LDL.13 Initially, it was observed that VLDL particles were poorly degraded by HepG2 hepatoma.
cells, Tabas et al identified that β-VLDL–derived apoE was resistant to lysosomal degradation and accumulated in widely distributed vesicles in mouse macrophages. However, in the same cells, β-VLDL–derived lipids were delivered to perinuclear, lysosomal compartments. Similarly, VLDL-sized apoE-containing triglyceride-reich emulsion particles were more resistant to degradation in HepG2 cells than emulsions containing LDL-derived apoB. As cells released intact apoE, Rensen et al concluded that after internalization by liver cells, apoE can escape degradation to be resecreted. These findings indicated that some TRL constituents are targeted along the degradative pathway, whereas others, such as apoE, are retroendocytosed. Similar to other TRL model particles, TRL isolated from patients with hyperchylomicronemia attributable to the lack of the essential coenzyme for LPL hydrolytic activity, apoC-II, exhibit a retarded degradation in human hepatoma cells and fibroblasts. We could show that internalized TRL components were differentially sorted in a peripheral cellular compartment. Whereas TRL lipids and apoB were directed to (pre)lysosomes, TRL-derived apoE, apoC, and LPL were recycled back to the cell surface, where resecretion could occur.

Since then, evidence has accumulated that the complex processing of internalized TRL also exists in vivo. Rensen et al showed that after intravenous injection of 125I-apoE and 3H-cholesteryl oleate–labeled emulsions in C57BL/6 mice, only 15% to 20% of radiolabeled apoE was degraded in hepatocytes, whereas 75% of the 3H-cholesteryl oleate was hydrolyzed. Fazio et al injected iodinated mouse VLDL particles into C57BL/6 mice and consistently identified iodinated apoE in Golgi-enriched fractions. Similar results were obtained in LDLR-deficient mice, again indicating that apoE recycling involves LRP1-mediated TRL internalization (see above). In follow-up studies, Swift et al showed recycling of apoE in livers of apoE knockout mice transplanted with wild-type bone marrow apoE (+/+ cells), a model in which circulating apoE is derived exclusively from macrophages. In these studies, up to 60% of internalized apoE appeared to be reused. Using 1,1′-dioctadecyl-3,3′,3′′-tetramethylinodocyanine (DiI) as a fluorescent TRL-phospholipid analogue, we demonstrated that intravenously injected DiI-labeled TRLs were rapidly cleared from the plasma and immediately disintegrated after internalization in rat liver. Whereas TRL-derived phospholipids accumulated in perinuclear regions, TRL-derived apoE was localized in endosomal compartments. Substantial amounts of apoE were found in the receptor recycling compartment (RRC), indicating a potential resecretion of TRL–apoE via recycling endosomes. And, indeed, pulse-chase experiments of perfused rat livers demonstrated a serum-induced release of internalized apoE into the perfusate. Fast performance liquid chromatography (FPLC) analysis of the secreted proteins then identified 80% of the recycled intact apoE in the HDL fraction. These findings provided the first evidence that recycling of TRL-derived apoE could play an important role in the modulation of HDL particles in vivo.

For the intracellular recycling pathway of TRL-derived apoE, it could be shown that TRLs disintegrate in peripheral sorting endosomes, and TRL-derived apoE is then targeted to recycling endosomes. This route is clearly distinct from the perinuclear transferrin recycling compartment because apoE-containing recycling vesicles are widely distributed throughout the cytoplasm. Fazio et al identified internalized VLDL-derived apoE to be associated with nascent lipoproteins in liver Golgi fractions. Because RRC preparations from rat liver contain 5′nucleotidase and sialyl-transferase activity, recycling of apoE could be mediated in part by Golgi-derived secretory vesicles. However, the majority of TRL-derived apoE is probably resecreted from peripheral endosomal compartments, in which apoE recycling is connected to HDL metabolism (see below).

**Intracellular Link Between TRL-Derived ApoE and HDL Metabolism in Early Endosomes**

HDL or purified apoA-I stimulates the release of internalized apoE in hepatocytes and fibroblasts and accelerates resecretion of VLDL-derived apoE from apoE(−/−) mouse hepatocytes. Similarly, HDL or apoA-I–induced apoE recycling occurs in mouse macrophages and human neuronal cells.

Because HDL and apoE can independently promote cholesterol efflux, we investigated whether recycling of TRL-derived apoE could be linked to intracellular cholesterol transport. In human hepatoma cells and fibroblasts, HDL-induced apoE recycling is accompanied by cholesterol efflux, and internalized TRL-derived apoE colocalized with early endosome antigen 1 (EEA1), a marker for early endosomes. ApoE- and EEA1-positive endosomes also contain cholesterol, and on HDL incubation, apoE recycling and cholesterol efflux occurred simultaneously from peripheral early endosomes. This points to a direct link between HDL-induced apoE recycling and cholesterol efflux from early endosomal compartments. Although internalized TRL-derived apoE was not detected in adaptor protein 1–positive Golgi vesicles, and apoE recycling was unaffected in the absence of an intact Golgi apparatus, this does not completely rule out that apoE recycling affects cholesterol efflux via the Golgi network, in which cholesterol-rich membranes are assembled and moved forward to the plasma membrane. At first, we and others favored HDL to act at the plasma membrane to promote apoE recycling and cholesterol efflux. TRL-derived apoE and cholesterol probably associate intracellularly, but complex formation of apoE, cholesterol, and HDL would occur at the plasma membrane. New findings addressing this question clearly challenge this model. In ATP binding cassette (ABC) A1 (ABCA1) overexpressing RAW macrophages, Smith et al obtained a punctate staining pattern of apoA-I by immunofluorescence, most likely representing internalized apoA-I in endocytic vesicles. In hepatoma cells, HDL-derived apoA-I was shown to colocalize with apoE and cholesterol in EEA1-positive endosomes. Subsequent electron microscopy analysis identified TRL-derived apoE to colocalize with HDL-derived apoA-I in peripheral endosomes. This strongly suggested that HDL-derived apoA-I is internalized and targeted to pre-existing apoE/cholesterol–containing endosomes to promote apoE recycling and cholesterol efflux. Time-lapse confocal micro-
ApoE recycling initiates HDL particle formation. At the endothelial cell surface of muscle and adipose tissue, LPL mediates the hydrolysis of CMs leading to the formation of CRs. LPL remains associated with CRs, which become simultaneously enriched with HDL-derived apoE. This is followed by a rapid internalization of CRs into the liver via binding of apoE and LPL to LRP1. Once internalized, CRs immediately disintegrate in early sorting endosomes. Whereas the lipid core with apoB48 is targeted to late endosomes/prelysosomal compartments, CR-derived surface remnants containing apoE with LPL and some lipids are retained in early endosomes to mobilize cellular cholesterol from intracellular pools. As indicated by the question marks, it is not yet known whether cellular cholesterol can be mobilized from late endosomal compartments or from Golgi-derived vesicles. This results in the formation of apoE/cholesterol complexes within peripheral recycling endosomes. HDL or liver-derived lipid-poor apoA-I can be internalized and targeted to apoE/cholesterol-containing endosomes, which leads to the intracellular formation of HDL-E particles and the stimulation of apoE recycling and cholesterol efflux. In the postprandial state, resecretion of HDL-E can facilitate the enrichment of CRs with apoE and thereby ensure the efficient hepatic clearance of CRs. This model illustrates the postprandial apoE cycle for the isoform apoE3.

copy confirmed that HDL-derived apoA-I is indeed targeted to TRL-derived apoE/cholesterol–containing endosomes in the cellular periphery.24 Similarly, FPLC analysis of secreted proteins from macrophages identified recycled apoE in fractions that contained small HDL, indicating that TRL-derived apoE exits cells in a remodeled, lipidated form.25 Thus, in macrophages, HDL-induced apoE recycling may maximize the removal of cholesterol from the periphery, thereby preventing foam cell formation. In liver, apoE recycling could secure the maintenance of high apoE-containing HDL levels in plasma and accelerate the enrichment of CRs with apoE in the postprandial state. After food intake, the recycling of apoE would overcome any shortage of HDL-E and therefore stimulate the efficient hepatic clearance of CRs. The current concept for hepatic recycling of apoE3 with regard to its potential role for HDL metabolism is illustrated in the Figure.

TRL Receptors and the Differential Recycling of ApoE Isoforms

Although CRs are rapidly cleared from the plasma via LRP1 and the LDLR, it is yet unclear whether both receptors are involved in the regulation of apoE recycling. Studies with apoE proteoliposomes favor a role for the LDLR in apoE reseccretion.15 However, the recycling of apoE from apoB48-containing TRLs does not depend on the LDLR and suggests that LRP1 is involved in this process in the postprandial state.21,22 Supporting this, we observed that internalized TRL-derived apoE and cholesterol remain associated with LRP1 in EEA1-positive endosomes24 (Laatsch et al, unpublished data, 2005). In the absence of the LDLR together with reduced LRP1 expression, the recycling of apoE was not markedly impaired in primary mouse hepatocytes.29 It remains to be determined whether a complete loss or overexpression of LRP1 affects apoE recycling. In further support of LRP1 targeting ligands into specialized endocytic compartment important for reseccretion, recent findings identified that LRP1 is essential for endocytosis and re-presentation of chaperoned peptides in antigen-presenting cells.33,34 Adaptor proteins specific for LDLR and LRP1 might contribute to target apoE–receptor complexes into specific endocytic membrane subdomains. For example, the autosomal recessive hypercholesterolemia protein35 connects the LDLR with clathrin and the endocytic machinery to regulate LDLR clustering in clathrin coated pits and LDLR internalization to EEA1-positive endosomes in hepatocytes.36,37 In the case of LRP1, the sorting protein nexin 17 (Snx 17) is part of a machinery that regulates cell surface levels of LRP1 by promoting its recycling. Furthermore, the phosphorylation of the cytoplasmic tail after ligand binding modifies the association of LRP1 with adaptor proteins and modulates its endocytic function.38,39

Notably, TRL model particles used in the various studies differ to a great extent in their apolipoprotein and lipid composition. Despite the different experimental settings, recycling of apoE has been observed in all of the above studies. Therefore, apoE itself seems to contribute to the determination of its intracellular destiny.29,31 This exciting new concept is supported by the different extent of recycling of apoE isoforms.40 ApoE exists in 3 common isoforms that strongly affect their binding properties to the LDLR (apoE2 Cys112 and Cys158; apoE3 Cys112 and Arg158; apoE4 Arg112 and Arg158). ApoE2 does not exhibit a high binding affinity to the LDLR,41 but the binding of apoE4 to LDLR and LRP1 and clearance of apoE4-TRL remnants is similar or even more efficient compared with apoE3.42–45 Nevertheless, epidemiological studies clearly show that apoE3 and apoE4 have very differential effects on lipoprotein metabolism. ApoE4 corre-
lates with high LDL cholesterol, elevated triglyceride, and low HDL levels and is associated with atherosclerosis and Alzheimer’s disease (AD). But despite apoE4 being a risk factor, the cellular mechanisms responsible for the differences between apoE3 and apoE4 are not well understood. Cell surface binding, internalization, and endosomal transport and disintegration of apoE3-TRL and apoE4-TRL in early endosomes are comparable in hepatoma cells. Thus, dissimilar recycling of apoE isoforms could contribute to the development of apoE4-associated diseases. In agreement with this model, apoE4 is less efficient compared with apoE3 in promoting cholesterol efflux in fibroblasts and astrocytes, indicating that apoE isoforms differentially affect the mobilization of cellular cholesterol. And, indeed, we could demonstrate that HDL-induced recycling of TRL-derived apoE4 is impaired and associated with a decreased cholesterol efflux. The biophysical characteristics of apoE3 and apoE4 might provide an explanation for the reduced efficiency of intracellular apoE4 processing. ApoE3 binds preferentially to HDL, and apoE4 has a higher affinity to VLDL, suggesting that TRL-derived apoE3 might associate more rapidly with internalized apoA-I and cholesterol to form HDL particles. Furthermore, at low pH, apoE4 has a greater propensity than apoE3 to form a molten globule and an increased binding affinity to lipids. The drop in pH after acidification in early endosomes could lead to a conformational change of internalized apoE4, but not apoE3, and promote binding of apoE4 to subdomains of the inner leaflet of endosomal membranes that are not directed into the recycling compartment. This would ultimately inhibit an efficient transfer of apoE4 to lipid-poor HDL particles during recycling. It is tempting to speculate that the inefficient processing of apoE4 and its effects on intracellular cholesterol transport could contribute to explain the association of apoE4 with atherosclerosis and the onset of AD.

Potential Relevance of ApoE Recycling for Cardiovascular and AD

ApoE regulates lipoprotein metabolism at various levels, making it difficult to dissect the multiple functions in vivo and relate the development of disease specifically to apoE recycling. In fact, depending on the apoE isoform, different aspects of TRL metabolism seem to contribute to the development of hyperlipidemia or the formation of lipid-loaded macrophages. In subjects with apoE2, the defective binding to the LDLR decreases hepatic clearance of TRL and leads to elevated remnant levels in plasma, which is an established risk factor for lesion formation. Subjects homozygous for apoE4 show elevated LDL cholesterol, high triglyceride, and low HDL levels. The molecular mechanisms leading to this proatherogenic lipoprotein profile are not yet understood. However, the impaired recycling of internalized TRL-derived apoE4 could contribute to the atherogenic effects of apoE4. Recycling of TRL-derived apoE3 stimulated by HDL provides an efficient mechanism to resupply plasma with HDL particles, whereas in the postprandial state, HDL supplies apoE for the enrichment of CRs and thereby stimulates the hepatic clearance of TRL. In contrast, apoE4 accumulates intracellularly and is not recycled and transferred efficiently to HDL during the recycling process. This not only leads to low HDL levels but also to decreased CRs clearance and subsequent remnant accumulation and postprandial hypertriglyceridemia. Overall, the reduced amounts of HDL-associated apoE attributable to impaired apoE4 recycling could explain the decelerated turnover of remnant particles in apoE4 subjects. Because cellular accumulation of apoE4 is also associated with decreased cholesterol efflux, this could contribute to an increased risk of atherosclerosis. In support of these data, Hopkins et al showed that apoE3-expressing mice have higher HDL levels and produce larger HDL particles compared with apoE4. Furthermore, apoE3 was far more efficient than apoE4 in normalizing proatherogenic TRL levels in apoE knockout mice. Similar results were obtained in the Arg-61 apoE mouse model, in which the apoE4 lipoprotein interaction domain was introduced into mouse apoE.

Elevated LDL levels observed in apoE4 subjects have been thought to reflect the cholesterol-induced downregulation of the hepatic LDLR caused by enhanced uptake of apoE4-TRL remnants. This is in agreement with our model because apoE4-TRL uptake, followed by impaired apoE4 recycling and consecutive accumulation of intracellular cholesterol, would lead to transcriptional downregulation of the LDLR expression. Next to LDLR downregulation, impaired intracellular apoE4 trafficking could directly act on lipid metabolism and account for the adverse effects of apoE4 in atherosclerosis. Malloy et al showed that apoE4, but not apoE3, induced dyslipidemia, lesion formation, and elevated plasma cholesterol levels in mice with transgenic overexpression of hepatic LDLR. This is indicative of an enhanced uptake of TRL-derived apoE4, and Malloy et al postulated a trapping of apoE4 on the cell surface or intracellularly, leading to the accumulation of apoE-poor remnants. This is in agreement with our studies demonstrating reduced apoE4 recycling from peripheral endosomal compartments. As a consequence, apoE4 would not be available for HDL particle formation or clearance of CRs. Furthermore, the intracellular accumulation of nonrecycled apoE4 and the tight binding of apoE4 to LDLR or LRP1 might inhibit the recycling of lipoprotein receptors back to the cell surface and prevent subsequent uptake of LDL and TRL remnants.

Although the bulk of circulating apoE originates from the liver, significant amounts of apoE are produced and metabolized in macrophages, including those within atherosclerotic lesions. In macrophages, the antiatherogenic properties of endogenous and exogenous apoE have been attributed mainly to the induction of cholesterol efflux, thereby promoting reverse cholesterol transport. With TRL-derived apoE being the focus of this review, we discuss only the protective role of exogenous apoE in foam cell formation. Hepatic overexpression of apoE in apoE knockout mice prevents the development of atherosclerotic lesions. Liver-derived apoE3 is targeted into pre-existing atherosclerotic lesions, suggesting that plasma apoE can gain access to the arterial intima. Recycling of apoE has also been demonstrated in murine peritoneal macrophages, implicating that apoE modulates cholesterol efflux after uptake in macrophages.
Because both apoE3 and apoE4 correct hyperlipidemia, but apoE4 is less protective in preventing progression of atherosclerosis, impaired recycling of apoE4 is likely to be involved in cholesterol accumulation and the accelerated foam cell formation of apoE4 carriers. It should be noted that in addition to liver- and macrophage-derived apoE, the ectopic expression of apoE in adrenals and muscle can inhibit progression of atherosclerosis but will not correct hyperlipidemia. Thus, systemic apoE can promote cholesterol efflux from macrophages via apoE recycling, which underlines the antiatherosclerotic properties of exogenous apoE and its physiological relevance in lipid homeostasis and development of atherosclerosis.

The apoE gene is involved in the development of late onset of AD because individuals with an apoE4 allele show an increased risk and an earlier onset of the disease. AD patients are characterized by the aggregation of amyloid-β peptides (Aβ) in amyloid plaques in the brain. Aβ is derived from the amyloid-precursor protein (APP), and therefore, efforts for understanding the development of AD have focused on the processing of APP. APP is a single-pass transmembrane protein that is predominantly cleaved by α-secretases within the Aβ region to produce an α-stub. In contrast, APP cleavage by β- and γ-secretase results in the formation of neurotoxic Aβ42/Aβ40. Proposals to explain the contribution of apoE4 in AD include modulation of Aβ clearance and deposition, dietary effects, and oxidative stress and have been reviewed previously. A direct connection between the development of AD and cholesterol metabolism arises from the observation that treatment with cholesterol-lowering drugs remarkably reduced the onset of AD. Furthermore, depletion of cellular cholesterol inhibits the generation of Aβ in vitro and in vivo, whereas in rabbits, a cholesterol-rich diet induces the formation of amyloid plaques. The molecular mechanism linking APP processing to cholesterol metabolism involves the activity of α-, β-, and γ-secretases. Cholesterol depletion promotes the nonamyloidogenic cleavage of APP by α-secretase, whereas the activity of β- and γ-secretases is reduced. Thus, accumulation of cholesterol caused by an impaired recycling of apoE4 would favor the amyloidogenic processing of APP by the β-/γ-secretase pathway, leading to the increased formation of Aβ. In addition, Cam et al showed that the overexpression of LRPI modulates the cell surface distribution and processing of APP, and the authors postulated that the interaction of APP with LRPI is critical for the formation of Aβ. Thus, binding of nonrecycled apoE4 to LRPI in the endosomal compartments could reduce LRPI levels at the cell surface and inhibit the protective function of LRPI on the amyloidogenic processing of APP. In summary, impaired recycling of apoE4 could contribute to apoE4-associated diseases by at least 2 mechanisms. (1) Reduced recycling of apoE4 leads to the concomitant accumulation of cholesterol in intracellular compartments. This can affect lipid metabolism in the liver, promote foam cell formation, and modify secretase activity, ultimately leading to the development of atherosclerosis or AD. (2) Tight binding of apoE4 to LDLR and LRPI in endosomal compartments interferes with receptor recycling, thereby preventing further uptake of lipoproteins or physiological interaction of LRPI with APP. To promote the potential antiatherogenic effects of apoE recycling and to shed more light on the pathophysiological role of apoE4 in the development of dyslipidemia and atherosclerosis, several issues have to be addressed in the future research. In particular, the receptors, secretory pathways, and potential HDL/apoE–induced signals that might be involved in the intracellular assembly and recycling of HDL/apoE with apoE/cholesterol complexes still have to be identified. Similarly, studies on the molecular mechanisms of how apoE4 interferes with cholesterol transport and the different secretase activities in neuronal cells will provide further clues on the contribution of the apoE4 allele in the development of AD.

Because apoE recycling requires the docking of HDL/apoA-I to the cell surface, binding to receptors such as ABC transporters or scavenger receptor class B I (SR-BI) could facilitate the internalization of HDL/apoA-I. Because hepatic SR-BI plays a key role in the selective HDL cholesteryl ester uptake and subsequent biliary cholesterol secretion, we currently favor an involvement of ABCA1 in the transport of apoA-I to apoE/cholesterol–containing endosomes. This would be in agreement with the postulated role of ABCA1 in the so-called retroendocytosis model, which proposes an intracellular pathway regulated by ABCA1 to remove excess cellular cholesterol via internalized apoA-I. Nevertheless, there is yet little direct evidence that links endogenous ABCA1 with apoA-I/HDL–induced apoE recycling. In mouse peritoneal macrophages, Hasty et al determined increased apoE recycling on upregulation of ABCA1. In contrast, the lack of ABCA1 in Tangier fibroblasts and elevated ABCA1 levels in human hepatoma cells did not significantly affect apoA-I– or HDL-induced apoE recycling in vitro. Thus, more research is necessary to clarify the molecular mechanism, physiological relevance, and potential contribution of ABCA1 or other members of the ABC family in the regulation of apoE resorption.

Acknowledgments

This work was supported by grants to J.H. (DFG: HE 3654/2–1 and GRK336 “Molecular Endocrinology and Metabolism”) and T.G. (Gretl Raymond Foundation, National Heart Foundation of Australia G04S1650, Cure Cancer Australia Foundation RM02987).

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Arterioscler Thromb Vasc Biol. 2006;26:442-448; originally published online December 22, 2005;
doi: 10.1161/01.ATV.0000201282.64751.47
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

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